The PANCREAS

AN INTEGRATED TEXTBOOK OF BASIC SCIENCE, MEDICINE, AND SURGERY

EDITED BY HANS G. BEGER, MARKUS W. BÜCHLER, RALPH H. HRUBAN, JULIA MAYERLE, JOHN P. NEOPTOLEMOS, TOORU SHIMOSEGAWA, ANDREW L. WARSHAW, DAVID C. WHITCOMB, and YUPEI ZHAO



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The Pancreas

An Integrated Textbook of Basic Science, Medicine, and Surgery

Fourth Edition

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Preface

The fourth edition of *The Pancreas* presents the most comprehensive and latest knowledge about the genetic and molecular biological basis of embryology, anatomy, physiology, pathophysiology, and pathology for all disorders of the pancreas. Compared to the first edition, published in 1998, the fourth edition contains three newly addressed diseases of the pancreas: autoimmune pancreatitis, benign and premalignant cystic neoplasms, and neuroendocrine tumors. The understanding of the functions and dysfunctions of the exocrine and endocrine pancreas is derived from increasingly profound molecular biological data on the actions of compounds in subcellular compartments and intracellular transcription pathways. In the respective chapters, the presentation of the inflammatory (acute or chronic) and oncological diseases (benign, premalignant, or advanced cancer) is based on molecular biological understanding of pathomorphological processes and clinical phenomena. In clinical pancreatology, new and improved technical devices enable the gastroenterologist and the gastrointestinal surgeon to identify lesions by high-resolution imaging techniques, imaging of metabolic processes, and intrapancreatic ductal morphologic processes. The molecular profiling of pancreatic ductal adenocarcinoma has provided a deeper understanding of the genomic alterations that drive pancreatic ductal adenocarcinoma, including driver genes, actionable mutations, copy number alterations, patterns of genomic aberrations, structural variations, and mutational signatures. These findings have transformed our biological genomic understanding, but are still of limited clinical utility. Significant progress has been made in understanding the molecular pathogenesis of pancreatic cancer and identification of various molecular subtypes. However, this improved understanding has unfortunately not yet led to relevant progress for the patient's cure, although survival gain after radical cancer resection in addition with neoadjuvant chemotherapy is significant for selected groups of patients.

The synergistic interaction of basic scientists, pathologists, gastroenterologists, and gastrointestinal tract surgeons in the field of investigative and clinical pancreatology has led to a better understanding of pancreatic diseases through combining the knowledge of each to achieve the best management. Most importantly, the decision-making for patients with an option to be successfully treated for pancreatic disease is increasingly based on high-evidence data from clinical trials on treatment. New technical devices—endoscopic visualization of cellular abnormalities, laparoscopic minimally invasive surgical approaches, and robotic surgery—have led to significant clinical improvement. The establishment of local, parenchyma-sparing surgical approaches for the increasing number of benign tumors, cystic neoplasms, and neuroendocrine tumors have significantly improved the patient's outcome compared to classical pancreatic resections.

The goal of this fourth edition is to provide the clinician with the most current evidence-based synthesis of understanding of pancreatic diseases, functional assessment, diagnostic and technical devices, treatment options, and outcome results. All chapters are written by leading international experts on the topic. A major part of this edition has been contributed by international basic scientists, who provide an understanding of the molecular basis of pancreatic functions and dysfunctions. The editors acknowledge and are deeply indebted to all authors who have contributed to this edition. Their diligent efforts have provided state-of-the-art knowledge, particularly in regard to decision-making based on clinical evidence.

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Section 1

Anatomy of the Pancreas

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1

Development of the Pancreas and Related Structures

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Anatomy of the Pancreas

The pancreas is a unique exocrine and endocrine organ located in the retroperitoneal region of the upper abdominal cavity. In humans, when fully formed, the organ has a distinct head, body, and tail, with the head of the pancreas contacting the duodenal region of the intestines (the main pancreatic duct drains into the duodenum) and the tail of the pancreas abutting the spleen. The greatest mass of the organ is present in the head, which is composed of tissue derived from two independent anlagen (see later). In other mammals, such as dogs and mice, the organ has a far less distinct structure and is identified as an amorphous pink tissue adjacent to the mesentery that runs along the upper intestinal wall.

The cells of the pancreas are arranged into distinct lobules composed primarily of the digestive enzyme-producing cells of the exocrine pancreas, which are arranged into acini (so-called acinar cells), the ductal structures that conduct these digestive enzymes to the intestines, and distinct clusters of endocrine cells, the islets of Langerhans, that secrete hormones and function to regulate glucose uptake and release and serum glucose levels. There are five recognized cell types within the islets, the α, β, δ, ε, and PP cells, which produce the hormones glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively. The majority of the pancreatic tissue mass (more than 90–95%) is present within the exocrine compartment of the organ, with the islets of Langerhans, scattered throughout the tissue. The pancreas also has connective tissue, derived from the embryonic mesenchyme, which forms the septa that separate the many lobules of the organ. Mesenchyme-derived stromal cells are also present in the interlobular regions surrounding the pancreatic ducts, blood vessels, and nerves. In the following sections, we explore how these disparate cell types come together to form the pancreas.

Organogenesis in the Region of the Pancreas

Around day 14, the embryonic bilaminar germ disk is composed of a layer of epiblast and a layer of hypoblast. At this time, a faint groove appears along the longitudinal midline of the germ disk that develops into a structure called the primitive streak [1]. Around day 15, epiblast cells near the primitive streak undergo a morphologic change and migrate through the primitive streak into the space between the epiblast and hypoblast in a process known as gastrulation (Fig. 1.1). Some of the ingressing epiblast cells invade the hypoblast, which is eventually replaced by a new layer of epiblast-derived cells known as the definitive endoderm. Additional migrating epiblast cells occupy the space between the epiblast and the definitive endoderm to form a third layer of cells called the intraembryonic mesoderm (Fig. 1.1). As cells of the germinal disk migrate anteriorly to form a head process and lateral regions roll underneath to form an approximately cylindrical body shape, the endoderm is rolled into a tube that projects into the developing head region of the embryo surrounded by the mesoderm layer. This is the primitive digestive tube. The pancreas is specified by two separate outgrowths that arise on the dorsal and ventral surfaces of the primitive digestive tube. The epithelial cells of the pancreas originate from the interior lining of the primitive gut tube, which consists of a single layer of endoderm. A layer of mesenchyme, from which the muscle and

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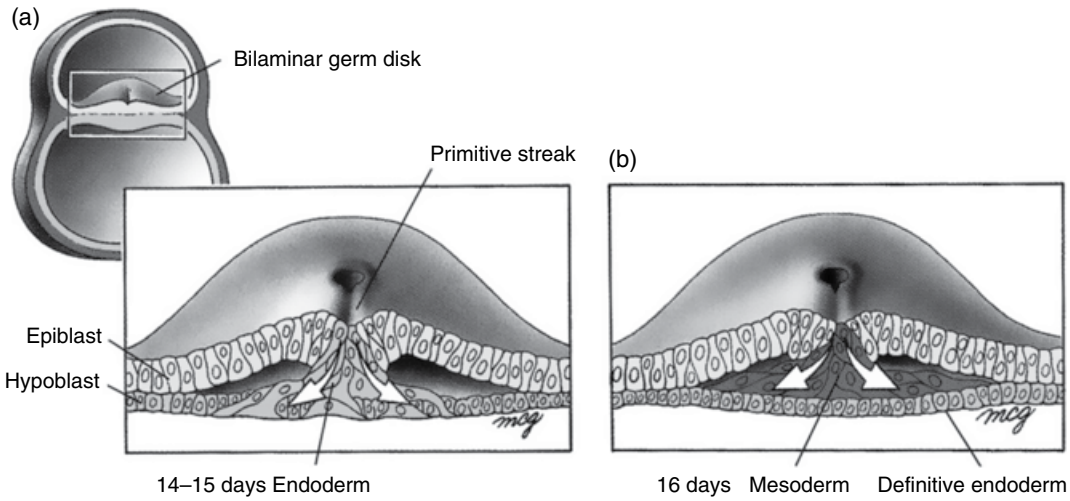


Figure 1.1 Germ disks sectioned through the region of the primitive streak, showing gastrulation. (a) On days 14 and 15, the ingressing epiblast cells replace the hypoblast to form the definitive endoderm. (b) The epiblast that ingresses on day 16 migrates between the endoderm and epiblast layers to form the intraembryonic mesoderm. *Source:* Larsen 2001 [1]. Reproduced with permission of Elsevier.

connective tissue of the gastrointestinal organs are derived, surrounds the endoderm.

The anterior regions of the endoderm form the foregut; regions posterior to the foregut form the midgut and hindgut. The most anterior regions of the foregut give rise to the esophagus and stomach. Just posterior to the foregut, the endoderm is continuous with the yolk sac, which extends outside the embryo, in a region known as the anterior intestinal portal. Endodermally derived cells close to the anterior intestinal portal specify the pancreas. The duodenum and liver are also specified by foregut endoderm in this region.

Thus, many gastrointestinal tissues are specified at the same time from a fairly restricted region of the gut endoderm. How are each of these organs specified in the appropriate anatomic location, and how do they differentiate properly into mature functional organs? The epithelial organs of the developing embryo originate as buds from the endoderm as the appropriate temporal and spatial cues are received. Thus, proper initiation and location of endodermally derived organs are regulated by the activation status of important signal transduction pathways involved in animal development, including the hedgehog, Notch, and fibroblast growth factor (FGF) signaling pathways.

Early Pancreatic Development

During the fourth week of gestation, two buds appear on the dorsal and ventral sides of the foregut near the anterior intestinal portal. These epithelial buds indicate the specification of the pancreas. These buds initially grow and differentiate independently, but later fuse to form a single organ. The anlage on the dorsal side, the dorsal pancreatic bud, appears first and gives rise to the dorsal pancreas. The cells of the dorsal pancreas will give rise to the head, body, and tail of the mature pancreas. The second pancreatic anlage appears shortly after the appearance of the dorsal pancreatic bud. This bud, which appears on the ventral side of the gut tube, is appropriately called the ventral pancreatic bud and develops into the ventral pancreas, which forms part of the head of the pancreas. Both pancreatic buds develop simultaneously, and the proliferating epithelial cells grow as projections into the surrounding mesenchymal tissue. During this time, the development of the intestines, and importantly the duodenum, continues. Rotation and asymmetric growth of the duodenum move the originally ventral part to a dorsal location, carrying with it the ventral pancreas and the primordial common bile duct. As the duodenum begins to rotate into its appropriate anatomic location, the ventral pancreas also rotates around the gut tube such that the ventral and dorsal pancreata lie adjacent to each other. These pancreatic rudiments then fuse to form a single organ. While both developing pancreatic buds independently form pancreatic ducts, the lumens of which are continuous with the lumen of the primitive gut, after they fuse their primary ducts anastomose to form the main pancreatic duct (Fig. 1.2). The region of the primary duct of the ventral pancreas proximal to the duodenum fuses with the primary duct of the dorsal pancreas and becomes the primary drainage into the duodenum, entering the duodenum immediately adjacent to the common bile duct. The proximal region of the primary duct of the dorsal pancreas sometimes

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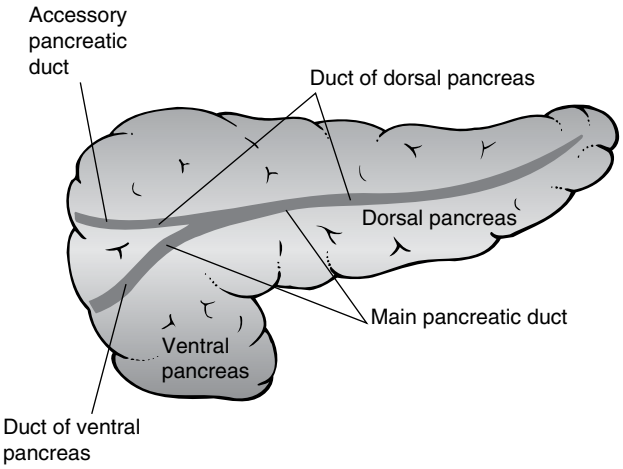


Figure 1.2 Contributions of the dorsal and ventral pancreas to the definitive organ. The ventral pancreas becomes most of the head. The dorsal pancreas becomes the remainder of the head, plus the body and tail. The duct of the dorsal pancreas contributes a large part of the main pancreatic duct plus the accessory duct. The duct of the ventral pancreas becomes the part of the main duct nearest the duodenum.

remains as an accessory drainage but often regresses. The ducts sometimes fail to fuse, in which event two independent duct systems drain into the duodenum.

Signaling Governing Early Pancreatic Development

Early pancreatic development and establishing pancreatic identity are governed by the interplay between several critical transcription factors and intercellular signaling pathways. PDX1 and PTF1A are among the earliest transcription factors expressed in the pancreatic progenitor populations, and their functions are critical for pancreatic development [2–5]. In mice, PDX1 expression is first detected in the primitive gut tube at embryonic day 8.5 (E8.5), which corresponds to ~25–27 days in humans. PDX1 expression demarcates the prospective pancreatic domain, which is then followed by PTF1A expression in pancreatic endoderm at E9.5 [5–7]. Mice lacking either transcription factor display pancreatic agenesis [2,3,5,8].

In addition to the transcription factors, several key intercellular signaling pathways between gut endoderm and mesenchyme, including the hedgehog, FGF, Notch and Hippo pathways, play important roles in establishing the pancreatic identity and controlling the expression of these transcription factors. Research studies have shown that sonic hedgehog (SHH), the ligand of the hedgehog pathway, is excluded from the prospective pancreatic region, but is present in the region of foregut that becomes the duodenum, and ectopic expression of SHH in the pancreas induces an intestinal fate, suggesting that SHH signaling may specify a duodenal versus pancreatic fate in the posterior foregut [9,10]. Another well-understood pathway mediating the mesenchymal–epithelial interaction is the FGF signaling pathway, in particular the FGF10–FGFR2 ligand-receptor pair. During early pancreatic development, FGF10 is highly expressed in the primitive mesenchyme, whereas its receptor FGFR2 is present in the pancreatic epithelium [11]. Mouse genetic experiments demonstrated that FGF10 provides the pro-proliferative signal to promote the expansion of the progenitor pool in the pancreatic epithelium [11]. In addition, FGF10 signaling from the mesenchymal cells is critical for maintaining the epithelial expression of SOX9 [12]. SOX9 is another transcription factor critical for early pancreatic development, and it exerts its function in part by controlling the expression of the FGF10 receptor FGFR2 [12,13]. Together, the complex regulatory loop between these signaling pathways and transcription factors in the epithelium and mesenchyme coordinates early organ growth and the establishment and maintenance of pancreatic identity.

Differentiation of Pancreas Cell Types

The acinar, ductal, and endocrine cells of the pancreas are all produced through the proliferation and differentiation of the epithelial cells of both pancreas primordia. The cells appear homogeneous during the early stages of development as they proliferate and grow into the surrounding mesenchyme as finger-like projections. The epithelial cells form undifferentiated tubules that branch and anastomose as they penetrate into the mesenchyme to generate a tubular network, which resembles an immature (and nonfunctional) duct system. The acinar cells appear as clusters of cells at the ends of branches of this tubular network. The endocrine cells appear as cells that delaminate from the tubular epithelium and reaggregate in isolated clusters embedded within the developing parenchyma. The existing cells within these small isolated endocrine clusters proliferate, and these clusters therefore expand to form the islets.

Apparent differentiation of pancreas epithelial cells into endocrine cells can be identified beginning at 12 weeks of gestation with the detection of endocrine granules. Most of the endocrine differentiated cells identified at this time express glucagon and are therefore believed to be α cells. Importantly, lineage-tracing experiments performed in mice demonstrated that these early α cells do not act as endocrine progenitors, as β cells, the predominant cell type in the mature islet, are derived from glucagon-negative cells [14]. Differentiation of

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acinar cells is detected at approximately 16 weeks, as identified by the appearance of zymogen granules. Interestingly, not all enzymes are elaborated at once—detection of trypsinogen does not occur until approximately 22 weeks. The digestive enzyme-positive cells arise as clusters from the undifferentiated tubules, the expansion of which is rapid such that the acinar cells become the dominant population within the organ. Although they are not yet mature acinar cells, the cells in the acinar clusters display some of their hallmark features, including basolaterally located nuclei. As differentiation continues, the cells become arranged in recognized acini and defined lobules surrounded by connective tissue. The ductal system arises after maturation of the immature tubular network. The specific morphologic changes that accompany this change are unclear, although some work suggests that Wnt signaling is involved in this transition [15].

Transcriptional Mechanisms Underlying Pancreatic Cell Fate Decision

Much information about pancreatic cell fate determination and cell type differentiation has been obtained from studies in animal models. Elegant genetic and cell-based experiments in mice have identified a gene regulatory network controlled by many transcription factors to specify different cell lineages in the developing pancreas.

Development of the Endocrine Lineage

Endocrine cell specification begins with the expression of NGN3, a bHLH (basic helix–loop–helix) transcription factor, in a subset of progenitor cells within the trunk region of the pancreatic bud [16–18]. The NGN3-expressing cells eventually give rise to all endocrine cell types: insulin-producing β cells, glucagon-producing α cells, somatostatin-producing δ cells, ghrelin-producing ε cells, and pancreatic polypeptide-producing PP cells [16–18]. NGN3 initiates endocrine lineage specification by inducing the expression of downstream transcription factors, including NeuroD, NKX2.2, PAX4, and ARX. Among them, NKX2.2, NeuroD, and PAX4 play key roles in the specification of β cells [19–21]. Mutant mice lacking any of these transcription factors display a phenotype of dramatic or total loss of β cells [19–21]. Further studies revealed that the opposing actions of PAX4 and ARX determine the fate choice between α and β cells. During endocrine differentiation, loss of ARX leads to a complete loss of α cells, but a concomitant increase in β and δ cells [22], whereas loss of PAX4 results in an opposite phenotype with loss of β and δ cells and expansion of α cells [20,22]. It is believed that this effect on cell fate choice is mediated by the reciprocal transcriptional repression between these factors.

Differentiation of Acinar Cells

Pancreatic acinar cells are primarily derived from precursor cells in the tip region, and their differentiation is coordinated by the transcription factor PTF1A, a master regulator of pancreatic development. Prior to exocrine differentiation, PTF1A forms a complex with the bHLH transcription factor RBP-Jk, and is required for activation of RBP-Jl, an acinar-specific paralog of RBP-Jk [23,24]. The more active RBP-Jl then replaces RBP-Jk to form the complex with PTF1A, thereby directly inducing the expression of many acinar-specific genes, including secretory peptides and digestive enzymes [23,24]. Interestingly, PDX1, another factor important for early pancreatic morphogenesis, is also involved in acinar differentiation. Although not essential for initial acinar specification, it appears that PDX1 is required for terminal differentiation of acinar cells [25]. Other transcription factors, such as NR5A2 and MIST1, are also required for acinar differentiation and homeostasis, likely through the interaction with the PTF1A/RBP-Jk/l complex [26,27].

Ductal Cell Differentiation and Lineage Plasticity

During development, NGN3-positive cells in the trunk region of the pancreatic bud give rise to endocrine cells, whereas NGN3-negative trunk epithelial cells contribute to the ductal system [28,29]. A number of transcription factors, such as SOX9, PROX1, HES1, and HNF6, are expressed in the ductal lineage and play various roles in ductal differentiation, including primary cilia formation in the ductal epithelial cells [30–33]. The Notch signaling pathway is the main determinant for promoting and maintaining the ductal cell identity [31]. Although the three lineages (endocrine, exocrine, and ductal) are specified during early development, the adult pancreatic cells from different lineages show remarkable plasticity and trans-differentiation capacity in pancreatic injury, pancreatitis, and tumorigenesis, which may shed light on the mechanisms underlying these pancreatic pathologies.

Development and Disease

Molecules important in the development of the pancreas are also causally associated with pancreatic disorders. Several of the signaling pathways involved in normal

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pancreas development, such as the Notch, hedgehog, Hippo/YAP and Wnt signaling pathways, are commonly dysregulated in pancreatic ductal adenocarcinomas [34–40]. Aberrant activation of Wnt signaling drives the development of other pancreatic tumor types such as acinar carcinomas, pancreatoblastoma, and mucinous cystic neoplasms [41–43].

In diabetes, mutation of the transcription factor PDX1, which is important for pancreas specification and for proper β-cell maturation and function, is a cause of maturity-onset diabetes of the young (MODY) [44]. Other transcription factors that are critical for β-cell development (as determined by genetic studies in the mouse), such as hepatocyte nuclear factor 1α (HNF1α), HNF1β, HNF4α, and NeuroD, are all also mutated in additional MODY complementation groups [44]. More recently, scientists have utilized our growing understanding of normal pancreas development to promote the differentiation of induced pluripotent stem cells into insulin-producing cells in a new potential therapeutic approach for diabetes [45–47].

Collectively, these findings illustrate the importance of key regulators of pancreas development and differentiation in pathologic disease states and how knowledge of normal pancreas development may drive new therapeutic strategies for pancreatic diseases.

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2

Anatomy, Histology, and Fine Structure of the Pancreas

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Introduction

This chapter reviews the anatomy, histology, and ultrastructure of the pancreas, including both the exocrine and endocrine portions. The exocrine pancreas produces and secretes digestive enzymes (e.g., trypsin, chymotrypsin, amylase, lipase) into the duodenum. The exocrine portion includes acinar cells and ducts with associated connective tissue, vessels, and nerves that comprise more than 95% of the pancreatic mass. The endocrine pancreas (islets of Langerhans) makes and secretes insulin, glucagon, somatostatin, and pancreatic polypeptide into the blood. The islets comprise 1–2% of pancreatic mass.

When the anatomic terms *anterior* and *posterior* are used in this chapter, they pertain to relationships in the human, standing erect. Similarly, *superior* and *inferior* mean toward the head and toward the feet, respectively. We will adopt the convention that *right* and *left* (unqualified) indicate the subject's right-hand and left-hand sides. However, when describing the location of structures within an image, *image right* and *image left* are used to denote relationships without reference to the subject's right or left side.

The organization and content of this chapter are based in part on a recent Pancreapedia chapter on pancreatic anatomy and histology [1].

Gross Anatomy

The pancreas (meaning all flesh in Greek) lies in the posterior portion of the upper abdomen behind the stomach. It is largely retroperitoneal and is covered by peritoneum on the anterior surface of the head and body and is surrounded by fat in this region. It is customary to refer to various portions of the pancreas as head, body, and tail. The head abuts the C-shaped second portion of the duodenum in the right upper quadrant of the abdomen. The tail emerges into the peritoneal cavity (covered by peritoneal serosa) and extends toward the hilum of the spleen in the left upper quadrant. The pancreas weighs about 100 g and is 14–25 cm long [2]. Figure 2.1 shows a human pancreas that has been dissected to isolate it from surrounding fat and adjacent organs and Fig. 2.2 is a drawing depicting a pancreas that has been dissected to reveal the pancreatic and common bile ducts.

The pancreas is intimately associated with several adjacent organs. Relationships of the pancreas to surrounding organs and structures are depicted in Figs 2.3, 2.4, 2.5, and 2.6. As noted above, as the duodenum exits the stomach it loops around the head of the pancreas. The tail of the pancreas lies near the hilum of the spleen. The body of the pancreas lies posterior to the pyloric region of the stomach.

The portion of the pancreas that lies anterior to the aorta is somewhat thinner in the anterior–posterior axis than the adjacent portions of the head and body of the pancreas. This region is designated as the neck and marks the junction of the head and body (Fig. 2.1b). The proximity of the neck of the pancreas to major blood vessels posteriorly, including the superior mesenteric artery, superior mesenteric-portal vein, inferior vena cava, and aorta, limits the options for a wide surgical margin during pancreatectomy (Fig. 2.5).

There is no anatomic landmark for the junction between the body and tail of the pancreas [3]. Hellman defined the tail as one-fourth of the pancreas from the tip of the tail toward the head [4] whereas Wittingen and

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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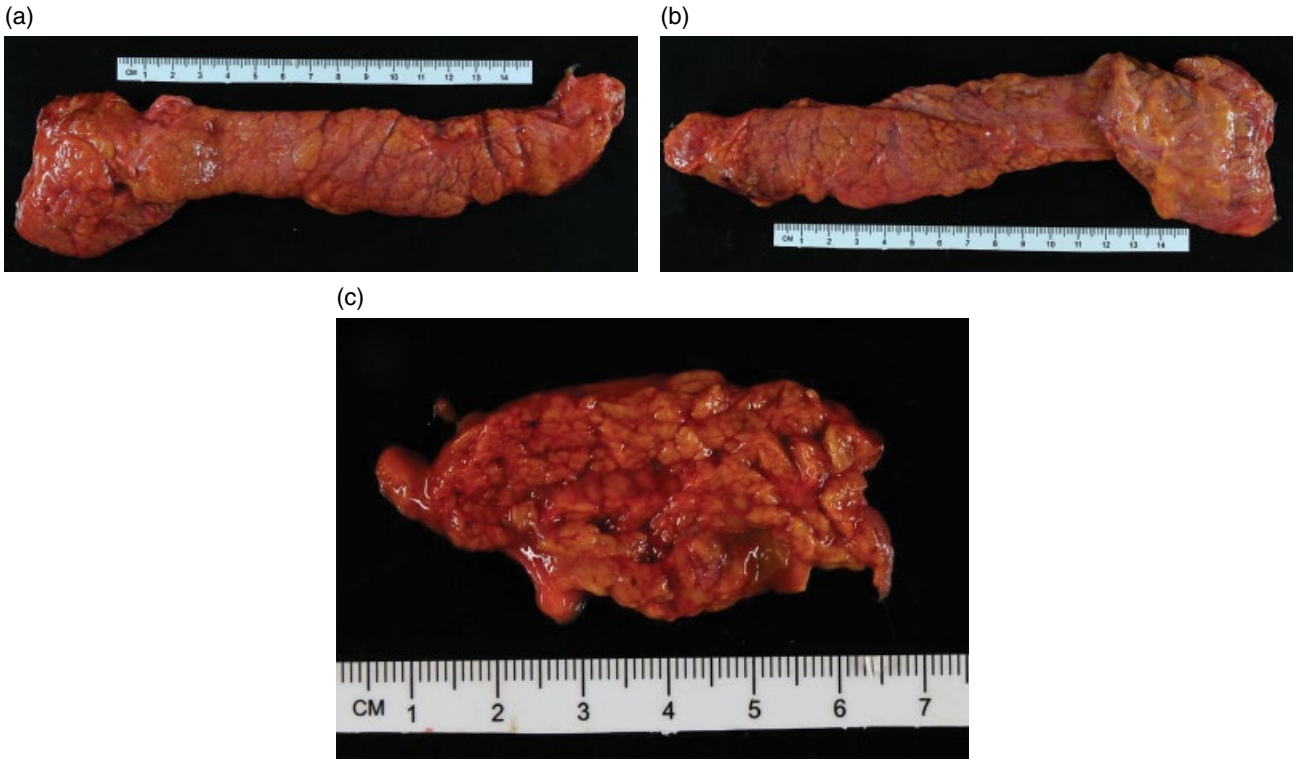


Figure 2.1 This pancreas, from the autopsy of a 47-year-old woman, measures 22.5 cm in length and has been dissected free of most surrounding fat. (a) Anterior view with the head at image left. (b) Posterior view. A thin layer of fat (translucent yellow) covers a portion of the head at image right. Note the thin neck region just to the left of the head. (c) Cut surface of a transection through the head of the pancreas showing the lobular pancreatic parenchyma. *Source:* Dissection and photo by Catherine M. Nicka, MD.

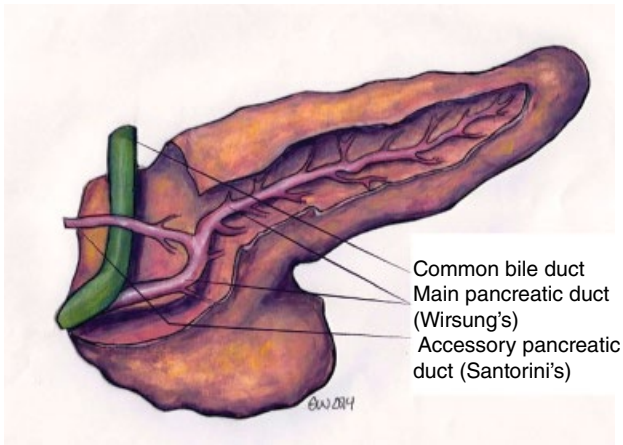


Figure 2.2 A pancreas dissected to reveal the pancreatic ducts and common bile duct as it traverses the head of the pancreas, ending as it joins the main pancreatic duct near the ampulla of Vater. Interlobular branches of the main duct are depicted but smaller ducts (intralobular ducts and ductules) are not. Eponyms identify the anatomist, embryologist, or physician who is credited with first describing a structure. Wirsung and Santorini were such scientists. *Source:* Drawing by Emily Weber.

Frey defined the junction between the body and tail as the point where the gland sharply narrows [5]. This point is difficult to define in some pancreases.

The common bile duct passes behind the upper portion of the head and then runs through the pancreas to join the main duct in the duodenal wall (Figs 2.2, 2.5, and 2.7b). The accessory pancreatic duct drains into the duodenum at the minor papilla in most humans, and the main pancreatic duct enters the duodenum at the major papilla (ampulla of Vater, Fig. 2.3). See Chapter 3 for discussion of pancreas divisum and other anomalies with possible clinical significance.

Typically, the bile duct and main pancreatic duct join into a "common channel" referring to the fused portion of the bile and pancreatic ducts proximal to its entry into the duodenal lumen. The common channel varies in length from a few millimeters to about 1 cm. A long common channel due to junction of the bile and pancreatic ducts proximal to the duodenal wall is regarded as an anomaly [6]. Less often, there is no common channel because the ducts open separately into the duodenum at the major

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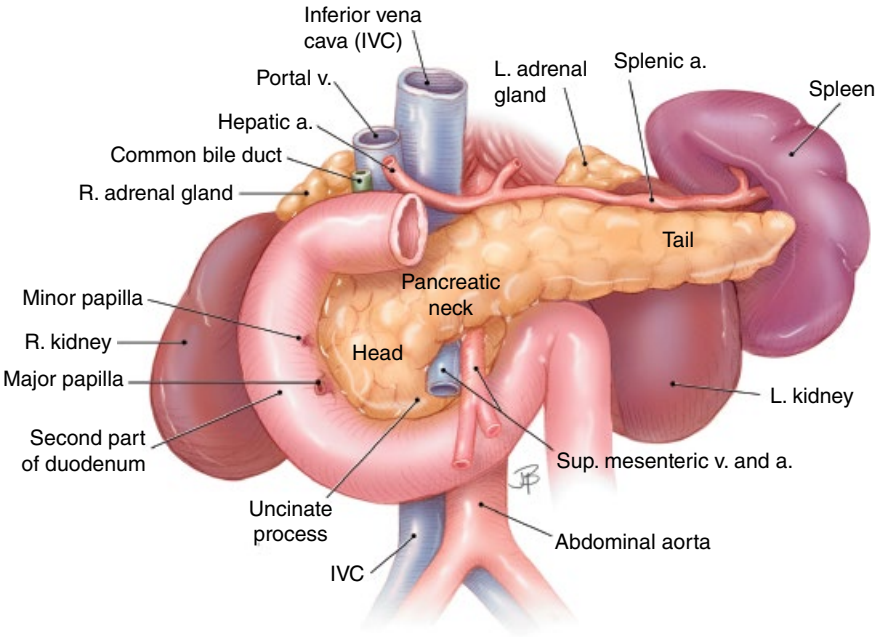
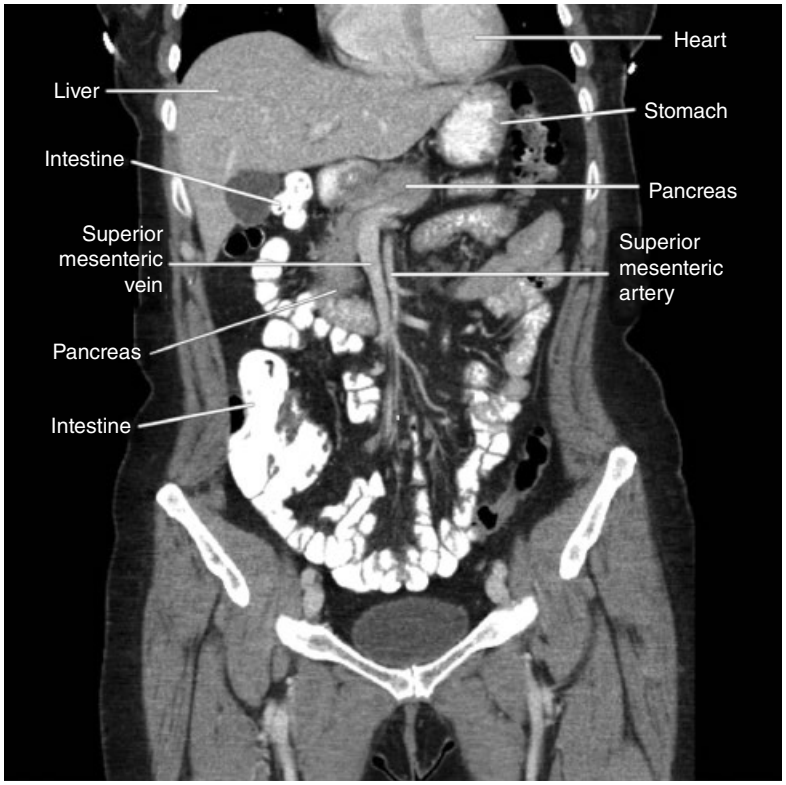


Figure 2.3 Relationships of the pancreas to surrounding organs. This two-dimensional drawing depicts structures that lie in several different planes; for example, the kidneys lie lateral to the spine and posterior to the pancreas. The superior mesenteric artery and vein lie anterior to the aorta and inferior vena cava. *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

Figure 2.4 Frontal CT scan in the plane of the head and body of the pancreas. The technology dictates that all structures shown lie in the same plane. The tail of the pancreas is not shown because it lies posterior to the depicted plane. *Source:* Image provided by Jason Ferreira.



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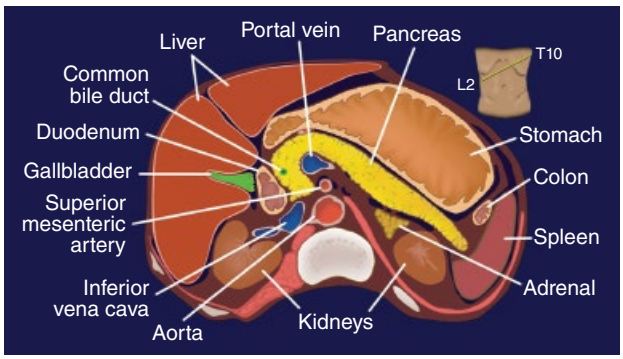


Figure 2.5 Diagram of the upper abdomen at the level of the pancreas based on a CT scan. Note that the plane of the image is angled upward on the left as indicated, upper image right. The vertebral column is unlabeled bottom center. *Source:* Image contributed by Fred Gorelick.

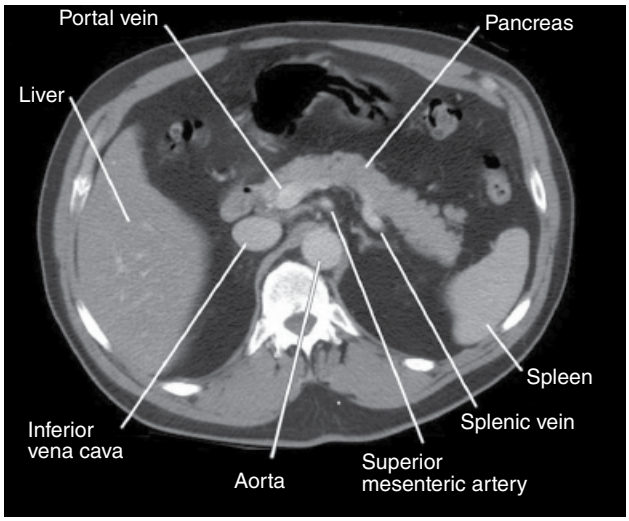


Figure 2.6 Axial CT scan of the upper abdomen at the level of the pancreas. This scan is oriented with the abdominal wall at the top and the spine and muscles of the back at the bottom as viewed from below. Key structures are labeled. *Source:* Image provided by Jason Ferreira.

ampulla. The common channel has received much attention because stones in the biliary tract (gallstones) may lodge in the common channel, causing obstruction of both pancreatic and biliary duct systems. Such an obstruction is frequently the cause of acute pancreatitis.

The arterial blood supply to the pancreas is through branches of the celiac trunk and the superior mesenteric artery (Fig. 2.7). Both arise from the abdominal aorta and have multiple branches that supply several organs. Anastomosis of their branches provides collateral circulation that generally assures a secure arterial blood supply to the pancreas. Most of the arteries are accompanied by veins that drain into the superior mesenteric, portal, and splenic veins as they pass behind the pancreas, as shown in Fig. 2.7b. The superior mesenteric vein becomes the portal vein when it joins the splenic vein (Fig. 2.7b).

The typical locations of lymph nodes surrounding the pancreas are shown in Fig. 2.8. There is significant individual variation in the location of lymph nodes, so the locations shown are a generalization. In general, two systems of lymph nodes drain the organ: one surrounding the edges of the pancreas (Fig. 2.8a), and the other associated with the anterior surface of the aorta and celiac trunk (Fig. 2.8b). Various node groups have been assigned "station numbers" that may be used to designate their location [1,2,7]. These are rarely used in Western literature and are not illustrated here. Lymphatics arise in the interstitium of the pancreas and course with blood vessels and nerves draining to the nodes and then to the thoracic duct.

A rich plexus of autonomic nerves lies behind the head, neck, and body of the pancreas connecting to the celiac ganglia that lie along the aorta (Fig. 2.9).

Histology and Ultrastructure

Overview

The exocrine pancreas is a network of tubules composed of acinar and duct cells that synthesize, secrete, and carry digestive enzymes into the intestine. The small tubules in the lobular tissue are largely composed of acinar cells. The acinar tubules connect to the smallest terminal portions of the duct system that are commonly called ductules, although intercalated duct has also been used to denote these components of the duct system. In this chapter, we will use *ductule* to denote these small terminal portions of the duct system that link the acinar tubules to larger ducts, including small intralobular ducts. At the level of gross anatomy, the acinar tubules, ductules, and small ducts appear as solid lobular tissue as seen in Fig. 2.1c. The following descriptions include both histology and ultrastructure for each major cell type.

Acinar Tissue

An acinus is a cluster of acinar cells that contain zymogen granules, the storage compartment for pancreatic digestive enzymes. For many years, it was considered that acinar tissue was composed of clusters of acini arranged like grapes at the ends of a branching duct system. However, more recent studies have demonstrated that pancreatic acini and tubules are arranged as an anastomosing tubular network [8]. The duct cells at the interface of acinar tubules and ductules are referred to as centroacinar cells and these cells may also be interspersed within acini. An

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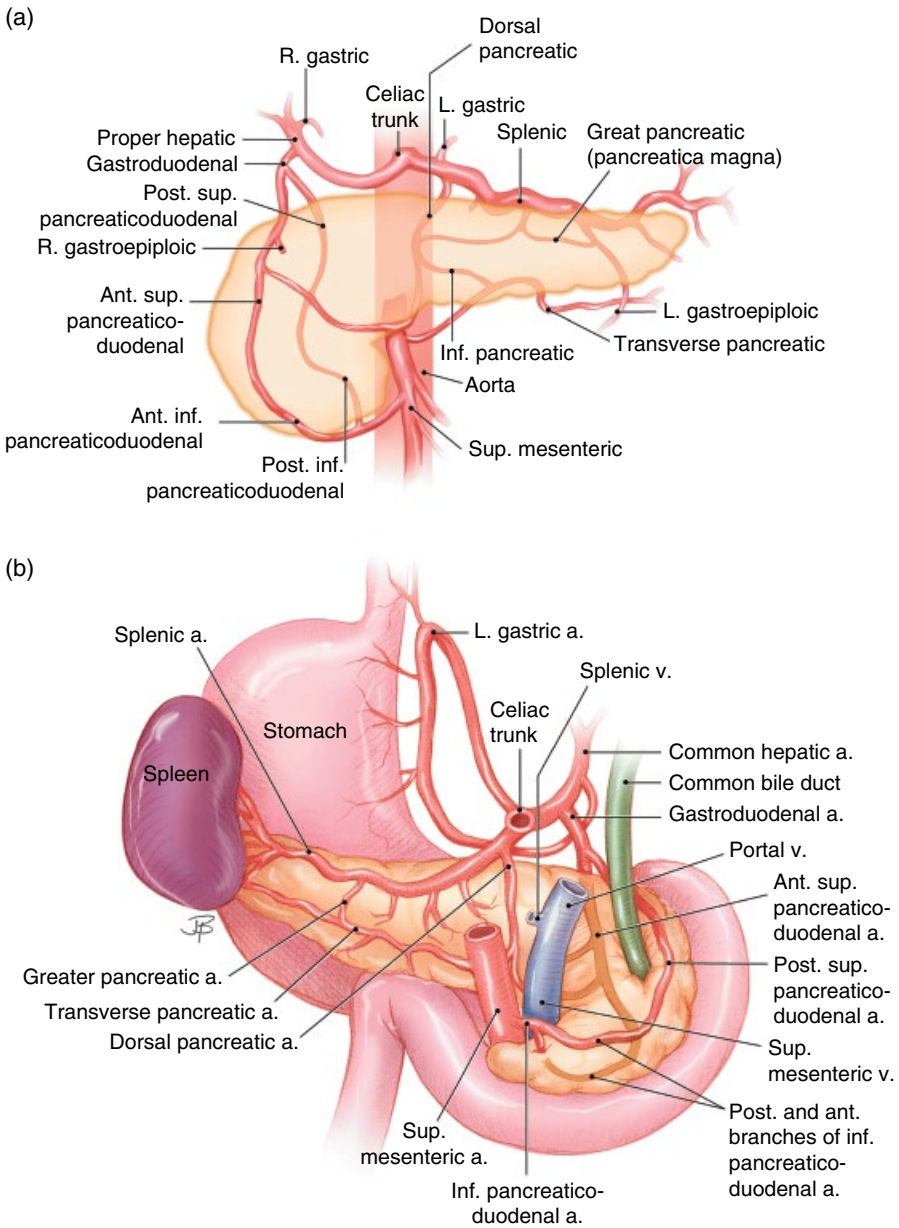


Figure 2.7 The arterial blood supply of the pancreas. Image (a) is visualized from the front (anterior) and (b) is seen from the back (posterior). *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

acinus may occur as a cul-de-sac at the end of a tubular network and also as an intermediate structure with ductules on either side. Recognizing this pattern provides a basis for understanding the changes that the pancreas undergoes with the development of cancer and pancreatitis [9,10]. The tubular complexes that are observed as a result of these diseases are contributed to by the transition of acinar cells into ductular-like cells, a process sometimes referred to as acinar to ductal metaplasia [11].

At the histologic level in sections stained with hematoxylin and eosin (H&E), individual acinar cells have bluish cytoplasm in the basal (perinuclear) region, reflecting the high content of RNA (Fig. 2.10). Central to the nucleus, the cytoplasm is eosinophilic (pink), reflecting the higher content of protein in the Golgi and zymogen granules. Many acinar cells are binucleate [12,13]. Although the detailed histologic characterization of binucleation is based on the rat pancreas, the observation

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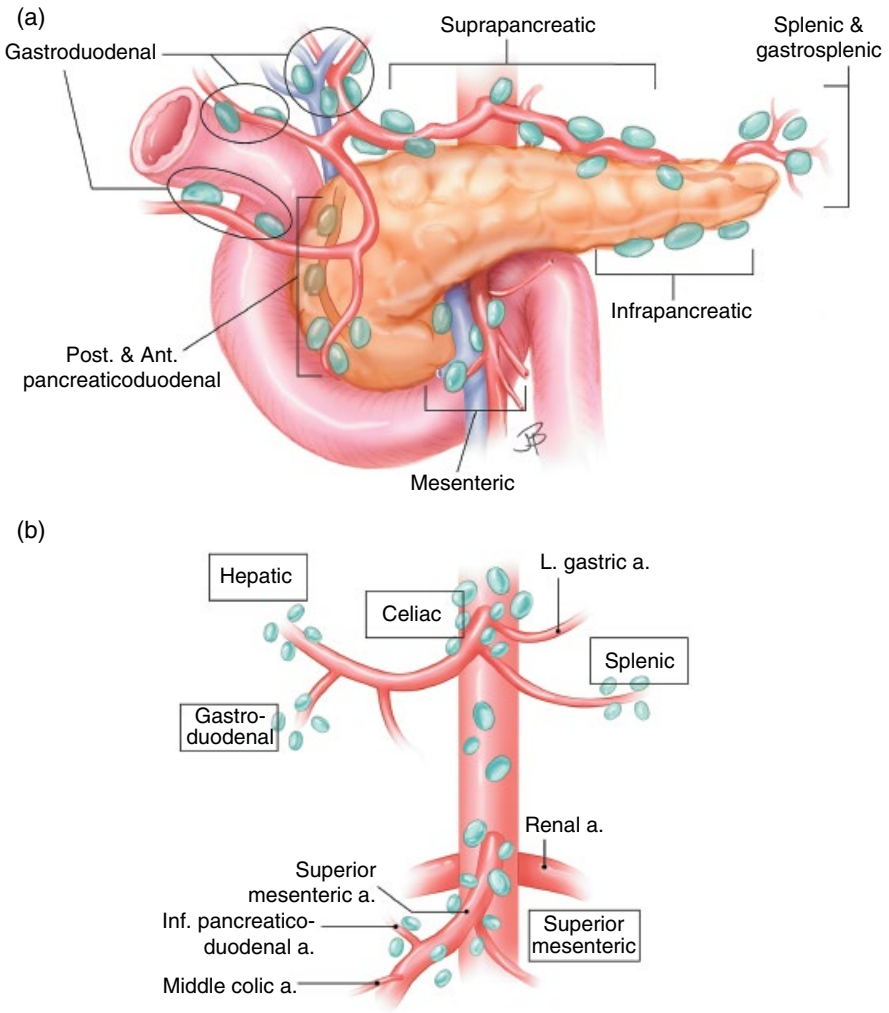


Figure 2.8 Lymph nodes draining the pancreas. There is considerable individual variation in the location and size of lymph nodes, so this drawing is somewhat schematic. Both (a) and (b) are anterior views; (b) includes some nodes that lie posterior to the pancreas. *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

also appears to pertain for the human pancreas but is of unknown significance.

The acinar cell ultrastructure reflects cell function, that is, the synthesis and secretion of digestive enzymes, and it will be described in the context of this function. The basilar cell membrane has an extracellular basement membrane that abuts the interstitial space where capillaries and nerve endings lie (Fig. 2.11). The lateral cell membranes are closely apposed to the cell membranes of adjacent acinar or centroacinar cells and these membranes are linked by linear tight junctions (Figs 2.12 and 2.13). The most distinctive feature of the luminal membrane is the formation of microvilli, which are narrow, finger-like extensions into the lumen of the acinus (Fig. 2.13).

The basilar and perinuclear cytoplasm of acinar cells contains abundant rough endoplasmic reticulum (RER) that forms flattened cisternae with a smooth luminal side, whereas the external surface is studded with ribosomes (giving rise to the "rough" designation). The RER is folded into stacks that generally lie in the plane of the adjacent cell membrane (Fig. 2.12).

Mitochondria are scattered throughout the cytoplasm of the acinar cells but their density is highest in the basal and central portion of the cell (Fig. 2.12). They are sparse in the cytoplasm adjacent to the luminal surface.

On the luminal side of the nucleus, small membrane-bound transport vesicles appear to bud from the RER and then to lie free in the cytoplasm. Central to this region are small stacks of flattened smooth-walled vesicles called the Golgi that appear to arise from the fusion of multiple transport vesicles. At the luminal side of the Golgi, the vesicles begin to round up and progressively to contain

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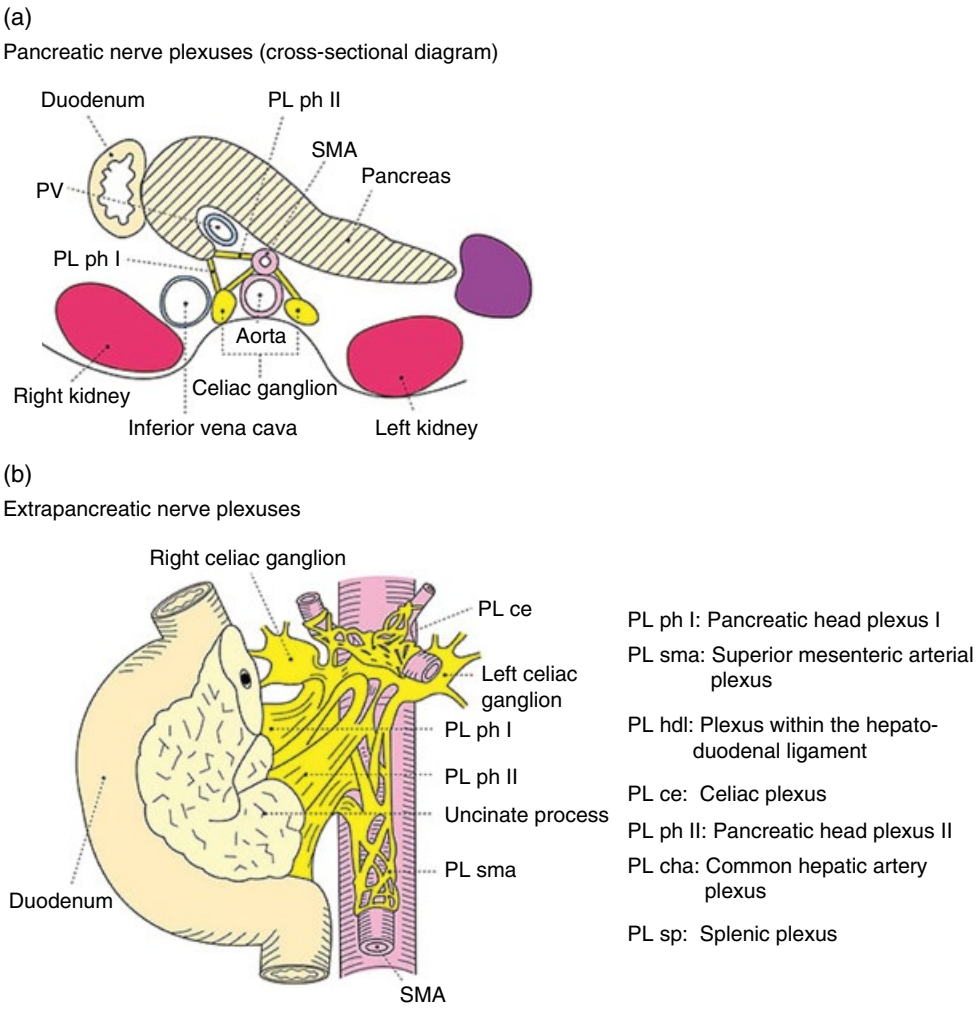


Figure 2.9 Nerves (yellow) serving the pancreas. The cross-sectional image (a) emphasizes the location of the celiac ganglia of the autonomic system lateral to the aorta while (b) emphasizes the rich nerve plexus that connects these ganglia to the pancreas. SMA, superior mesenteric artery; PL, plexus. *Source:* Classification of Pancreatic Carcinoma, 2003 [7]. Reproduced with permission of the Japan Pancreas Society.

homogeneous densities. These are nascent zymogen granules (also termed immature zymogen granules or condensing vacuoles) and they progressively lose membrane as contents condense to become mature zymogen granules.

The apical cytoplasm near the acinar lumen is occupied by variable numbers of mature zymogen granules. These are usually spherical (appearing round in cross-section) with a single bilayer membrane surrounding homogeneous dense content (see Figs 2.12, 2.13, 2.18, and 2.22). Fusion of the membranes of zymogen granules and adjacent lumenal cell membrane is observed prior to secretion of the zymogen into the lumen. See Longnecker [1] for additional electron micrographs that illustrate acinar cell ultrastructure.

Acinar cell cytoplasm may contain fat or autophagic vacuoles (sometimes called residual bodies) that are walled-off areas of damaged cytoplasm (Fig. 2.12).

Duct System

The components of the duct system are the main pancreatic duct (duct of Wirsung); its major branches, called interlobular ducts, that drain into the main duct throughout the pancreas as depicted in Fig. 2.2; smaller intralobular ducts; and ductules that link acinar tubules to the smallest intralobular ducts. The small intralobular ducts and ductules are ordinarily seen only at the level of light and electron microscopy. The accessory duct (duct of Santorini; Fig. 2.2) that connects the main duct to the duodenum at the minor papilla in some humans (Fig. 2.3) is of variable importance and is similar in structure to the main duct, although typically it is slightly smaller.

Enzymes from acinar cells are released into a bicarbonate-rich solution that is secreted by the centroacinar and ductal cells and flows from the acini and

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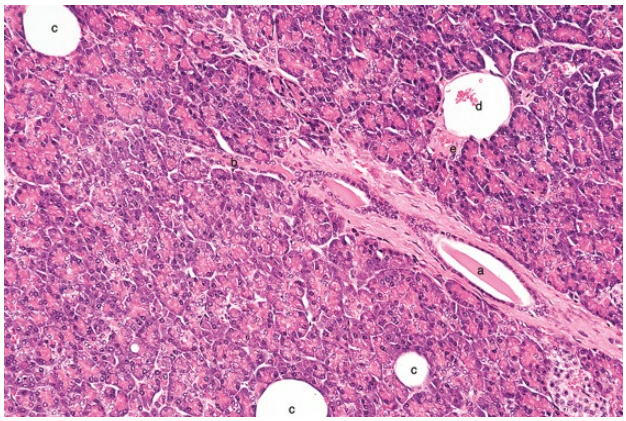


Figure 2.10 Pancreatic lobular tissue with acinar cells, small duct, ductule, and small islet. This H&E-stained section is largely composed of acini and acinar tubules cut in cross-section or tangentially. A small intralobular duct (a) is shown image right and at its upper end it gives rise to a ductule (b) with virtually no connective tissue evident in its wall. Liquid content of the duct and ductule is homogeneous and pink (eosinophilic). Large, clear spaces are fat cells (c). A small vein (d) and artery (e) are at image right above center. A small islet is near the lower image right corner. *Source:* Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology; 2007. Reproduced with permission.



Figure 2.11 Pancreatic tissue with acinar, centroacinar, and ductal cells. The acinar cells are easily identified because of the darkly stained zymogen granules (ZG) and are larger than centroacinar and ductal cells. The basal portion (B) of the acinar cells lies next to the interstitial space that contains vessels (V), nerves, and connective tissue. Nuclei (N) with nucleoli (n) are in the basal portion of the acinar cells. The Golgi (G) lies at the junction of the basal (B) and apical (A) portions of the cell that borders the lumen (L) of the acinus. Centroacinar cells (CAC) have pale cytoplasm with no secretory granules. A small ductule (D) extends from image right to below center. Mitochondria (m) are identified at the top of the field. This is a 1 µm thick section of plastic embedded tissue prepared for electron microscopy that was stained with toluidine blue. *Source:* Micrograph contributed by James Jamieson.

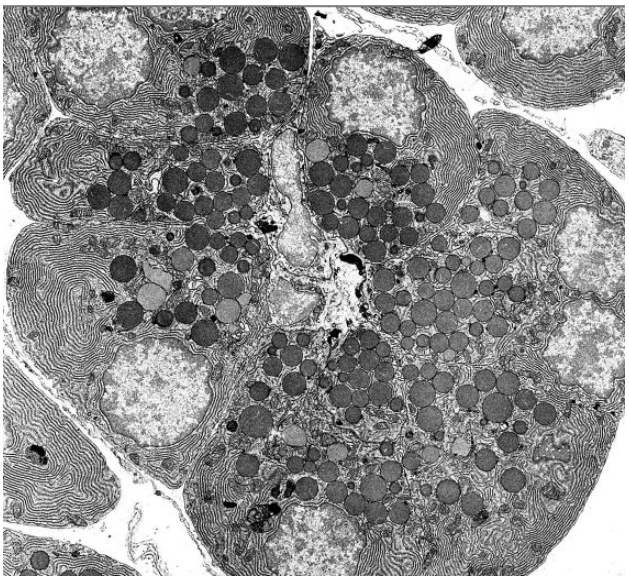


Figure 2.12 Acinar cells with RER, mature, and immature zymogen granules. Two centroacinar cells are near the center. The acinar cell at 3 o'clock, image right, is binucleate. Numerous mitochondria are present in the acinar cells. There are several electron-dense residual bodies in the acinar cells. It appears that two have been extruded into the interstitial space at the top of the image and others are being extruded into the acinar lumen near the center of the image. These pathways for clearing the cell of autophagic vacuoles and residual bodies have been documented in an animal model (rat) of acute pancreatitis [14]. *Source:* Micrograph contributed by James Jamieson.

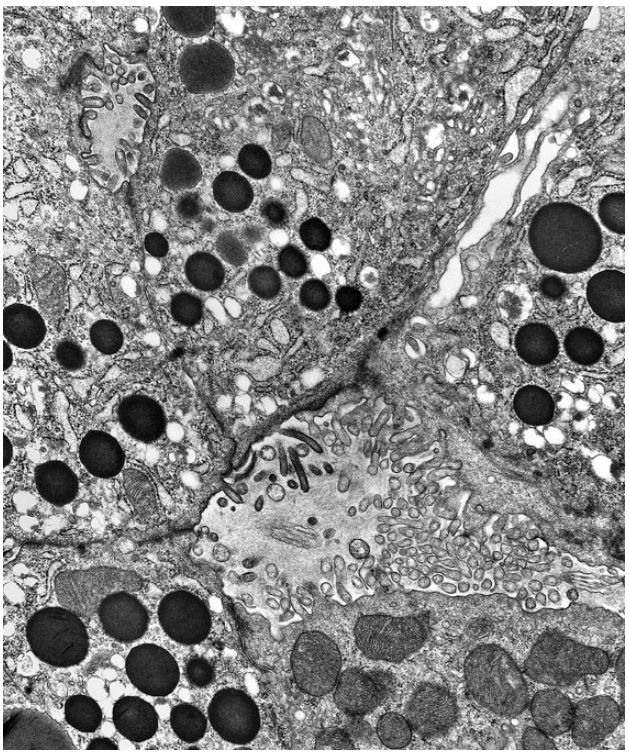


Figure 2.13 Apical portions of several acinar cells border two luminal spaces, lower image right and upper image left. A centroacinar cell with numerous mitochondria borders the lumen, lower image right. Microvilli protrude into the lumens from the luminal aspect of the acinar and centroacinar cells. Zymogen granules are prominent in all acinar cells. *Source:* Micrograph contributed by James Jamieson.

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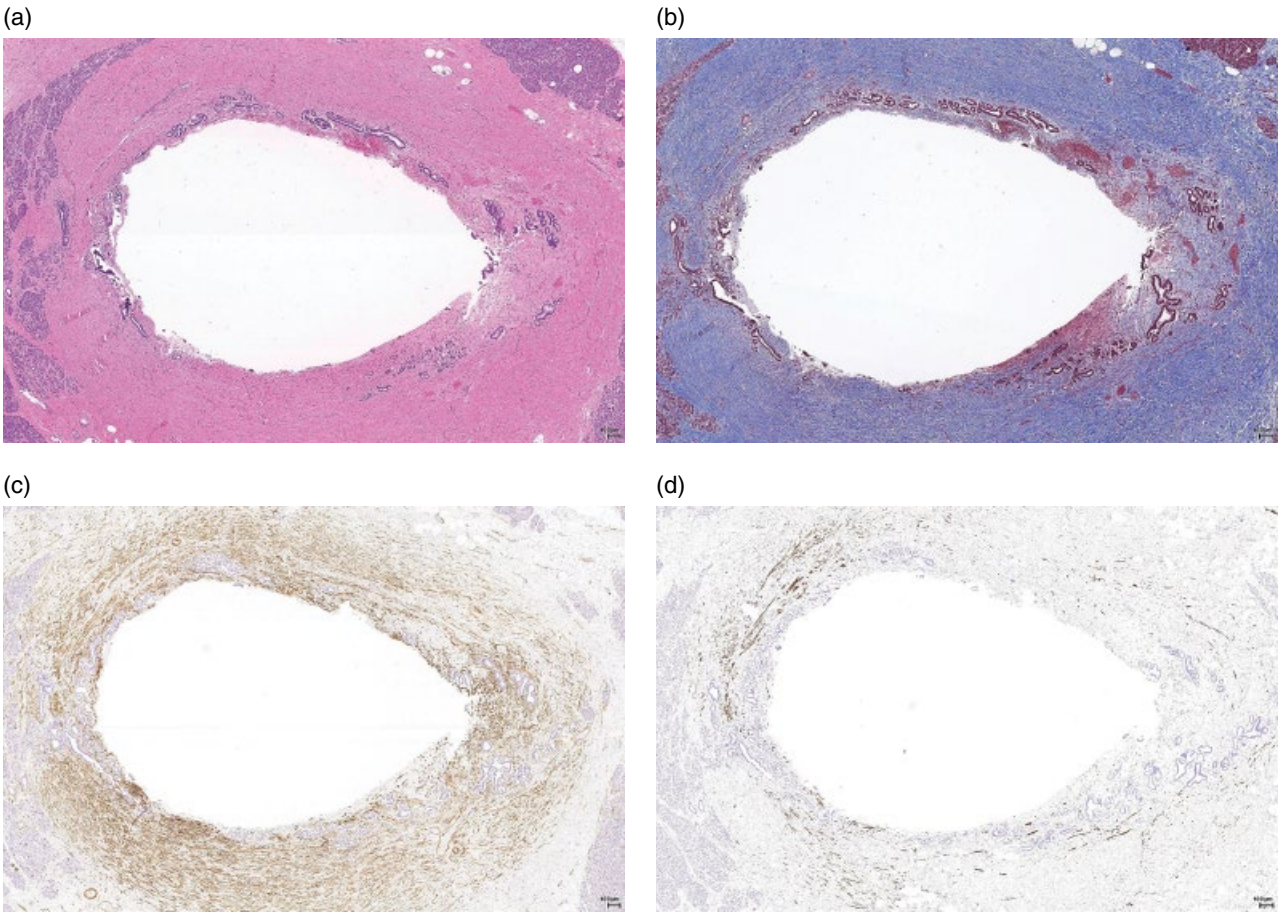


Figure 2.14 Serial cross-sections of main pancreatic duct (a) (H&E stain) stained to demonstrate collagen (b) (trichrome stain), myofibroblasts (c) (immunoperoxidase stain to demonstrate smooth muscle actin, a marker for myofibroblasts), and smooth muscle (d) (immunoperoxidase stain to demonstrate desmin, a marker for smooth muscle). The lining epithelium has been lost, probably reflecting preoperative ERCP and stenting of the pancreatic duct. The patient underwent a Whipple procedure because of chronic pancreatitis. There are many myofibroblasts and fewer smooth muscle cells in the wall of the main duct. *Source:* Micrographs contributed by Arief A. Suriawinata.

acinar tubules into the ductules that join to form the intralobular ducts, then into the interlobular ducts and main duct, and finally into the duodenum at the major or minor papillae. Ducts are illustrated in Figs 2.10, 2.11, 2.14, 2.15, and 2.16.

The integrity of the duct system is of key importance in preventing entry of the exocrine enzymes into the interstitial space, where they may be activated and cause tissue damage manifested as pancreatitis. As ductules anastomose to form intralobular ducts, the duct walls begin to develop a connective tissue wall (Fig. 2.10) that becomes progressively thicker as the smaller ducts join to form larger ducts and the main pancreatic duct. The main and interlobular ducts have thick, dense, collagenous walls that contain myofibroblasts and smooth muscle cells (Fig. 2.14). The connective tissue component of the duct wall becomes progressively thinner and contains fewer myofibroblasts and smooth muscle cells as the ducts branch and become narrower in the lobules (Fig. 2.15). The smallest intralobular ducts lack smooth muscle cells. Intercellular tight junctions, also called zonula occludens, between duct cells, centroacinar cells, and acinar cells play a major role in preventing leakage of the duct system. Kern provided excellent images and discussion of these tight junctions [15].

The lumen of the duct system is normally lined by a single layer of cuboidal epithelial cells that have a single nucleus and a smaller amount of cytoplasm than acinar cells (Figs 2.10, 2.15, and 2.16). The cytoplasm is pale pink and homogeneous in H&E-stained sections. The duct lumen may contain homogeneous material reflecting the protein content of the secretions (Figs 2.10 and 2.16). Sometimes epithelial cells may be shed into the lumen.

Ductal epithelium may undergo squamous metaplasia or mucinous metaplasia. In the latter process, the ducts are lined by tall columnar cells with abundant pale apical

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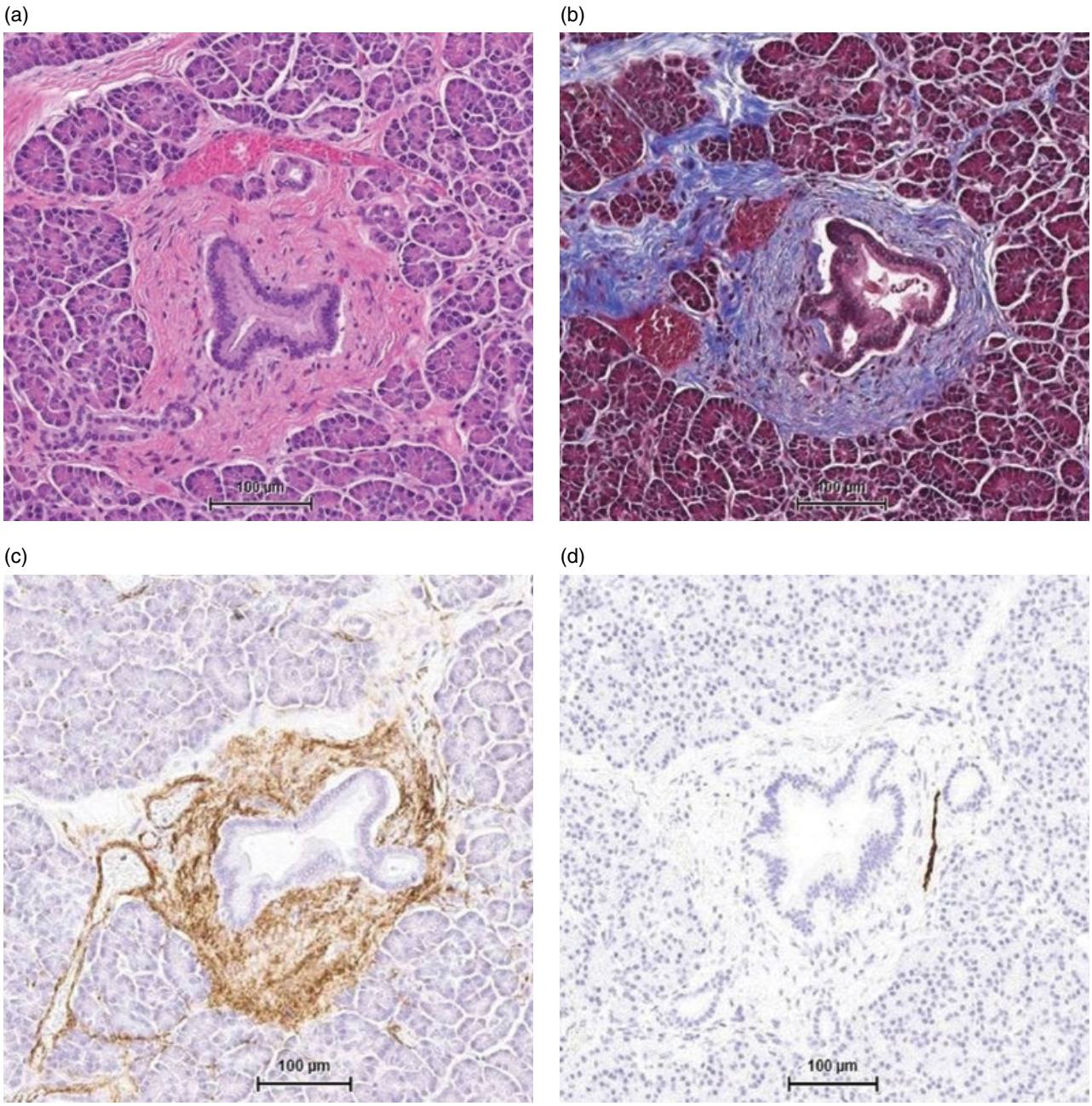


Figure 2.15 Serial cross-sections of a small intralobular duct surrounded by acinar tissue from the same patient as in Fig. 2.14. (a) H&E stain. Note the origin of a ductule branching into acinar tissue at 7 o'clock. (b) Trichrome stain with blue-staining collagen. There is fibrosis around acinar lobules (upper image left). (c) Immunoperoxidase stain with antibody to smooth muscle actin (SMA) to demonstrate the abundant myofibroblasts. (d) Immunoperoxidase stain with antibody to desmin to demonstrate smooth muscle cells. There is little staining. *Source:* Micrographs contributed by Arief A. Suriawinata.

cytoplasm that contains mucin. This type of change is characteristic of low-grade pancreatic intraepithelial neoplasia (PanIN) lesions and is possibly an early step in the development of PanIN.

At the ultrastructural level, duct cells have a simple structure compared with acinar cells. RER is sparse but mitochondria are numerous, and there are no secretory granules. The luminal surface gives rise to numerous microvilli, similar in appearance to those arising from acinar cells (Fig. 2.13). Ductal cells have single cilia, although they are difficult to detect without special tissue preparation and labeling [16].

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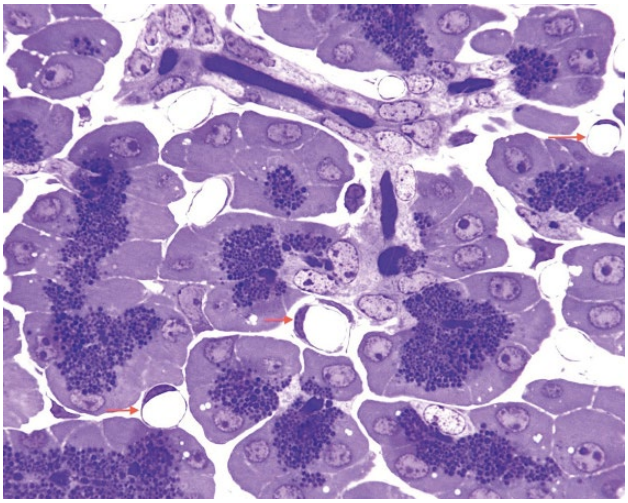


Figure 2.16 Pancreas ductule (top center) branches (upper image right) to reach several acini or acinar tubules (upper image right and near the center). Blue zymogen granules are conspicuous in the acinar cells and the liquid content of the ductule is also dark blue. Ductal and centroacinar cells have pale cytoplasm. The presence of numerous round empty capillaries (arrows) in the interstitial spaces indicates that the pancreas was perfused with fixative. Toluidine blue stain, 1 μm thick plastic embedded tissue. *Source:* Micrograph contributed by James Jamieson.

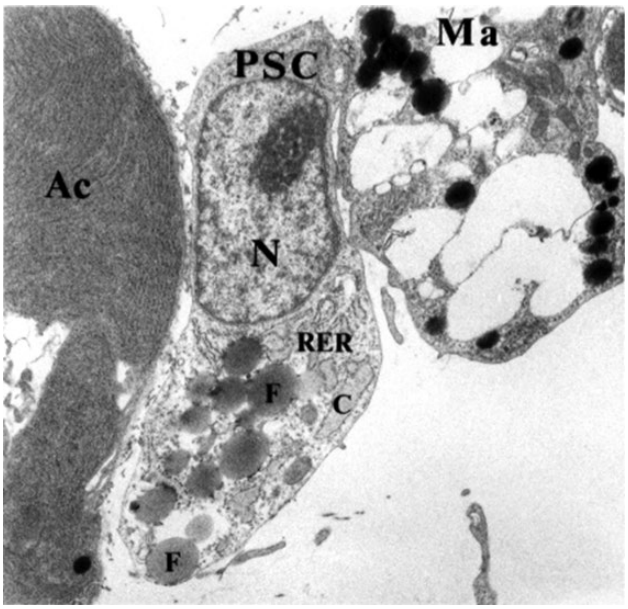


Figure 2.17 Pancreatic stellate cell (PSC) from a patient with acute pancreatitis. The PSC is near a macrophage (Ma), image right, and an acinar cell (Ac), image left. Fat droplets (F) and RER are conspicuous in the PSC cytoplasm below the nucleus (N). Original magnification 6000×. *Source:* Bachem et al. 1998 [17].

Interstitial Tissue

The interstitium contains capillaries, arteries, veins, lymphatics, nerve fibers, fat cells, and stellate cells. The stellate cells are undifferentiated connective tissue cells with characteristic structure (Figs 2.17 and 2.18) that are activated by inflammation to form fibroblasts and contribute to fibrosis associated with chronic pancreatitis and some neoplasms [17] (see Chapter 10).

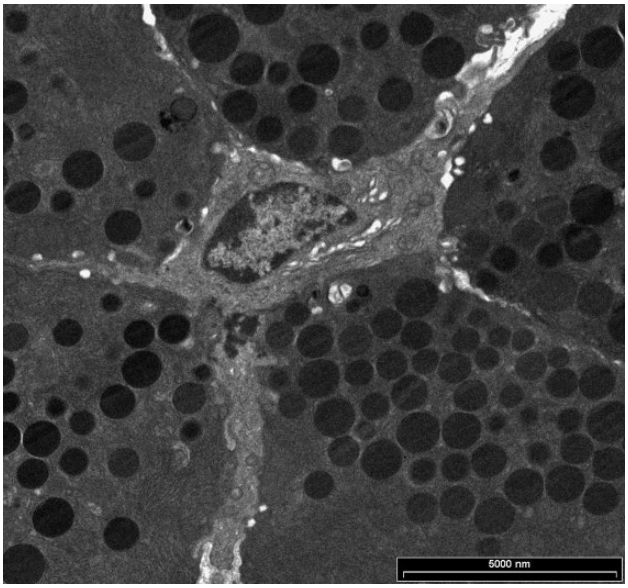


Figure 2.18 A pancreatic stellate cell (PSC) in situ is surrounded by multiple acinar cells containing zymogen granules. Extensions of PSC cytoplasm between acinar cells are conspicuous, upper image right and lower image left. The dark, irregular cytoplasmic inclusions at the origin of the latter interstitial extension may represent lipid droplets—a characteristic of PSC. *Source:* Contributed by the Pancreatic Research Group, UNSW, Australia, with special thanks to Dr. Murray Killingsworth.

Endocrine Pancreas

The pancreatic islets (islets of Langerhans) collectively comprise the endocrine pancreas that synthesizes and secretes insulin, glucagon, pancreatic polypeptide, and somatostatin. Most islets are too small to be seen by gross examination, hence they were not depicted in Figs 2.1 to 2.7. Islets vary greatly in size and ~70% are in the size range 50–250 μm in diameter in humans, with an average in the range 100–150 μm [18]. Small islets are dispersed throughout the acinar lobules (Fig. 2.19) and most larger islets lie along the main and interlobular ducts of the pancreas. Most islets are spherical or ellipsoid, but they can be irregular in shape—sometimes reflecting the presence of an adjacent structure, often a duct, or limitation by a tissue plane. Several reports provide support for the presence of a higher population

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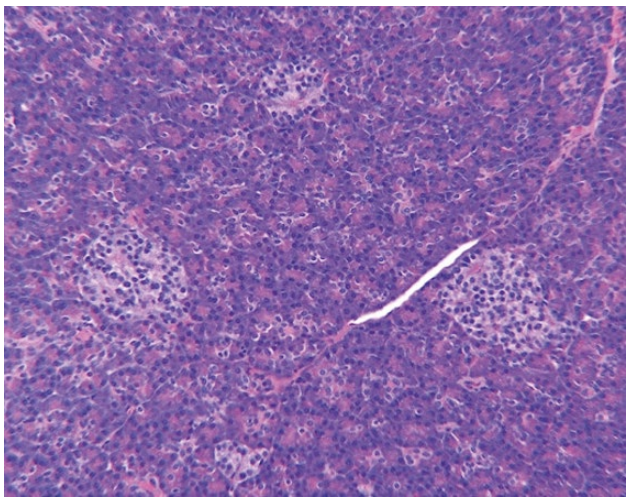


Figure 2.19 Pancreatic lobules with acinar cells and four islets at 12, 3, 6–7, and 9 o'clock. The islets are paler than the surrounding acinar tissue. The upper and lower islets are small and the lateral islets are medium size. H&E stain.

density of islets in the tail of the pancreas than in the head and body [5,19], although another study found no difference [20]. In adult humans, the number of islets is estimated to be 5×10^5–10^6 [21], whereas there are far fewer in smaller animals [22]. Islets comprise 1–2% of the pancreas in adults of most mammalian species. In addition to the islets, isolated islet cells may be found dispersed in the acinar lobules or in association with ducts.

Several of the images of islets are from sections that have been immunostained using antibodies to specific islet peptide hormones to demonstrate various islet cell types, including β cells (insulin), α cells (glucagon), δ cells (somatostatin) (Fig. 2.20), and pancreatic polypeptide (PP) (Fig. 2.21). In the portion of the pancreas derived from the dorsal pancreatic anlage, the majority of islet cells are β cells (75–80%), followed by α cells (about 15%), δ cells (about 5%), and very few PP cells. Most PP cells are in the portion of the pancreas derived from the ventral

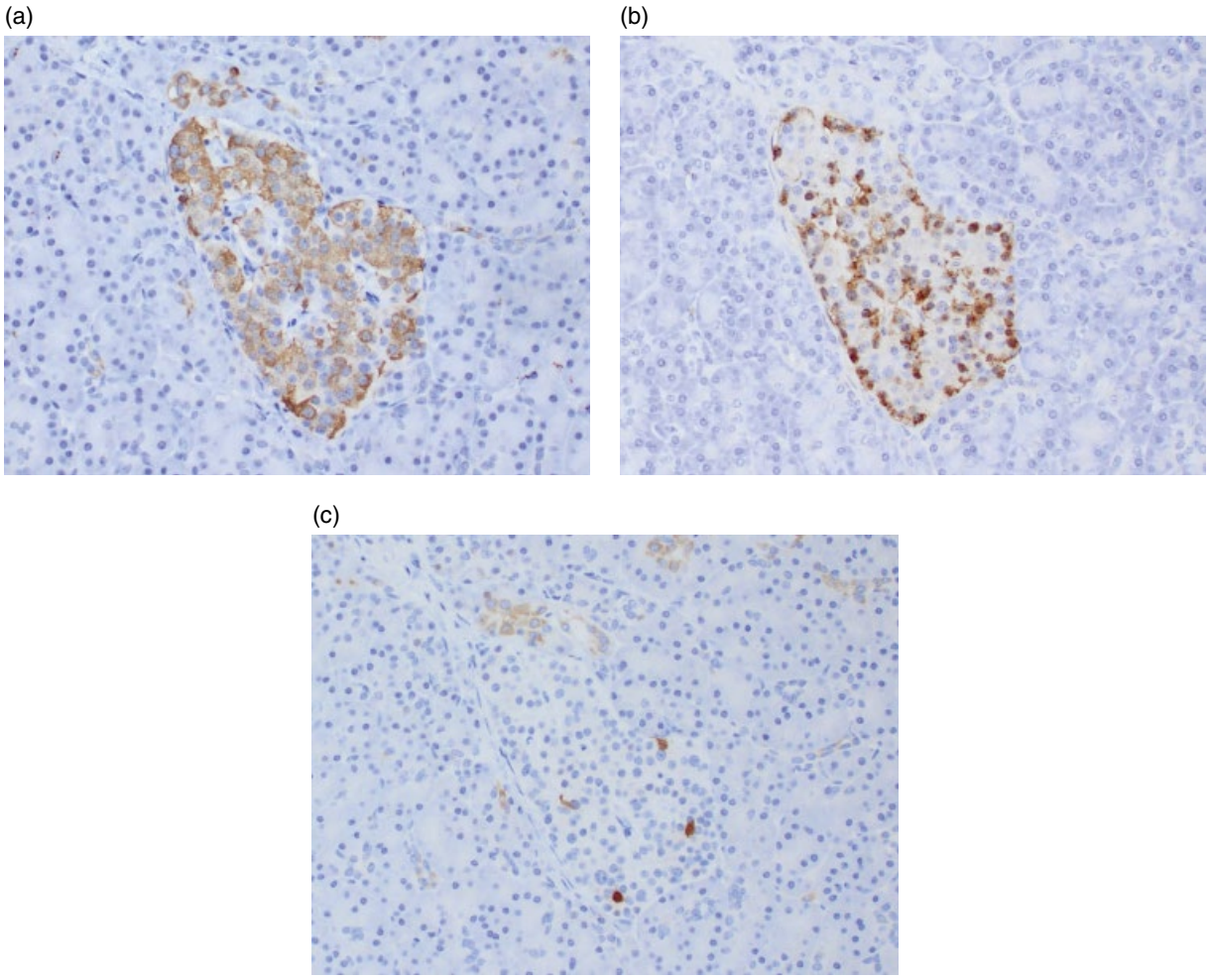


Figure 2.20 Serial sections of a human islet immunostained using antibodies to insulin (a), glucagon (b), and somatostatin (c). The presence of the hormones is indicated by brown staining. The predominance of insulin-secreting β cells is obvious. In (b) and (c), the location of α cells and δ cells is primarily at the border of groups of β cells. *Source:* Photos provided by Arief A. Suriawinata.

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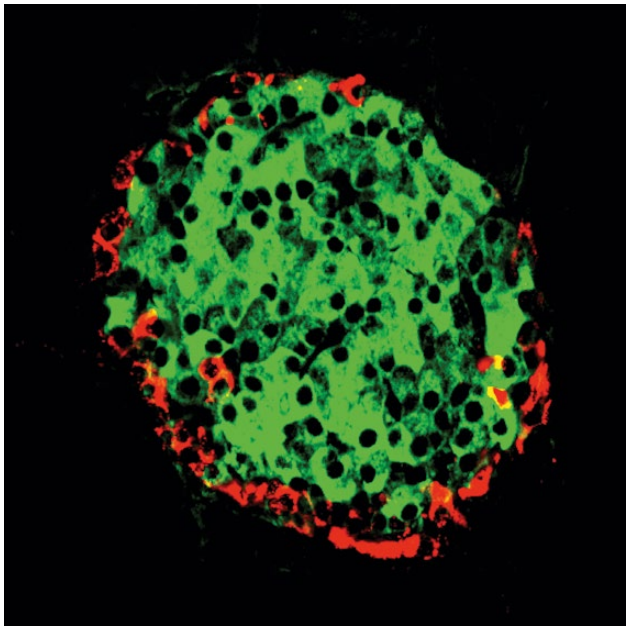


Figure 2.21 Mouse islet stained to demonstrate pancreatic polypeptide (red) and insulin (green). Immunofluorescence using antibodies to insulin and neuropeptide Y (NPY) that cross-reacts with PP. *Source:* Micrograph contributed by Susan Bonner-Weir.

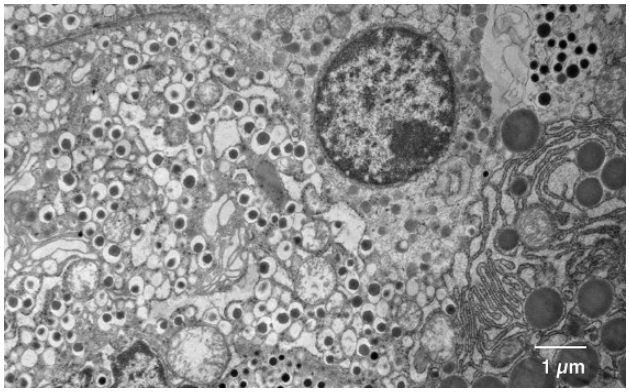


Figure 2.22 Mouse islet with β-cell cytoplasm containing insulin granules (image left), a δ cell with nucleus and less dense secretory granules (right of center), and α-cell cytoplasm with glucagon granules (upper image right corner) and at the bottom margin near the center. In murine species, β-cell granules have a wide halo surrounding the dense core. Acinar cell cytoplasm with zymogen granules, RER, and mitochondria is present (lower image right). *Source:* Micrograph contributed by Fred Gorelick.

pancreatic anlage, namely the uncinate process that is reported to comprise about 10% of the pancreas [23,24]. In the uncinate process, islets contain few α cells and many more PP cells. Stefan et al. presented data from a study of 13 nondiabetic human pancreases, showing that the PP cells comprise 54.3–93.7% of the volume of islets in the uncinate region, displacing most α cells and some

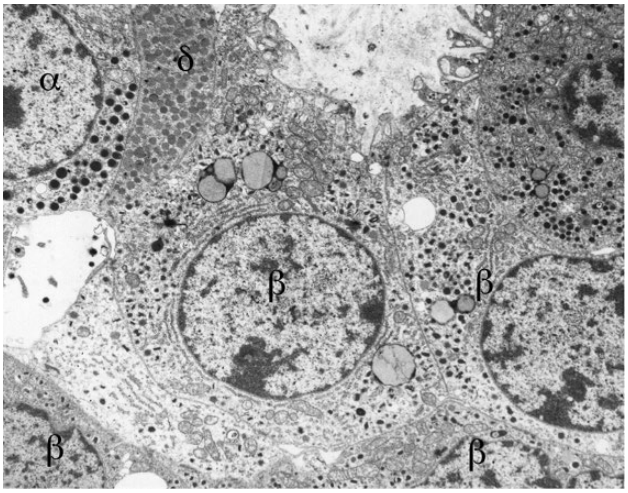


Figure 2.23 Human islet from transplant isolation with α, β, and δ cells labeled. The α-cell granules are typically slightly larger than β-cell granules; δ-cell granules are typically less densely stained than the granules in α and β cells. The cytoplasm of several islet cells contains lipid—most notably in the central β cell where lipid bodies lie at 4 and 11–12 o'clock around the nucleus. *Source:* Micrograph contributed by Susan Bonner-Weir.

β cells [24]. They provided data that indicated that PP cells were the second most prevalent endocrine cell type overall in the pancreases of their 13 subjects.

At the ultrastructural level, islet cells contain numerous mitochondria, a modest amount of RER, and small secretory granules (islet hormones). The granules vary in size and density with cell type and hormone and show some variation between species (Figs 2.22 and 2.23).

Capillaries in the islets connect with capillaries serving the adjacent acinar cells before draining into veins. These proximal acinar cells are exposed to higher concentrations of islet hormones than the majority acinar cells that are more distant from islets. The proximal acinar cells sometimes are larger and contain more zymogen than more distant acinar cells, and they form a halo around the islets. This unique feature of islet–acinar blood supply has been referred to as an insulo-acinar portal system [25].

Acknowledgments

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3

Congenital and Inherited Anomalies of the Pancreas

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Introduction

Most congenital anomalies of the pancreas are attributable to disturbances in the three critical developmental steps: tissue differentiation, rotation, and fusion. Differentiation and rotation defects are usually rare, while defective fusion is common but mostly asymptomatic.

Primary Malformations

Pancreatic Agenesis

Complete (aplasia) or incomplete (hypoplasia) agenesis of the pancreas are very rare developmental disorders that can occur isolated or in combination with other defects such as polysplenia syndrome, congenital heart defects, or cerebellar agenesis. Their exact incidence is unknown. Partial agenesis is more common and is known as congenital short pancreas.

The clinical presentation is dependent on the degree of agenesis. Aplasia manifests clinically with neonatal diabetes mellitus, exocrine pancreatic insufficiency, and severe intrauterine growth retardation [1]. The last-mentioned appears to relate to the fact that insulin is a major intrauterine growth factor. Complete agenesis is incompatible with life, whereas the clinical presentation of hypoplasia varies from an asymptomatic course to endocrine and exocrine pancreatic insufficiency; pancreatitis may be an associated presentation. Pancreatic agenesis can be monogenic and half of the patients have heterozygous *GATA6* mutations [2]. The pancreatic phenotype ranges from aplasia to hypoplasia and most patients have cardiac malformations. Other features include gallbladder agenesis, biliary atresia, developmental delay, transient hypothyroidism, pituitary agenesis, and intestinal abnormalities. *GATA6* mutations have also been detected in a few patients with adult-onset diabetes with subclinical or no exocrine insufficiency [3].

In isolated families with autosomal recessive inheritance, defects in other genes have been described including pancreatic transcription factors *PDX1* (also known as insulin promoter factor 1, *IPF1*) and *PTF1A* [4,5]. Pancreatic agenesis appears to be isolated in *PDX1* mutated patients. Interestingly, heterozygotes are predisposed to maturity-onset diabetes of the young (MODY4); some patients show only subclinical or no exocrine insufficiency [4]. PTF1A plays a pivotal role in mammalian pancreatic development. *PTF1A* coding mutations cause pancreatic and cerebellar agenesis, whereas mutations in a *PTF1A* downstream enhancer cause isolated pancreatic agenesis [5,6]. Pancreatic agenesis associated with holoprosencephaly can be caused by defects in *CNOT1* [7].

In mice, a lack of hepatocyte nuclear factor-1-beta (Hnf1b) leads to pancreas agenesis [8]. In humans, heterozygous *HNF1B* mutations are associated with renal cysts and diabetes syndrome. Some of these patients show pancreatic atrophy/hypoplasia and exocrine insufficiency [9].

Partial agenesis of the pancreas mostly affects the dorsal part [10]. With this entity only a pancreatic head is seen on imaging. Dorsal pancreatic agenesis may be isolated or associated with polysplenia syndrome and can be accompanied by diabetes and pancreatitis [11]. It has been observed in patients with PDX1-MODY. Since most of the islet cells are located in the absent distal pancreas, the risk of diabetes mellitus is increased [12].

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Ectopic Pancreas

In ectopic pancreas, also designated as heterotopic, aberrant or accessory pancreas, normally developed pancreatic tissue is anatomically separate from the gland and lacks ductal or vascular continuity. It can be found in various locations and can be made up of any cell found in the pancreas. Autopsy studies indicate that ectopic pancreas is quite common (0.5–15%), but its clinical manifestation is very rare [13]. In most cases, ectopic tissue is discovered in the submucosa of the stomach (particularly along the greater curvature of the antrum) and the duodenum (Fig. 3.1) as an incidental finding during endoscopy, where it appears as a 0.3–3 cm nodule. Other locations include the jejunum, ileum, a Meckel diverticulum, liver, spleen, biliary tract, mesentery, or umbilicus [12]. Although ectopic pancreas is primarily located in the submucosa, in some cases it is found in the muscularis or serosa.

The mechanisms leading to ectopic pancreas remain elusive. Misplacement of pancreatic cells into the developing gastrointestinal system, pancreatic metaplasia of other endodermal areas during embryogenesis, and an inaccurate differentiation of pluripotent endodermal stem cells are discussed.

Although ectopic pancreatic tissue can undergo similar changes as the orthotopic pancreas, particularly cystic degeneration, ectopic pancreatitis, and even pancreatic cancer formation, in most cases ectopic pancreas remains asymptomatic. If patients with ectopic pancreas become symptomatic, this may be due to the mass effect, which can cause either obstruction of the intestinal passage (mainly in the prepyloric localization) [14] or bowel intussusception, gastrointestinal hemorrhage secondary to mucosal ulcerations close to the pancreatic tissue [15], pain secondary to pancreatitis, and exceptional malignant transformation [16].

Diagnosis is made endoscopically or radiographically in antral localization. In other localizations, diagnosis is made at the time of surgery. The definite diagnosis relies on histology. The treatment is either surgical or endoscopic.

Annular Pancreas

In annular pancreas, the duodenum is completely, or rarer partly, surrounded by a ring-like band of pancreatic tissue. Early autopsy and surgical series reported an incidence of 3 in 20,000 but the increased use of imaging has raised the incidence to approximately 1 in 1,000.

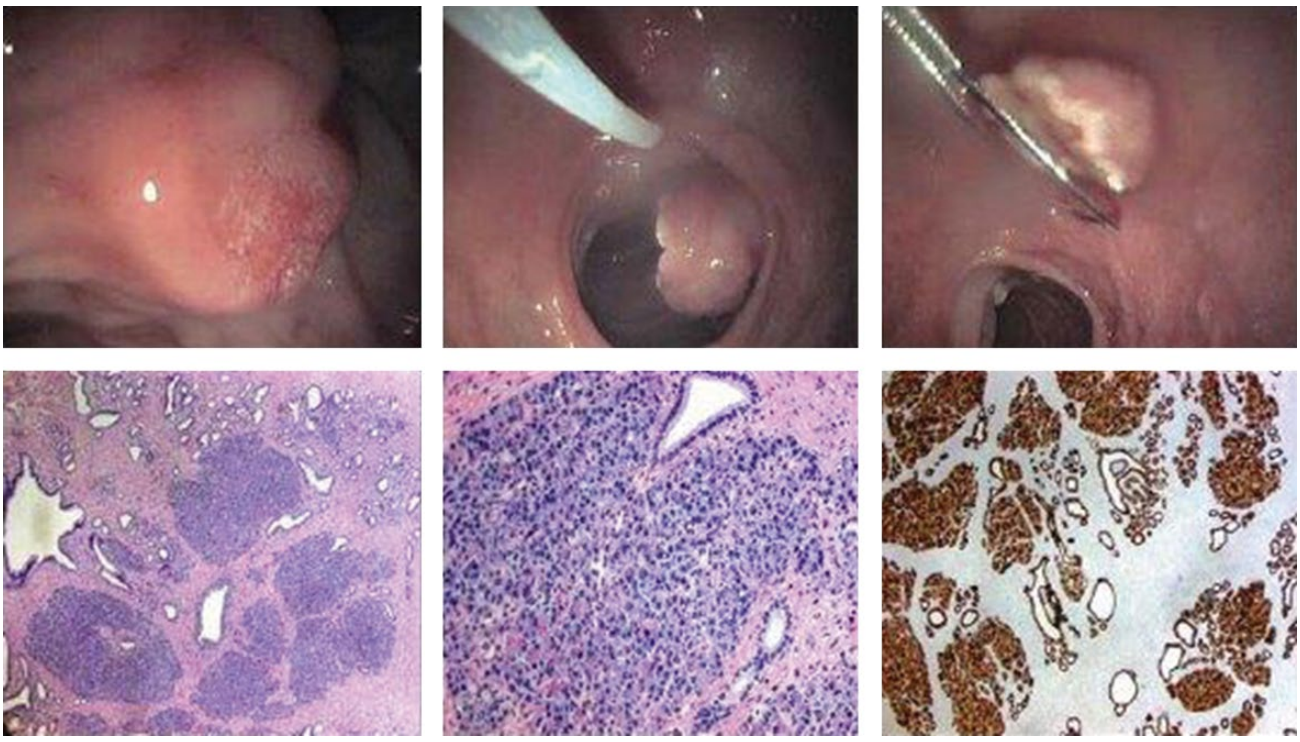


Figure 3.1 Ectopic pancreas under endoscopic vision and during endoscopic snare dissection (top images) and histologically (bottom panels, right cytokeratin staining). Note the complete absence of endocrine cells on histology, which corresponds to a type II ectopic pancreas according to Heinrich (1909). *Source:* Courtesy of M. Androshchuk and G. Lorenz, Greifswald.

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Annular pancreas is frequently associated with other anomalies such as duodenal stenosis or atresia (40%), tracheoesophageal fistula (9%), congenital heart defects (7%), intestinal malrotation, and anal atresia [17]. A considerable number of affected individuals have chromosomal disorders, particularly Down syndrome (11–16%) [18]. This suggests that annular pancreas represents an early embryologic malformation. Agenesis of the dorsal pancreas may also be associated with annular pancreas [17].

Although most cases of annular pancreas are sporadic, there have been some cases of familial recurrence with different patterns of transmission. Annular pancreas can be found in Mitchell–Riley syndrome, in Martinez–Frias syndrome, and in congenital alveolar capillary dysplasia with misalignment of pulmonary veins [19].

Annular pancreas may manifest at any age or remain asymptomatic. The majority of symptomatic cases present in the first week of life as duodenal compression with bilious vomiting and feeding intolerance [18]. The diagnosis is suggested in >50% of cases during prenatal ultrasonography. A plain abdominal radiograph may demonstrate two large air filled spaces, the so-called "double-bubble" sign, if the obstruction is complete: Due to post-duodenal obstruction not only the stomach but also the upper duodenum is filled with gas.

Patients in whom annular pancreas becomes symptomatic later in life may suffer from recurrent vomiting, chronic gastric distension, pain resulting from pancreatitis, or peptic ulcers [20]. Upper gastrointestinal studies or a contrast-enhanced CT or MRI, which allow direct visualization of the ring, can aid the diagnosis.

Surgical therapy with duodenal bypass either in the form of a duodeno-duodenostomy or a duodeno-jejunostomy eliminates the obstruction with an excellent long-term prognosis [18]. Resection of the ring is not recommended because of the risk of pancreatic peritonitis, postoperative pancreatitis, fistulae, and late fibrosis. The prognosis depends on the age of onset and shows the highest mortality in the newborn period due to the high proportion of other coexisting organ malformations.

Pancreas Divisum

The fusion of the ventral and dorsal pancreas also merges the ducts of both parts of the gland. As a result, various anatomical variants of the pancreatic duct system can occur. In pancreas divisum, the most common anatomic variant, there is a separate outflow of the ventral part into the major papilla and the dorsal part via the Santorini duct into the minor papilla, which drains about 80% of the pancreatic juice [12]. Sometimes a small side branch connects both duct systems (incomplete pancreas divisum).

The estimated incidence varies from about 4–14% in autopsy series. Diagnosis relies on MRCP, especially secretin-enhanced MRCP. Endoscopic ultrasound and ERCP are invasive second-line investigations (Fig. 3.2).

The clinical significance of the pancreas divisum is disputed: while some consider it an insignificant normal variant, others postulate that the narrow opening of the minor papilla leads to a relative, functional stenosis and thus predisposes to obstructive pancreatitis. Since the prevalence in patients with chronic pancreatitis is similar to the frequency in the population, it is unlikely to cause pancreatitis alone [21]. Thus, other exogenous or genetic factors probably must be present. Interestingly, *PRSS1*, *SPINK1*, and *CFTR* mutations are more common in patients with chronic pancreatitis and pancreas divisum than in patients without this anomaly [22]. In chronic pancreatitis, the question arises whether endoscopic sphincterotomy and stent insertion at the minor papilla is beneficial and influences the natural course [23].

Anomalies of the Pancreaticobiliary Junction

The junction of the main duct of the pancreas with the bile duct is also very variable and most abnormalities are harmless variations in the norm and are incidental

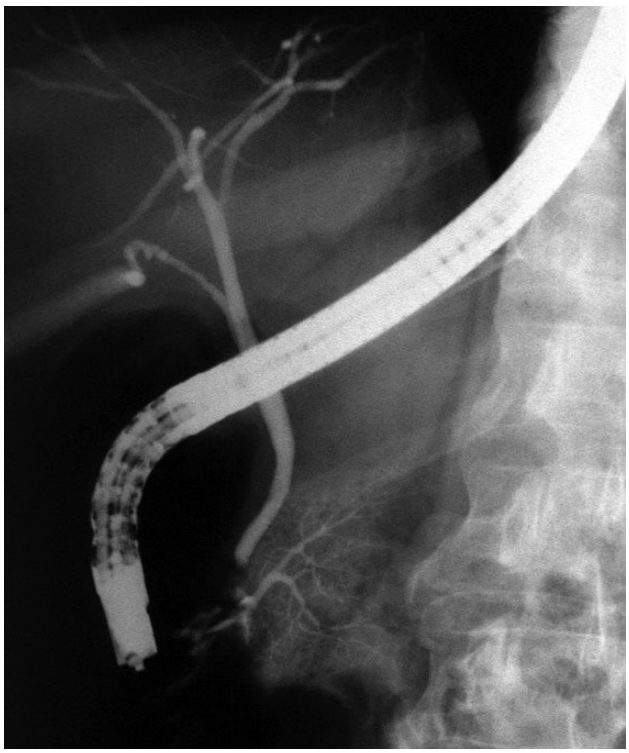


Figure 3.2 Pancreas divisum on ERCP. Whereas the intra- and extrahepatic bile ducts are of regular size and proportions, the pancreatic duct is short and tender (already overfilled with contrast medium) and supplies only the head of the pancreas.

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findings on endoscopy, ERCP, or MRI/MRCP [24]. Pancreaticobiliary maljunctions, in which the common bile duct and the ventral pancreatic duct unite outside the duodenal wall, result in a long common segment (long common channel) found in 1.5–3% of individuals [25]. This promotes the reflux of pancreatic secretions into the bile duct, as shown by dynamic MRCP after secretin stimulation. Reflux can lead to biliary duct inflammation and dilatation with choledochal cyst formation, pancreatitis, and, in the long term, malignant transformation resulting in biliary carcinoma. The incidence of pancreatitis is 3–31% in patients with pancreaticobiliary abnormalities [26]. The reflux of bile into the pancreatic duct system, conversely, is controversially discussed as a cause of pancreatitis and is less likely since pancreatic secretion pressure constantly exceeds the bile duct secretion pressure. Inherited choledochal cysts, which are often associated with pancreaticobiliary maljunctions, may manifest as acute or recurrent pancreatitis.

Congenital Cysts

Most pancreatic cysts are acquired pseudocysts of inflammatory origin and are found in the context of pancreatitis or cystic fibrosis (Fig. 3.3). In contrast, congenital pancreatic cysts are epithelial-lined and are rare, accounting for less than 1% of pancreatic cysts diagnosed in children. However, with improved radiological imaging, the diagnosis of incidental cystic lesions is on the rise. In a population-based MRCP study, small cysts (<1 cm) of unknown etiology were found in about a quarter of healthy volunteers (mean age 51.9 ± 13.4 years) [24]. In children, congenital cysts have a female predominance

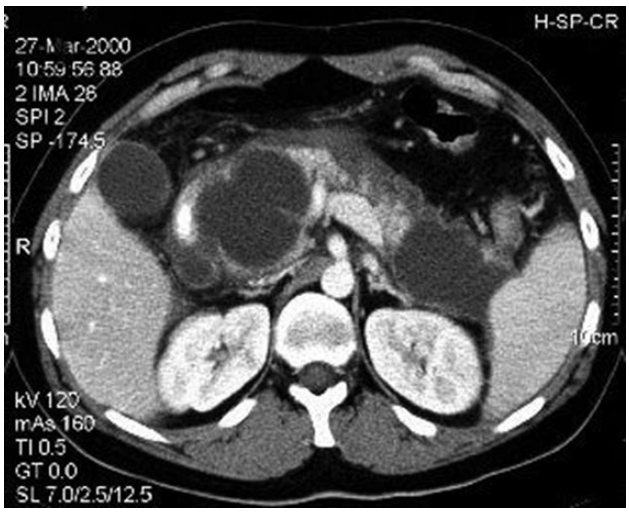


Figure 3.3 Large cysts in the pancreatic head and tail in a patient with chronic pancreatitis.

and may present as an asymptomatic palpable mass or with epigastric pain, jaundice, and vomiting by the compression of adjacent intestinal or biliary structures [27]. Symptoms often appear in the first two years of life. The cysts are more frequently located in the pancreatic tail or body than in the head, are more often unilocular than multilocular, and more often single than multiple [28]. Ductal communication is rare and, if present, suggests a pancreatitis-associated pseudocyst. The cysts are usually anechoic on ultrasound and are low attenuating structures without wall enhancement in CT or MRI studies. Associated anomalies may include renal tubular ectasia, polydactyly, anorectal malformations, polycystic kidneys, and asphyxiating thoracic dystrophy [28]. Multiple pancreatic cysts occur in about 10% of patients with polycystic kidney disease and in 30–70% of patients with von Hippel-Lindau disease (see below), but the cysts are rarely congenital in either disease.

Congenital Exocrine Insufficiency

Congenital exocrine pancreatic insufficiency is rare. Cystic fibrosis, which leads to progressive destruction of the pancreas and may result in clinical symptoms of secretory insufficiency from birth, account for the majority of cases with congenital exocrine pancreatic insufficiency. Cystic fibrosis and hereditary pancreatitis are discussed in dedicated chapters of this book.

Congenital exocrine pancreatic insufficiency, if complete, manifests from birth with loose and bulky stools, steatorrhea, failure to thrive, and hypoproteinemia leading to edema. Due to the large reserve capacity of the exocrine pancreas, clinical symptoms only appear when more than 90% of the exocrine cells are destroyed [29]. Pancreatic secretory insufficiency reflects either an isolated enzyme deficiency or early-onset degeneration of acinar cells resulting in fibrosis or lipomatosis of the gland.

Isolated Enzyme Deficiencies

Isolated inherited deficiencies of pancreatic digestive enzymes or duodenal enteropeptidase (enterokinase) are extremely rare. So far, isolated deficiencies of lipase, colipase, amylase, trypsin, and enteropeptidase as well as combined deficiencies of lipase and colipase have been reported [30]. Of clinical relevance are mainly deficiencies of trypsin and enteropeptidase, which manifest with failure to thrive, diarrhea, hypoproteinemia, and edema. In all deficiencies, enzyme replacement therapy is very effective.

When fat-digesting enzymes are affected, chronic diarrhea and steatorrhea are the leading symptoms, but failure to thrive is absent. Congenital deficiency of pancreatic lipase (PNLIP) is inherited in an autosomal recessive

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manner and is caused by loss-of-function mutations in *PNLIP* [31]. Interestingly, *PNLIP* variants that lead to increased proteolytic degradation by trypsin are associated with early-onset chronic pancreatitis [32]. Colipase deficiency has been reported in two brothers and the combined deficiency of lipase and colipase in another family and in a single case. Pancreatic amylase deficiency may lead to diarrhea induced by a high-starch diet, but the functional capacity of the carbohydrate-digesting enzymes is quite high, and so the deficiency is mostly compensated. To date, two children with trypsinogen and about a dozen patients with enteropeptidase deficiency have been described [33]. Enteropeptidase (TMPRSS15) is a transmembrane serine protease that localized to the brush border of the intestinal mucosa. Although enteropeptidase is not a pancreatic enzyme, its deficiency manifests clinically as a trypsin defect, since it activates trypsinogen.

Shwachman–Bodian–Diamond Syndrome

After cystic fibrosis, Shwachman–Bodian–Diamond syndrome (SBDS) is the second most common inherited cause of exocrine pancreatic insufficiency with an estimated incidence of 1:50,000. SBDS is inherited in an autosomal recessive manner and is characterized by the triad exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities. Histologically, there is hypoplasia of the acinar cells with replacement by adipose tissue (lipomatosis) (Fig. 3.4) [34]. The islet cells and the ductal architecture are preserved. In contrast to cystic fibrosis, water and bicarbonate secretion are not restricted. Exocrine insufficiency improves with age: while 90% of infants suffer from steatorrhea, around half of patients in the second decade of life are pancreatic sufficient. Neither diabetes nor pancreatitis are consistent features of SBDS.

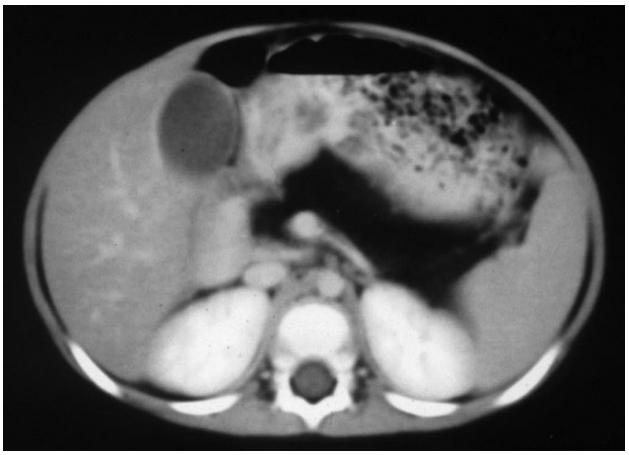


Figure 3.4 Fatty replacement of the entire pancreas (black central structure on the abdominal CT) in Shwachman–Bodian–Diamond syndrome. *Source:* Wilschanski M et al. (1994). Reproduced with permission of Wolters Kluwer Health.

The main hematological change is intermittent or permanent neutropenia, sometimes accompanied by anemia, thrombocytopenia, or pancytopenia. Infants in particular are at risk from serious bacterial infections. About 10–30% of patients develop myelodysplastic syndrome or acute leukemia [35].

Other manifestations include short stature, skeletal abnormalities (metaphyseal chondrodysplasia, shortened ribs), enamel defects with increased tooth decay, liver involvement with hepatomegaly and elevated transaminase levels, and often mild mental retardation [35].

In 90%, the syndrome is caused by gene conversion mutations in the *SBDS* gene [36]. Recently, the elongation factor-like 1 (*EFL1*) has been identified as second disease-causing gene [37]. Moreover, mutations in the genes encoding the DnaJ heat shock protein family (Hsp40) member C21 (*DNAJC21*) and the signal recognition particle 54 (*SRP54*) have also been associated with a SBDS-like phenotype [37].

Interestingly, all four genes are involved in ribosome biogenesis, reinforcing the postulate that the syndrome is a ribosomopathy. SBDS promotes by direct interaction with EFL1 the removal of the eukaryotic initiation factor 6 (eIF6) 60S subunit of the ribosome. This allows the 60S subunit to bind to the 40S subunit to generate a functional 80S ribosome. DNAJC21 is involved in the release of maturation factors from the pre-60S subunit. SRP54 recognizes the signal peptide of secretory proteins and mediates the targeting of the ribosome and the associated nascent polypeptide chain to the endoplasmic reticulum [37].

The diagnosis of SBDS is based on the clinical symptoms, imaging methods (skeletal X-ray, diffuse fatty degeneration of the pancreas in the MRI) and the corresponding laboratory parameters and should be confirmed by a mutation analysis. Because cytopenia can be cyclic, blood cell status should be measured repeatedly. Differential diagnoses include cystic fibrosis and other causes of neutropenia such as Diamond-Blackfan or Fanconi anemia, and congenital dyskeratosis.

Treatment is symptomatic. Because exocrine dysfunction improves with age, approximately 50% of patients in their second decade of life no longer require enzyme replacement therapy.

Pearson Marrow Pancreas Syndrome

Pearson syndrome is a rare multisystem mitochondrial disorder caused by deletions of mitochondrial DNA (mtDNA) [38]. Clinical characteristics are refractory

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sideroblastic anemia with vacuolization of marrow precursors and variable exocrine pancreatic insufficiency [39]. Severe, transfusion-dependent, macrocytic anemia usually starts in infancy and may be accompanied by thrombocytopenia and neutropenia. Other features include lactate acidosis, renal tubulopathy, liver cholestasis and/or fibrosis, adrenal insufficiency, diabetes mellitus, cardiomegaly, and cardiac conduction defects [39]. Some patients have recurrent episodes of acute pancreatitis [39]. In contrast to the Shwachman syndrome, the pancreas in Pearson syndrome shows fibrosis instead of lipomatosis. The disorders also differ in bone marrow morphology. A phenotypic shift from a predominantly hematopoietic disorder (Pearson syndrome) to a disease with overt muscle dysfunction (mitochondrial myopathy) was repeatedly observed, up to a fully developed Kearns–Sayre syndrome [39].

In laboratory tests, a subset of patients show complex organic aciduria with 3-methylglutaconic aciduria. Therapy is symptomatic and in selected cases bone marrow transplantation can be considered. The prognosis is poor and patients usually die in early childhood from intractable metabolic acidosis, sepsis, or liver failure [39].



Figure 3.5 Aplasia of the nasal wings as a characteristic feature or Johanson–Blizzard syndrome.

Johanson–Blizzard Syndrome

Johanson–Blizzard syndrome (JBS) is characterized by congenital exocrine pancreatic insufficiency, a peculiar nasal malformation with hypo- or aplasia of the nasal wings (Fig. 3.5), and oligodontia of permanent teeth [40]. These three characteristics are present in virtually all patients [41]. The majority of patients also present with hearing impairment, scalp defects, varying degrees of cognitive impairment, and short stature. Hypothyroidism, microcephaly, intrauterine growth retardation, congenital heart defects, urogenital and anorectal malformations, renal anomalies, and diabetes with onset during adolescence are additional features of the syndrome [41].

The condition is inherited as an autosomal recessive trait and has an estimated incidence of 1:250,000 [42]. JBS is caused by *UBR1* mutations that lead to severe deficiency of the homonymous ubiquitin ligase of the N-end rule pathway [42]. As this pathway is responsible for degradation of intracellular proteins, it is likely that the excess or increased half-life of hitherto unknown proteins are involved in the pathogenesis of the pancreatic and other defects. While >95% of patients with a clinical diagnosis have UBR1 defects, *CAPN15* mutations may cause a phenotype overlapping with JBS.

Histologically, there is an almost complete absence of acinar cells, which are replaced by fat and connective tissue, whereas ductal architecture and islets are less affected. Thus, the ductular output of fluid and electrolytes is preserved, while the secretion of zymogens is decreased. The acinar cell loss is likely caused by intrauterine destruction, resembling pancreatitis of prenatal onset [43]. However, *UBR1* variants are not associated with chronic pancreatitis. *Ubr1* deficient mice have milder pancreatic dysfunction such as decreased zymogen secretion and increased susceptibility to experimental pancreatitis [42].

Diagnosis of JBS is based on the characteristic clinical picture and can be confirmed by *UBR1* sequencing. Therapy is symptomatic and consists of the substitution of pancreatic enzymes and, if necessary, of thyroid hormones as well as the provision of hearing aids and surgical correction of the malformations. The prognosis depends on the associated malformations. Lethal malformations such as bilateral renal dysplasia are rare. Mental retardation is variable, but about a third of those affected show normal intelligence.

Other Hereditary Disorders Affecting the Pancreas

Pancreatic abnormalities have been described in a number of congenital or inherited multisystem disorders, in which they are rarely a cardinal symptom or may even remain clinically inapparent.

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Polycystic Kidney Disease

Multiple cysts of the pancreas can be present in autosomal recessive (ARPKD) and autosomal dominant polycystic (ADPKD) disease. Both diseases are genetically heterogeneous [44]. The estimated incidence of ARPKD is about 1 to 20,000 and of ADPKD about 1 to 400–1,000 [44]. The clinical presentation of ARPKD is highly variable. Newborns have markedly enlarged polycystic kidneys that can be associated with pulmonary hypoplasia. Liver involvement is evident in about half of infants and comprises cysts and periportal fibrosis. Pancreatic cysts and pancreatic fibrosis have been repeatedly reported on imaging or autopsy in children with ARPKD, but clinical significant pancreatic disease is exceptional. The same applies to ADPKD, in which sonographically detectable pancreatic cysts are much more frequent and are present in about 10% of adult patients but are rare in infancy. Occasionally, the cysts may lead to pancreatitis. Pancreatic involvement is typically less severe than renal and hepatic affection.

Von Hippel–Lindau Syndrome

Von Hippel–Lindau syndrome (VHL) is an autosomal dominant familial cancer syndrome with an estimated incidence of 1:36,000. It is caused by mutations in the *VHL* tumor suppressor gene [45], but genetic changes in cyclin D1 (*CCND1*) may further modify the phenotype. About 80% of cases are familial. Affected subjects are at risk of developing cerebellar, spinal, and retinal hemangioblastomas, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, pancreatic and renal cysts, and epididymal cystadenoma [46].

About 35–70% of patients with VHL present with pancreatic findings. Pancreatic cysts are reported in up to 30% of patients on imaging studies but can be found in up to 72% of patients at autopsy; however, they are typically not congenital [27]. Involvement ranges from a single cyst to multiple cysts virtually replacing the pancreas. Usually the cysts are multiple but asymptomatic. These cysts may precede any other manifestation by several years. In about 12% of patients, pancreatic cysts are the only sign of the disease.

Serous cystadenomas and neuroendocrine tumors are other pancreatic manifestations. By replacing the pancreatic parenchyma, cysts and cystadenomas can compress adjacent structures and may cause exocrine or endocrine deficiency. Neuroendocrine tumors become malignant and metastatic in 8% of patients [46]. Pancreatic carcinoma and adenocarcinoma of the ampulla of Vater have also been reported.

Beckwith–Wiedemann Syndrome

The cardinal features of Beckwith–Wiedemann syndrome (BWS) are (asymmetric) macrosomia, macroglossia, and exomphalos in the neonate. Pancreatic hypertrophy is an imaging feature, and severe hypoglycemia due to transient hyperinsulinism occurs in 30–50% of neonates with BWS. Histology of resected pancreatic tissue shows an increase in the volume of endocrine relative to acinar tissue with expanded islets and preservation of lobular architecture [47]. Other clinical features include abdominal wall defects, ear anomalies, naevus flammeus, organomegaly, and nephroureteral malformations [48]. About 10% of patients develop embryonic tumors such as nephroblastoma, hepatoblastoma, and neuroblastoma during infancy [48]. Pancreatoblastomas have been described in a few cases and usually present in infants aged 3 months and younger. BWS is genetically heterogeneous. Loss or gain of methylation, paternal uniparental disomy, and *CDKN1C* loss-of-function mutations result in epigenetic or genetic defects on chromosome 11p15.5 with disrupted expression of imprinted genes [48]. About 85% of cases are sporadic.

Jeune Syndrome and Other Ciliopathies

Ciliopathies constitute a large group of multisystem disorders with considerable clinical and genetic heterogeneity, and pancreatic involvement is part of the phenotypic spectrum. Jeune syndrome (asphyxiating thoracic dystrophy) belongs to the skeletal ciliopathies and is a rare autosomal recessive osteochondrodysplasia with characteristic skeletal abnormalities, nephronophthisis, retinal abnormalities, pulmonary insufficiency, and hepatic fibrosis. It may be associated with pancreatic cysts and pancreatic fibrosis, leading to exocrine insufficiency [49].

Fibrotic and cystic changes of the pancreas may also be found in renal-hepatic-pancreatic dysplasia and in other ciliopathies [50].

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Section 2

Physiology and Pathophysiology of Pancreatic Functions

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4

Physiology of Acinar Cell Secretion

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Introduction

The acinar cell is the dominant cell type in the pancreas. In terms of percentage volume, the pancreas consists of 82% acinar cells, 4% duct cells, 4% blood vessels, 2% endocrine cells, and 8% extracellular matrix [1]. However, the acinar cell itself is not the functional unit in the exocrine pancreatic tissue because acinar cells are organized into acini consisting of up to several hundred acinar cells linked by numerous gap-junctional channels that allow both direct chemical and electrical intercellular communication [2,3]. There is an additional cell type that has not previously featured much in descriptions of acinar cell function, namely the pancreatic stellate cells (PSC). These very thin periacinar cells come very close to the acinar cells, but are nevertheless functionally isolated from the acinar cells [4–6]. The PSC play an important role under pathophysiologic conditions where they exert effects on the acinar cells [4–7], but it is unknown whether they have any physiologic role in the control of acinar cell secretion.

The principal function of the acinar cells is to secrete a potent mixture of digestive enzymes in response to food intake. This secretory response is mediated by vagal nerve stimulation, releasing acetylcholine (ACh) from nerve endings close to the acinar cells, and the circulating hormone cholecystokinin (CCK). The digestive (pro) enzymes are packaged into secretory vesicles called zymogen granules (ZG) and the secretion process itself occurs by exocytosis, that is, fusion of the granule membrane with the apical (luminal) cell membrane and subsequent opening of a pathway (pore) allowing direct movement of the zymogens from the granule interior to the acinar lumen [7]. In order to move the zymogens into the duct system and thereafter into the gut, there is also a need for fluid secretion. The acinar cells secrete a neutral Cl^--rich fluid, produced in response to stimulation with ACh and CCK [7,8]. Additionally, the small ducts secrete a HCO_3^--rich fluid when stimulated by the hormone secretin [7]. The aim of this chapter is to explain the cellular mechanisms underlying the very acute and finely controlled normal physiologic regulation of acinar fluid and enzyme secretion.

Composition of Pancreatic Acinar Juice

ACh or CCK activates acinar cells to secrete an isotonic NaCl-rich fluid (Fig. 4.1a) containing a multitude of enzymes and precursor enzymes. The protease precursors are trypsinogen, chymotrypsinogen, and procarboxypeptidases. These precursors are activated in the small intestine, initiated by conversion of trypsinogen to trypsin by the intestinal enzyme enteropeptidase. Trypsin then activates trypsinogen autocatalytically and also activates the other precursors. The acinar fluid also contains active α-amylase, lipases, and colipase as well as various other enzymes (e.g., collagenase, elastase, phospholipase A, and ribonuclease) [11]. The neutral NaCl-rich fluid containing these enzymes and enzyme precursors is delivered to the small ducts, where it is mixed with the HCO_3^--rich fluid produced by the duct cells in response to stimulation with secretin (Fig. 4.1b, c).

Acinar Fluid and Enzyme Secretion

There is separate control of acinar and duct secretion, as shown in experiments on the isolated perfused pancreas

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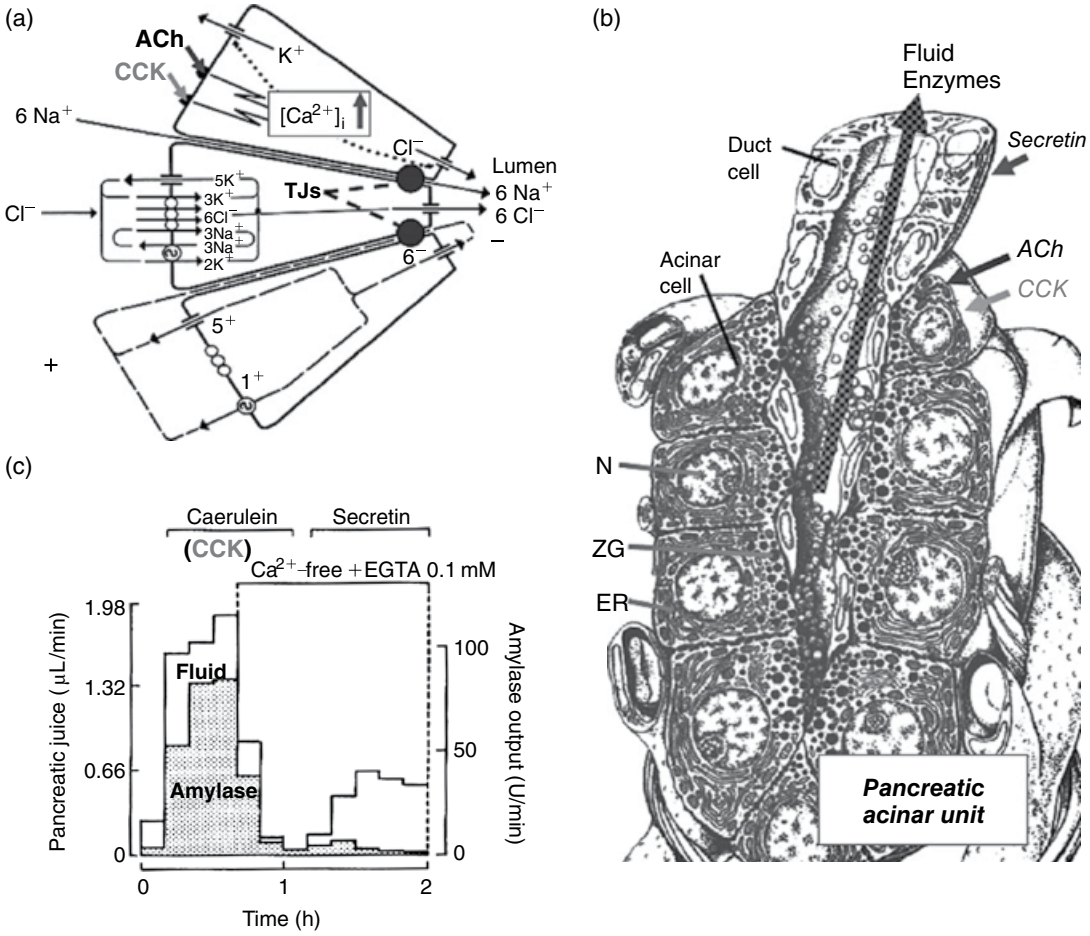


Figure 4.1 Fluid and enzyme secretion from acinar cells. (a) Acinar transport model illustrating the individual ion transport events that work together to produce an isotonic NaCl-rich fluid. For graphical convenience, different aspects of the processes are shown in separate cells. In the top cell it is shown that ACh or CCK binding to their respective specific receptors on the basolateral membrane elicits a rise in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$), which in turn activates Cl^+ channels in the apical (luminal) membrane and K^+ channels in the basolateral membrane (for graphical convenience all events in the basolateral membrane are shown only in the basal membrane). The middle cell illustrates transcellular Cl^- transport. The $Na^+/K^+/2Cl^-$ cotransporter, the K^+ channel, and the Na^+/K^+ pump are shown in the basal membrane and it is indicated that the net transport event is uptake of Cl^-, whereas at the apical membrane Cl^- exit into the lumen simply occurs through a Cl^- channel. The lower cell illustrates the overall electrical circuit and explains the transepithelial electrical potential difference. The $Na^+/K^+/2Cl^-$ cotransporter is electrically neutral, so the only electrogenic event at the basolateral membrane is the transport of cations (K^+ and Na^+) through the K^+ channel and Na^+/K^+ pump ($3Na^+$ pumped out for $2K^+$ taken in). This net outward (cation exit) current has to be matched by an inward (anion exit) current across the apical membrane and the completion of the circuit depends on the high conductance of the so-called tight junctions (TJs). *Source:* Adapted from [8] / With permission of American Physiological Society. (b) Model drawing of acinar unit with small duct segment attached. The polarity of acinar cells is shown with the nucleus (N) surrounded by endoplasmic reticulum (ER) in the basal part and zymogen granules (ZG) in the apical part. *Source:* Adapted from [9] / With permission of Springer Nature. (c) Fluid and amylase secretion from isolated perfused rat pancreas stimulated by the frog skin peptide cerulein (analog of CCK) and secretin. *Source:* Adapted from [10] / With permission of The Royal Society.

(Fig. 4.1c). Sustained fluid and enzyme secretion, due to stimulation with either ACh or CCK, is acutely dependent on the presence of Ca^{2+} in the extracellular solution, whereas the HCO_3^--rich fluid secretion evoked by secretin in the ducts occurs normally in the complete absence of external Ca^{2+} (Fig. 4.1c).

It is well established that exocytosis in general is activated by a rise in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) [7,11]. In nerve and endocrine cells, exocytosis is normally activated by Ca^{2+} entering the cell interior via special voltage-activated Ca^{2+} channels in the plasma membrane, which open on membrane depolarization caused by action potentials [11]. However, the pancreatic acinar cell is electrically nonexcitable and cannot fire action potentials [12]. Ca^{2+} needed for stimulus–secretion coupling is therefore delivered to

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the cytosol from intracellular stores [12]. It was established many years ago that the initial secretory response to stimulation with either ACh or CCK is independent of extracellular Ca^{2+} [13], whereas sustained secretion is acutely dependent on external Ca^{2+} (Fig. 4.1c). This is explained by the limited capacity of the intracellular Ca^{2+} stores and the fact that release of Ca^{2+} from stores into the cytosol inevitably activates Ca^{2+} pumps in the plasma membrane extruding Ca^{2+}, so that after a shorter or longer period of stimulation (depending on the intensity of stimulation) the contents of the intracellular Ca^{2+} stores have been exported to the extracellular solution [14]. A reduction of $[Ca^{2+}]$ in the intracellular stores activates a process known as store-operated Ca^{2+} entry. A signal is transmitted from the stores to the plasma membrane activating special Ca^{2+} channels (store-operated channels) that allow Ca^{2+} entry [15]. It is this Ca^{2+} entry process that sustains the secretory response during prolonged stimulation, after the stores have been emptied.

Ca^{2+} Signaling

It is well established that stimulation of acinar cells with either ACh or CCK elicits a rise in $[Ca^{2+}]_i$ (Fig. 4.2). At low, physiologically relevant, concentrations of neurotransmitter or hormone, the typical Ca^{2+} signal pattern consists of repetitive $[Ca^{2+}]_i$ spikes confined to the apical (granular) pole, as originally shown in 1993 [17]. Increasing the stimulating agonist concentration causes Ca^{2+} signal globalization, a process whereby a local Ca^{2+} signal initiated in the apical pole spreads as a wave from the apex to the base of the cell (Fig. 4.2).

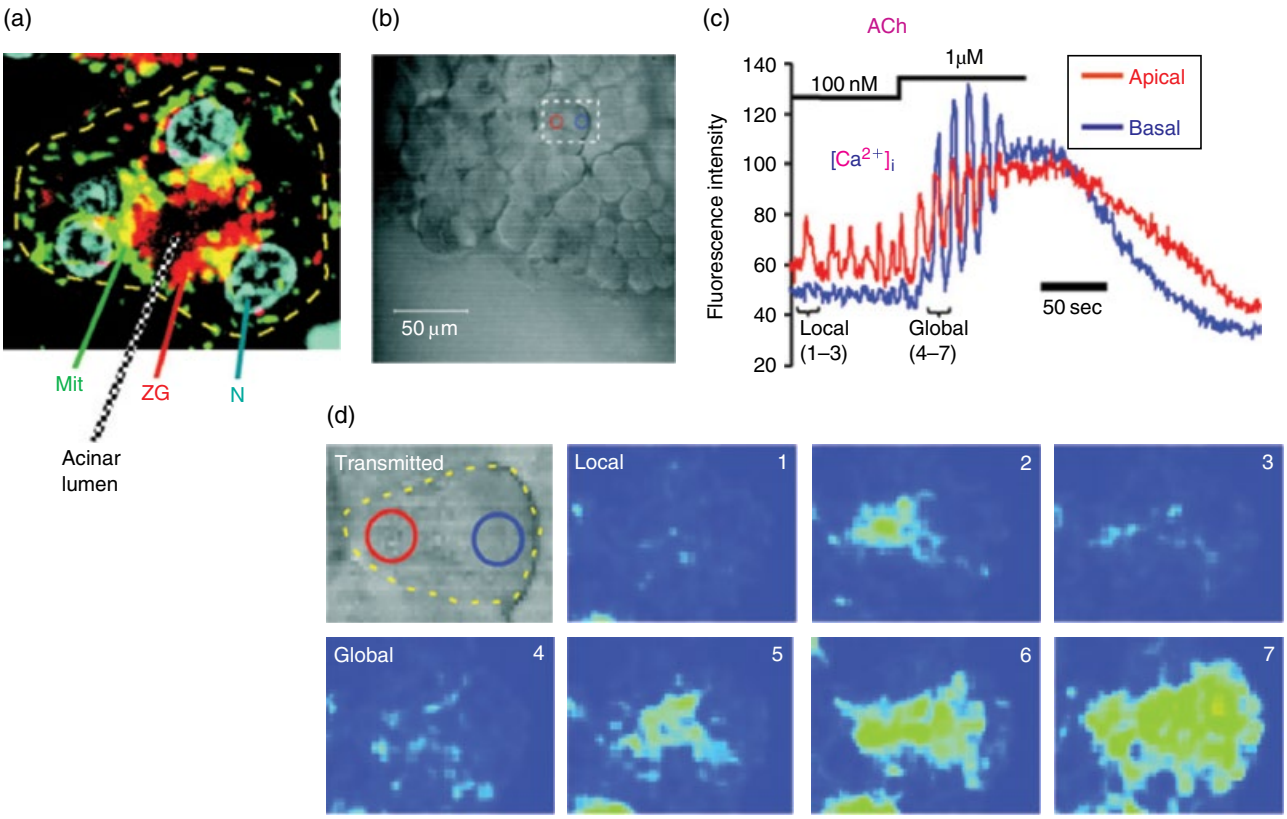


Figure 4.2 Ca^{2+} signaling and organelle distribution in the intact mouse pancreas. (a) Merged confocal images showing distribution of specific fluorescent markers for zymogen granules (ZG – red), nuclei (N – blue), and mitochondria (Mit – green). The optical slice goes through three cells (nuclei). The ZG are seen distributed around the lumen and are surrounded by mitochondria. Mitochondria are also located around the nuclei and close to the plasma membrane. (b) Confocal image of larger part of the pancreas showing many acinar units. One cell is highlighted by white dashed lines and in this cell apical (red) and basal (blue) regions of interest are signposted. The traces shown in (c) are from these two regions. (c) ACh-elicited cytosolic Ca^{2+} signals. At the low ACh concentration of 100 nM, repetitive Ca^{2+} spikes are seen exclusively in the apical pole. When the ACh concentration is increased to 1 µM, there is a rise in $[Ca^{2+}]_i$ in both the apical and basal regions. (d) Fluorescent images showing (upper row) a single local apical Ca^{2+} spike (numbers refer to time points in (c)) and (lower row) the initial Ca^{2+} wave generation following the increase in ACh concentration (numbers again refer to time points signposted in (c)). *Source:* Adapted from [16]/Elsevier/CC BY-4.0.

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Organelles Important for Ca^{2+} Homeostasis

Early work in the 1970s on Ca^{2+} transport in exocrine glands indicated that ACh evokes Ca^{2+} signals in acinar cells by causing release of Ca^{2+} from the endoplasmic reticulum (ER) [7] but, for many years, the link between ACh occupation of muscarinic receptors on the cell surface and the outflow of Ca^{2+} from the ER was obscure. In 1983, Irene Schulz and Michael Berridge discovered that the intracellular water-soluble messenger inositol 1,4,5-trisphosphate (IP_3), generated inside the cell by receptor-activated phospholipase C action on a membrane phospholipid, phosphatidylinositol 4,5-bisphosphate (PIP_2), releases Ca^{2+} from the ER in permeabilized pancreatic acinar cells [18]. All subsequent work on many different cell types confirmed the generality of the concept that hormone- or neurotransmitter-elicited intracellular Ca^{2+} release is mediated principally via IP_3-evoked Ca^{2+} release from the ER [7,19]. Although the original discovery of IP_3-evoked Ca^{2+} release was made on pancreatic acinar cells [18], there are difficulties in applying this concept to these particular cells. The problem is that the physiologically relevant Ca^{2+} signals occur specifically in the apical granular pole (see Fig. 4.2), which contains mostly ZG and little ER. This difficulty was finally overcome by the results of the so-called Ca^{2+} tunnel experiments, in which it could be shown that Ca^{2+} taken up at the base of the cell into the ER could diffuse easily in the ER lumen and reach the apex via thin ER extensions penetrating deeply into the granular area between the ZGs (see Fig. 4.3). Upon stimulation, Ca^{2+} is released primarily from the ER elements in the apical pole due to the high concentration of ER Ca^{2+} release channels specifically in this part of the cell (Fig. 4.3) [20,22].

It was initially a surprise that cytosolic Ca^{2+} signals initiated in the apical pole could remain local in such a relatively small cell (~20 µm diameter). This could not be easily understood before it was discovered that the mitochondria in the acinar cell are distributed in a very specific manner [23]. The mitochondria are primarily

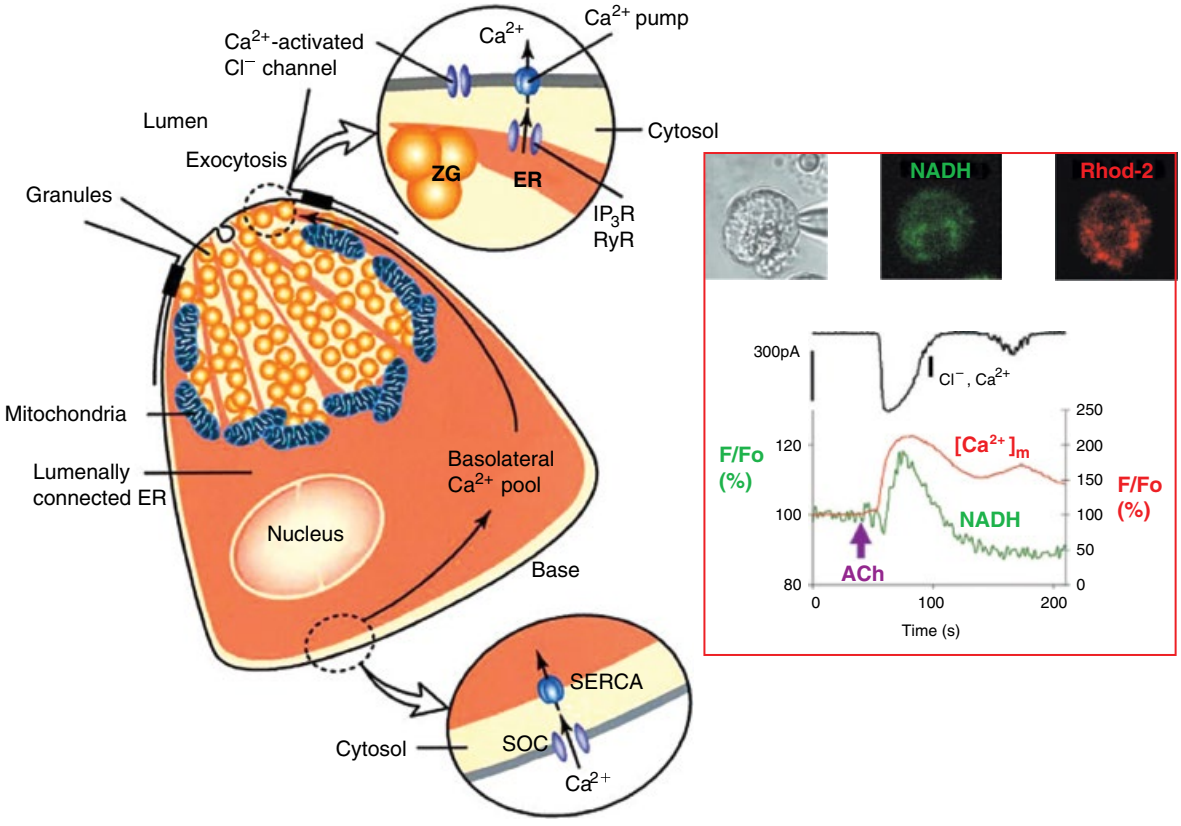


Figure 4.3 Organelle distribution and Ca^{2+} transport events in acinar cell. The main part of the figure shows a model cell with the distribution of organelles and Ca^{2+} transport pathways signposted. Insert (in red frame) shows triple measurements of Ca^{2+}-activated Cl^- current $\left(I_{Cl-,Ca^{2+}}\right)$, mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_m$—measured by Rhod-2 fluorescence—and concentration of NADH (autofluorescence). It is seen that ACh evokes a rapid rise in $I_{Cl-,Ca^{2+}}$, which is followed immediately by a rise in $[Ca^{2+}]_m$ and, after a small delay, by an increase in the NADH concentration signifying activation of mitochondrial metabolism and therefore ATP production. *Source:* Adapted from [21] / John Wiley and Sons and [20] / With permission of Elsevier.

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localized in a belt surrounding the ZG, separating the apical granular pole from the rest of the cell (see Figs 4.2 and 4.3). Due to their ability to take up Ca^{2+}, the mitochondria function as a Ca^{2+} diffusion barrier, effectively acting as a firewall preventing the spread of cytosolic Ca^{2+} signals from the apical pole into the basal part of the cell containing the nucleus (Fig. 4.3). The nucleus is well protected against Ca^{2+} signal invasion from the apical pole, since there is an additional mitochondrial belt surrounding the nucleus (Fig. 4.2). Finally, there is a concentration of mitochondria just beneath the plasma membrane (Fig. 4.2). The general concept that has emerged from studies of Ca^{2+} transport in the cytosol, ER, and mitochondria is that Ca^{2+} moves easily in the ER lumen, but with much more difficulty in the cytosol, due to the barriers created by the mitochondria [7,24].

The fact that the physiologically most important Ca^{2+} signals occur in the apical granular area has also prompted interest in the possibility that Ca^{2+} could be released from ZG and other acid pools in the apical pole. In studies on isolated ZG, it was shown that both IP_3 and another Ca^{2+}-releasing messenger, cyclic ADP-ribose (cADPR, derived from NAD) can liberate Ca^{2+} stored in this organelle (see Fig. 4.4). It has been clear for a long time that ACh causes intracellular Ca^{2+} release via generation of IP_3, acting primarily on the ER. It is now equally clear that CCK releases Ca^{2+} via generation of NAADP [7,26,27] and that NAADP primarily acts on acid stores (Fig. 4.4a). This may explain the somewhat different Ca^{2+} signal patterns that can be generated by CCK and ACh [28].

Mechanisms of Ca^{2+} Signal Generation

Figure 4.4 illustrates some of the most important steps. As already mentioned, there are two major signal transduction pathways, one initiated by hormonal (CCK) stimulation and the other by nervous (ACh) stimulation. CCK acts on high-affinity CCK1 receptors in the basolateral plasma membrane [29,30], whereas ACh acts on muscarinic M3 receptors, which are also localized predominantly in the basolateral membrane [16]. With state-of-the-art imaging technology, it is now possible to visualize some of the most important signal transduction steps.

Figure 4.5 demonstrates the ACh-elicited breakdown of PIP_2 in the basolateral membrane and the appearance of the water-soluble Ca^{2+}-releasing messenger IP_3 in the cytosol. The enzyme responsible for PIP_2 breakdown, phospholipase C, can in some cases be Ca^{2+} activated. However, the experimental result shown in Fig. 4.5 demonstrates that, at least in the pancreatic acinar cell, the disappearance of PIP_2 from the plasma membrane and the appearance of IP_3 in the cytosol are not secondary to Ca^{2+} signal generation, since a directly generated Ca^{2+} signal (via uncaging of Ca^{2+} in the cytosol) does not induce these effects, whereas ACh does.

Direct infusion of IP_3 into isolated cells elicits repetitive cytosolic Ca^{2+} spikes confined to the apical granular pole (see Fig. 4.6), in this way mimicking the effect of externally applied ACh (see Fig. 4.2). The importance of functional IP_3 receptors (IP_3R) for ACh-elicited Ca^{2+} signal generation and secretion in pancreatic acinar cells has been demonstrated very clearly by knockout experiments, in which it was shown that knockout of either type 2 or type 3 IP_3R had very little effect, whereas double knockout of both these receptors abolished ACh-elicited Ca^{2+} signal generation as well as secretion [34]. This directly confirms earlier data in which it was shown that intracellular infusion of the IP_3R antagonist heparin abolished both IP_3- and ACh-elicited Ca^{2+} spiking [35].

NAADP is a real intracellular messenger for CCK-induced activation of pancreatic acinar cells. Work from Galione's group in Oxford shows that physiologic CCK concentrations (1–10 pmol/L) evoke clear and dose-dependent increases in the cellular NAADP concentration. This effect is specific for CCK, since ACh has no effect on the NAADP level [26].

Intracellular infusion of NAADP, even at concentrations much lower (nanomolar) than those needed to obtain effects of IP_3 or cADPR, elicits repetitive cytosolic Ca^{2+} spikes in the apical pole that look very similar to those generated by IP_3 and cADPR [32]. The NAADP receptor has the interesting property that it can be inactivated by relatively high (micromolar) intracellular NAADP concentrations. Using such selective inhibition of the NAADP receptor, it has been shown that Ca^{2+} spiking evoked by physiologic CCK concentrations (<10 pmol/L) is blocked by a high intracellular NAADP concentration. This blocking effect is specific for the CCK response, since ACh-elicited Ca^{2+} spiking is unaffected [36]. Furthermore, the NAADP antagonist Ned-19 blocks CCK-elicited Ca^{2+} spiking, but has no effect on the action of ACh [27].

Although ACh and CCK initiate Ca^{2+} signaling via different pathways (see Fig. 4.4a), these ultimately converge and the measurable local apical Ca^{2+} transients are due to positive and negative feedback interactions between IP_3R and RyR on the ER (Fig. 4.4a). These Ca^{2+}-mediated positive and negative interactions are functionally important. For example, a Ca^{2+} signal initiated by an increase in the intracellular IP_3 concentration will subsequently activate RyR, inducing further Ca^{2+} release. This positive feed-forward effect explains the rising phase of the cytosolic Ca^{2+} spike. However, at a higher level of $[Ca^{2+}]_i$, a further $[Ca^{2+}]_i$ rise inhibits opening of both IP_3R and RyR. This explains the falling phase of the spike [7,37]. It has recently become clear that there is another class of channel involved in intracellular Ca^{2+}

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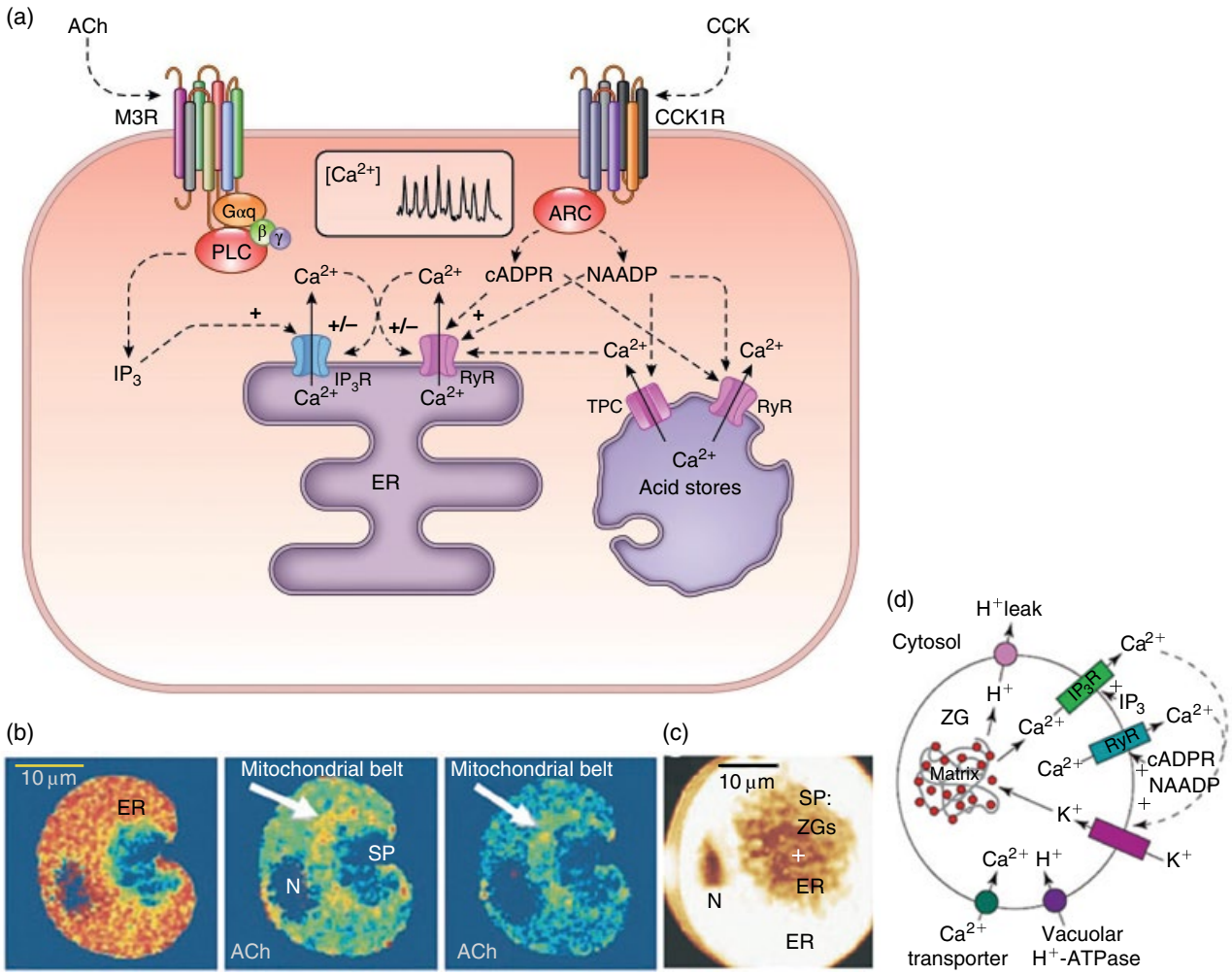


Figure 4.4 Ca^{2+} transport and signaling events in acinar cell. (a) Two receptor pathways are shown. ACh binding to muscarinic M3 receptors activates, via interaction with a classical trimeric G-protein, phospholipase C (PLC) generating the messenger IP_3 (as well as diacyl glycerol—not shown in diagram). CCK interaction with CCK1 receptors results in activation, via ADP-ribosyl cyclase (ARC), of two separate messengers, namely NAADP and cADPR. NAADP releases Ca^{2+} primarily from acid stores, via two pore channels (TPC). It also causes Ca^{2+} release from both acid stores and the ER via ryanodine receptors (RyR). cADPR releases Ca^{2+} via RyR from both acid stores and the ER. *Source:* Adapted from [7]. (b) Confocal fluorescent images illustrating changes in organellar [Ca^{2+}] following ACh stimulation. The left image shows the high resting [Ca^{2+}] in the ER (mostly in the basal (left) part of the cell). After maximal ACh stimulation, [Ca^{2+}] in the ER has been reduced markedly (shift from warm (red) to cold (green) color) and the perigranular mitochondrial belt is now clearly seen (yellow). This indicates that Ca^{2+} lost from the ER has been taken up in part by the mitochondria. The third image shows the almost complete loss of Ca^{2+} from the ER and the still elevated [Ca^{2+}] in the perigranular mitochondria. (c) Confocal image showing the distribution of fluorescent thapsigargin (white), a very specific marker for the ER Ca^{2+} pump. The optical slice goes through two cells (but only through one nucleus – N). It is seen that by far the highest ER Ca^{2+} pump density is in the basolateral parts of the cell, but it is important to note that there are some light elements in the darker granular (secretory pole – SP) areas signifying ER elements with Ca^{2+} pumps also in this part of the cell. (d) Schematic drawing of Ca^{2+}, H^+, and K^+ transports across the ZG membrane. *Source:* [25] / With permission of Elsevier.

release, namely the so-called two-pore channel (TPC) (Fig. 4.4a). In the pancreatic acinar cells, these channels are important specifically for the Ca^{2+} release evoked by CCK, which is mediated by NAADP. The sequence of events with regard to CCK-elicited Ca^{2+} signal generation is likely to be an initial release of a very small (trigger) amount of Ca^{2+} from endosomes/lysosomes, which is then amplified by a much more substantial liberation of Ca^{2+} from the ER and the acid stores occurring via RyR [7,27] (Fig. 4.4a).

Ca^{2+} Entry and Exit

Although the primary event responsible for activation of secretion by ACh or CCK is intracellular Ca^{2+} release, it

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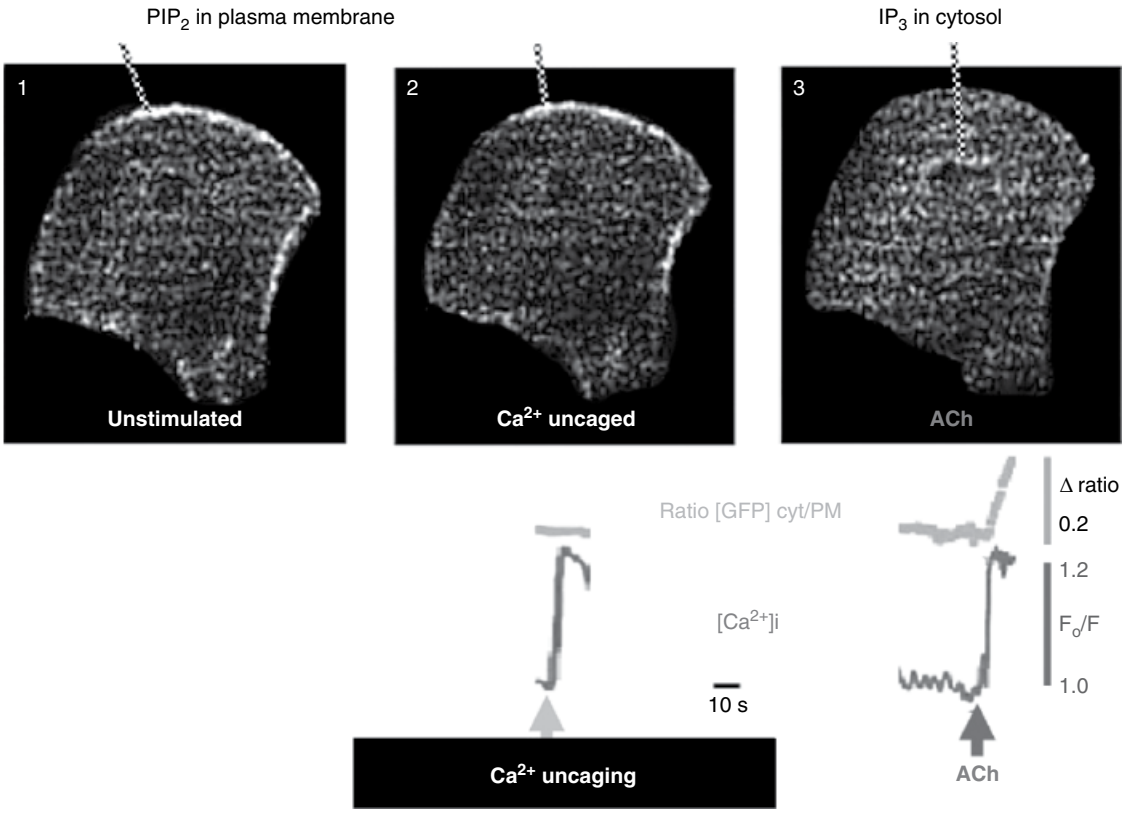


Figure 4.5 Acetylcholine (ACh)-induced breakdown of phosphatidylinositol 4,5-bisphosphate (PIP_2) in the plasma membrane (PM) and generation of inositol 1,4,5-trisphosphate (IP_3) in the cytosol (cyt). The green fluorescent protein (GFP)-linked PH domain of PLCδ1 binds with high affinity to both PIP_2 and IP_3. (1) Before stimulation, the main GFP fluorescence is seen in the basolateral membrane, indicating the presence of PIP_2 at this site. (2) Generation of a substantial rise in $[Ca^{2+}]_i$ by photolytic release of Ca^{2+} into the cytosol from caged Ca^{2+} does not cause any reduction in the PIP_2 concentration in the membrane. (3) ACh (1 µmol/L) causes a rise in $[Ca^{2+}]_i$ of similar magnitude to that seen after Ca^{2+} uncaging, but in this case there is loss of GFP fluorescence from the basolateral membrane, signifying loss of PIP_2, and appearance of fluorescence in the cytosol indicating appearance of IP_3. *Source:* Adapted from [31].

is also very important for both physiology and pathology to consider the overall cellular Ca^{2+} homeostasis, that is, Ca^{2+} entry and exit. All cells have to be protected against cellular Ca^{2+} overload, since it is well established that this causes cell death [38]. The plasma membrane must therefore be relatively impermeable to Ca^{2+} and there must be mechanisms for cellular Ca^{2+} extrusion. Ca^{2+} entry and exit across the plasma membrane of pancreatic acinar cells is controlled by specific transport mechanisms. Unlike many electrically excitable cells (e.g., cardiac cells), the acinar cells do not possess functional Na^+/Ca^{2+} exchangers, so that the only mechanism for extruding Ca^{2+} across the plasma membrane is via the plasma membrane Ca^{2+}-activated ATPase (PMCA) [25]. This pump is activated by increases in $[Ca^{2+}]_i$ above the basal level of 0.1 µmol/L, but has limited capacity. Interestingly, this pump is not uniformly distributed over the plasma membrane, but is specifically concentrated in the apical plasma membrane and therefore extrudes Ca^{2+} principally into the acinar lumen (see Fig. 4.7). The concentration of the pump in the apical membrane is functionally important, since the principal intracellular Ca^{2+} release sites are located in the apical pole (Figs 4.2 and 4.6), but carries the risk that Ca^{2+} overload, due to inappropriate Ca^{2+} entry across the basal membrane in pathologic conditions, cannot be dealt with adequately [25].

Physiologic stimulation of acinar cells does not primarily increase the permeability of the plasma membrane for Ca^{2+}, but after depletion of the ER Ca^{2+} store there is specific opening of the so-called store-operated Ca^{2+} channels in the basolateral membrane. This can most easily be visualized by measuring the uptake of Ca^{2+} entering the base of the cell into the peripheral mitochondria situated immediately beneath the plasma membrane, as shown in Fig. 4.7. In these types of experiments, the ER Ca^{2+} store is depleted by poisoning the Ca^{2+} pump in the ER very specifically with thapsigargin in the absence of external Ca^{2+}. Thereafter, Ca^{2+} is readmitted to the external solution and an increase in the Ca^{2+} concentration of those mitochondria situated very close to the plasma membrane can be visualized directly (Fig. 4.7). The nature of the store-operated Ca^{2+} channels

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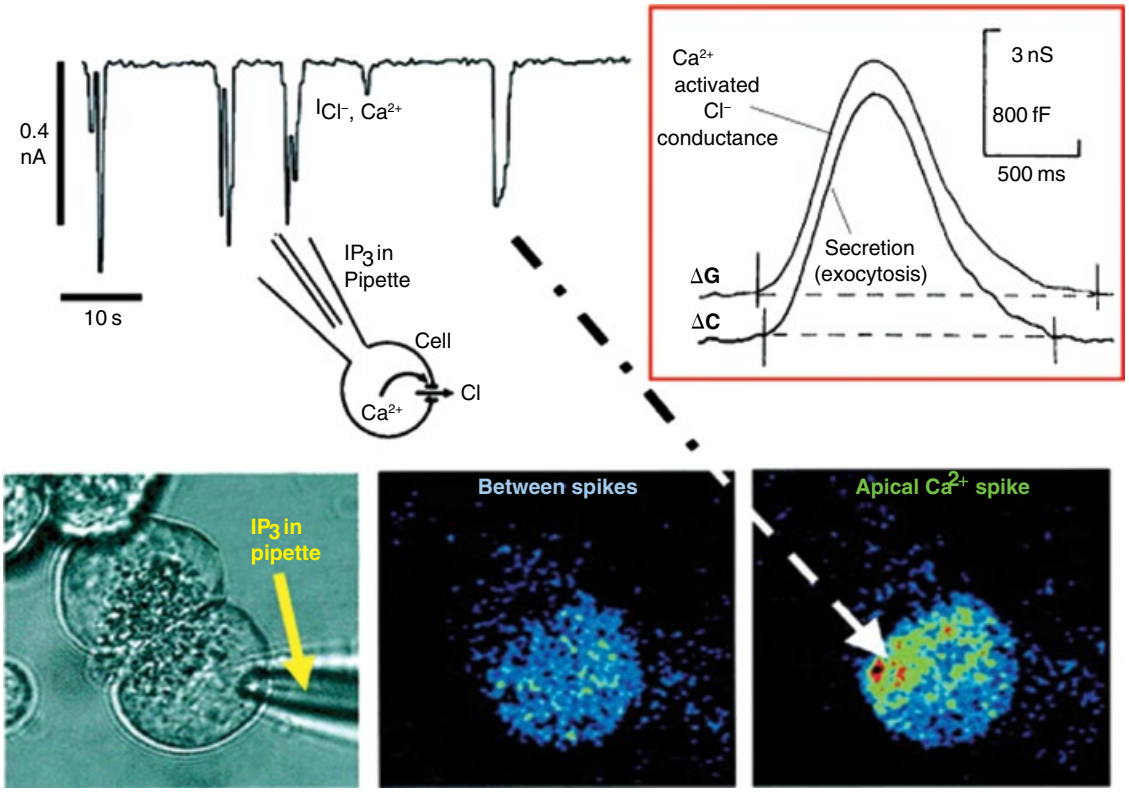


Figure 4.6 IP_3-elicited local apical Ca^{2+} spikes and exocytotic secretion. The main part of the figure shows the result from a patch clamp experiment with internal acinar cell perfusion. The trace shows the repetitive spikes of Ca^{2+}-dependent Cl^- current elicited by intracellular IP_3 infusion (10 μM). The images below illustrate the experimental configuration and the distribution of the elevated $[Ca^{2+}]_i$ during the height of a spike. It can be clearly seen that the Ca^{2+} signal occurs in the apical granular pole. *Source:* Adapted from [32]. The insert (in red frame) shows correlation between a single apical Ca^{2+} spike (during IP_3 infusion), recorded here as an increase in Cl^- conductance (ΔG), and the exocytotic response recorded as an increase in membrane capacitance (ΔC). It is seen that the increase in Cl^- conductance (a sensitive indicator of $[Ca^{2+}]_i$) slightly precedes the rise in capacitance and that the secretory response is completed just before $[Ca^{2+}]_i$ returns to the inter-spike level. *Source:* Adapted from [33] / With permission of Elsevier.

in the pancreatic acinar cells has been clarified by patch clamp studies, in which it has been possible to record directly the tiny Ca^{2+} currents flowing across the basolateral membrane upon depletion of the ER Ca^{2+} store. The biophysical properties of this current shows that the channels belong to the very Ca^{2+}-selective CRAC (Ca^{2+} release activated Ca^{2+}) channel type [41], which is also present in various immune cells [15]. These channels, including those in the acinar cells as well as other pancreatic cell types, can be blocked by very specific CRAC channel inhibitors [7,41–45].

During sustained stimulation with either ACh or CCK, one can usually observe a plateau of elevated $[Ca^{2+}]_i$, which represents a delicate balance of Ca^{2+} entry through store-operated Ca^{2+} channels in the basal membrane and Ca^{2+} exit mainly through Ca^{2+} pumps located in the apical plasma membrane [24]. Ca^{2+} extrusion is energy-dependent. Therefore, if intracellular ATP levels fall during pathologic conditions, for example when cells are exposed to nonoxidative alcohol metabolites [46], Ca^{2+} extrusion stops and dangerous Ca^{2+} overload occurs, resulting in necrosis [7,46].

Ca^{2+}-Mediated Control of Enzyme Secretion

It has been known for many years that intracellular Ca^{2+} is the main acute regulator of exocytosis [47]. In experiments on the isolated perfused pancreas, it has been demonstrated that during sustained stimulation with high concentrations of ACh or CCK, both fluid and enzyme secretion are acutely dependent on the presence of external Ca^{2+} (see Fig. 4.1). During this phase of the secretory response, the ER will have been partly depleted of Ca^{2+} and Ca^{2+} therefore has to be supplied by entry from the external solution through store-operated Ca^{2+} channels as described earlier. However, during physiologic stimulation, with low concentrations of CCK or ACh, there is not a sustained elevated $[Ca^{2+}]_i$ but rather a series of

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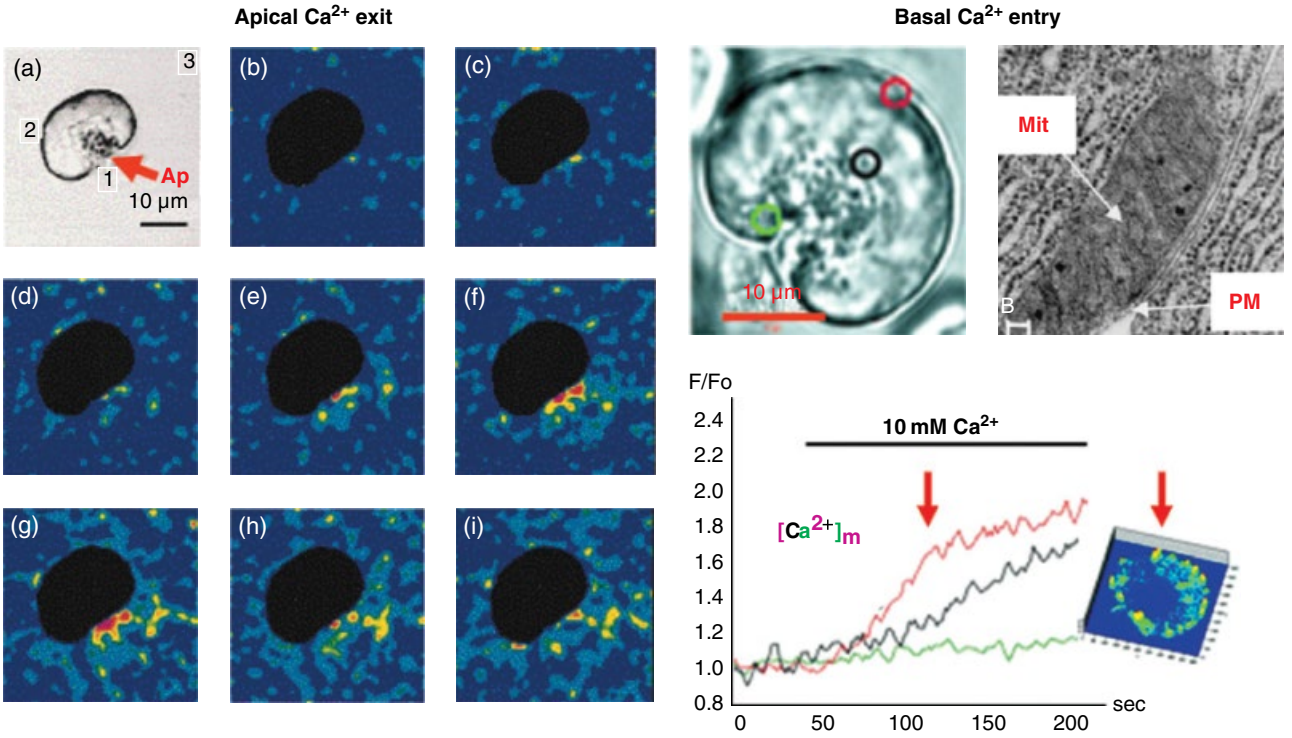


Figure 4.7 Overall Ca^{2+} homeostasis: Ca^{2+} entry and exit. The left part illustrates an experiment in which $[Ca^{2+}]$ is measured outside an isolated acinar cell by using a Ca^{2+}-sensitive fluorescent indicator linked to high molecular weight dextran, thereby limiting the indicator mobility. The morphology of the cell, with clear identification of the granular apical (Ap) pole is shown in (a). (b) to (i) are fluorescent images (taken at 3-s intervals) showing the distribution of the extracellular $[Ca^{2+}]$ rise immediately following stimulation with ACh (10 µM). It is clear that the Ca^{2+} extrusion from the cell occurs predominantly across the apical membrane. The right part of the figure illustrates the rise in $[Ca^{2+}]$ of mitochondria close to the basal plasma membrane during store-operated Ca^{2+} entry. Mitochondrial $[Ca^{2+}]$ ($[Ca^{2+}]_m$) was measured with a fluorescent probe and traces from three regions of interest (red, black, and green) are shown. The cell was initially poisoned with thapsigargin in the absence of external Ca^{2+} to deplete the ER of Ca^{2+}. During the time period indicated by the bar labeled 10 mM Ca^{2+}, Ca^{2+} was readmitted to the external solution and it is seen that there was a marked rise in $[Ca^{2+}]_m$ particularly in the red region of interest, very close to the basal plasma membrane. The image marked with a red arrow shows the distribution of the elevated $[Ca^{2+}]$ at the time indicated by a similar red arrow above the fluorescence traces. Clearly the elevation of $[Ca^{2+}]_m$ has essentially occurred in a region very close to the plasma membrane. The EM picture shows a mitochondrion (Mit) situated very close to the plasma membrane (PM). *Source:* Adapted from [39] and [40].

short-lasting Ca^{2+} spikes localized specifically in the critical apical region (Figs 4.2 and 4.6). These spikes are essentially independent of external Ca^{2+} and are due to repetitive release of small amounts of Ca^{2+} from the ER [7,48].

Can the short-lasting local Ca^{2+} spikes, evoked by low agonist concentrations or direct intracellular messenger infusion, control secretion? The most sensitive method for evaluating exocytotic secretion is measurement of membrane capacitance. When granules fuse with the plasma membrane, the surface area of the plasma membrane increases, but only transiently since the additional membrane inserted is subsequently removed by the process of endocytosis. As shown in Fig. 4.6 (inset), there is indeed a transient increase in the pancreatic acinar membrane capacitance during an individual short-lasting Ca^{2+} spike, which can most easily be recorded by electrophysiologic methods. Results, such as those recorded in Fig. 4.6, demonstrate clearly the very fine control exerted by the local apical $[Ca^{2+}]_i$ on exocytotic secretion.

Ca^{2+}-Mediated Control of Fluid Secretion

How is acinar fluid secretion regulated? The generally accepted model for isotonic fluid secretion by exocrine glands is illustrated in Fig. 4.1a. The principal step for activation of fluid secretion is Ca^{2+}-activated opening of Cl^- channels, which are specifically located in the apical plasma membrane [49]. This will cause Cl^- exit into the acinar lumen. The increased lumen negativity will attract cations and the principal extracellular cation, Na^+, will move through the very leaky junctions between the acinar

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cells, which are named (inappropriately!) tight junctions. These junctions sit very close to the apical membrane and separate the luminal fluid compartment from the basal and interstitial compartments, and also separate the very different properties of the apical and basolateral membranes (Fig. 4.1a). NaCl in the acinar lumen will osmotically attract water, which can pass through both the cell membranes (via aquaporins) and the tight junctions.

The principal activating step of acinar fluid secretion, namely the exit of Cl^- from the cell interior to the lumen through Ca^{2+}-activated Cl^- channels, only occurs if there is an electrochemical gradient favoring transport in this direction. The intracellular Cl^- concentration must be held above thermodynamic equilibrium and a Cl^--accumulating mechanism is therefore needed. As shown in Fig. 4.1a, a $Na^+/K^+/2Cl^-$ cotransporter is situated in the basolateral membrane (for graphical convenience shown in Fig. 4.1a only in the basal membrane). Energy for this process comes from the transmembrane Na^+ gradient established by the Na^+/K^+ pump, which is also situated in the basolateral membrane. Increased Cl^- secretion requires stimulation of the Na^+ pump, which occurs via the increased intracellular Na^+ concentration mediated by enhanced turnover of the $Na^+/K^+/2Cl^-$ cotransporter. This in turn requires additional K^+ cycling across the plasma membrane, which is mediated by Ca^{2+} activation of specific K^+ channels situated in the basolateral membrane (Fig. 4.1a).

As seen in Fig. 4.1a, it is the concerted Ca^{2+} activation of Cl^- and K^+ channels that controls the fluid secretion process. It is important to understand that the whole of the basolateral membrane is uniform with regard to distribution of surface membrane ion channels. Thus, the Ca^{2+}-activated K^+ channels are found not only in the basal membrane as illustrated in Fig. 4.1a, but also in the lateral membranes, up to the tight junctions. Therefore, local apical Ca^{2+} signals will be able to activate both Cl^- channels in the apical membrane and K^+ channels in the part of the lateral membrane close to the tight junctions. A limited amount of fluid secretion can proceed without special activation of K^+ channels, since rodent pancreatic acinar cells lack Ca^{2+}-activated K^+ channels [12]. If the resting K^+ permeability is sufficiently high, recirculation of K^+ can still occur. However, human pancreatic acinar cells, like all salivary and lacrimal glands in all species so far studied, do possess very sensitive Ca^{2+}-activated K^+ channels, which undoubtedly contribute to the fine regulation of human acinar fluid secretion [50]. In the human acinar cells, these Cl^- and K^+ channels will be activated by the short-lasting repetitive local Ca^{2+} signals in the secretory granule region, which have been directly demonstrated in response to stimulation with either ACh or physiologic concentrations (low pM) of CCK [51].

Dangers of Ca^{2+} Signaling

As described in this chapter, local Ca^{2+} signaling elicited by physiologically relevant agonist concentrations is a remarkably precise mechanism for fine regulation of pancreatic acinar secretion (Fig. 4.6). These Ca^{2+} signals also control the production of ATP (Fig. 4.3), which is required to fuel both fluid and enzyme secretion. However, Ca^{2+} signaling carries a risk of cellular Ca^{2+} overload, which has the capacity to kill cells [7]. This occurs when acinar cells are hyperstimulated with, for example, CCK. In this situation Ca^{2+} spiking is replaced by a sustained elevated $[Ca^{2+}]_i$ which, by a still poorly understood mechanism, activates the digestive proteases inside the cells [25]. The sustained elevated $[Ca^{2+}]_i$ is due to open CRAC channels and can be markedly reduced by CRAC channel inhibitors [7,41–43]. A sustained elevated $[Ca^{2+}]_i$, unlike repetitive short-lasting Ca^{2+} spikes, does not stimulate mitochondrial ATP production, but inhibits it [52]. The combination of a global and sustained high $[Ca^{2+}]_i$ with a low cytosolic ATP level is lethal [7,53].

Intracellular digestive enzyme activation is a hallmark of pancreatitis, which is mostly related to biliary disease or excessive alcohol intake. Both bile-related and alcohol-related acute pancreatitis are due to cytosolic and mitochondrial Ca^{2+} overload, which have been brought about by excessive opening of CRAC channels in the plasma membrane triggered by excessive release of Ca^{2+} from intracellular stores [7]. Both bile acids and the combination of ethanol and fatty acids (generating fatty acid ethyl esters) have the capacity to elicit excessive release of Ca^{2+} from intracellular stores [7]. The cytosolic Ca^{2+} overload leads to mitochondrial Ca^{2+} overload, which causes opening of the so-called mitochondrial permeability transition pore (MPTP) and this depolarizes the inner mitochondrial membrane resulting in loss of ATP production [7,46,52]. The dangerous effects of bile acids or fatty acid ethyl esters can be markedly inhibited by reducing the intracellular Ca^{2+} release via caffeine inhibition of IP_3 receptors [35,54], by reducing Ca^{2+} inflow via CRAC channels using specific CRAC channel inhibitors [7,41–43] or by inhibiting the MPTP [55]. The pancreatic acinar cell lives dangerously. It very effectively employs Ca^{2+} signaling as a finely coordinated mechanism for regulation of both fluid and enzyme secretion, but excessive intracellular Ca^{2+} release or Ca^{2+} entry has the capacity to cause necrosis.

The Ca^{2+}-mediated toxic actions on the acinar cells, initiated by bile acids or the combination of ethanol and fatty acids, are markedly amplified by interactions with the neighboring stellate cells as well as with the

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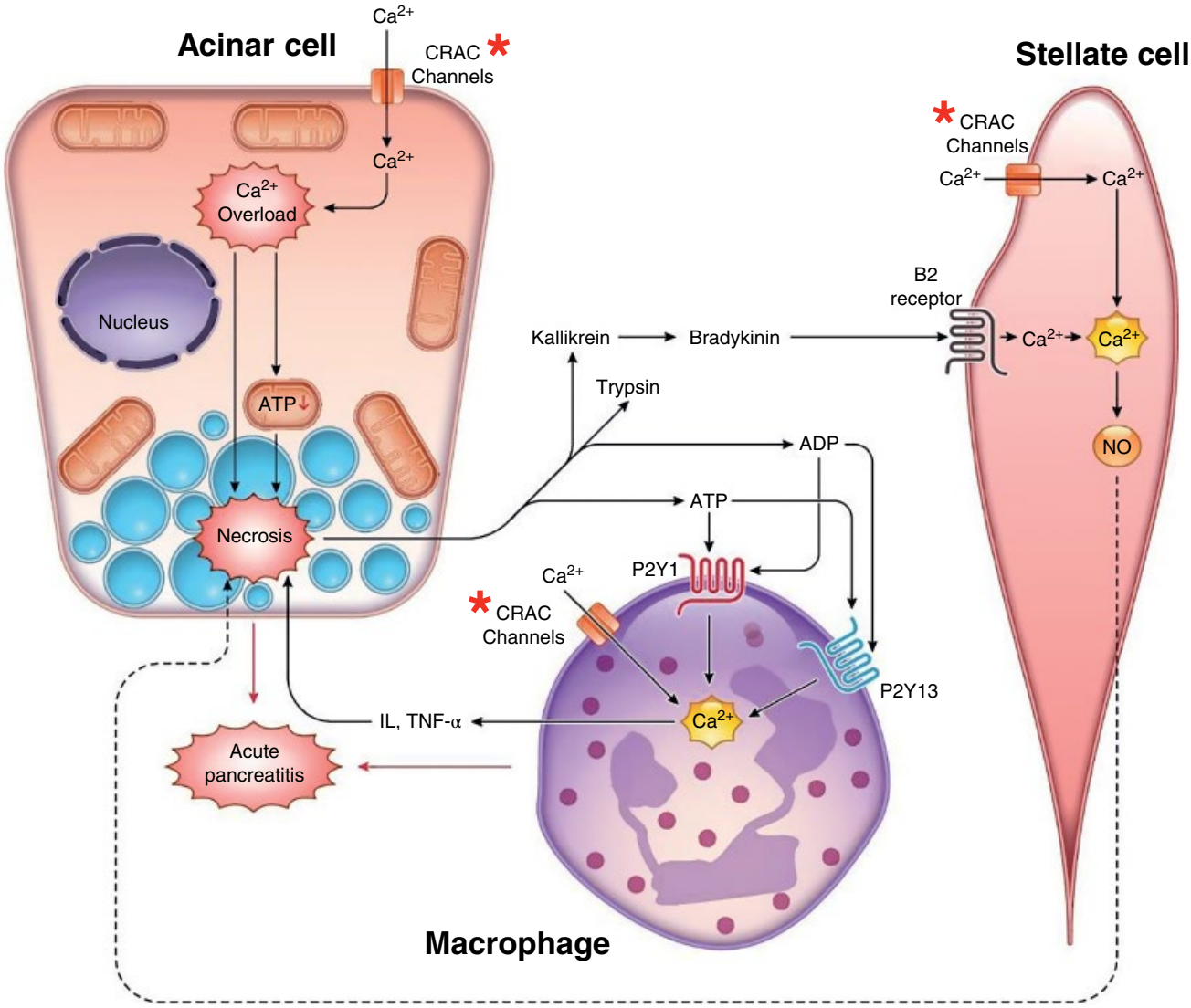


Figure 4.8 Ca^{2+}-dependent interactions, between acinar cells, neighboring stellate cells and resident macrophages in the acinar environment, drive the development of acute pancreatitis. Inhibition of Ca^{2+} influx in these three cell types through CRAC channels (denoted by red asterisks) would be a rational therapy against acute pancreatitis. For details, see text. *Source:* Adapted from [7].

macrophages that invade the pancreatic tissue in the early stages of acute pancreatitis (Fig. 4.8). Loss of kallikrein from the acinar cells that are most sensitive to the toxic actions will lead to generation of bradykinin (BK), which then acts on type 2 BK receptors on stellate cells, releasing Ca^{2+} from internal stores that in turn opens CRAC channels. The generation of Ca^{2+} signals in the stellate cells activates nitric oxide formation [6], which, via an unknown mechanism, promotes necrosis of the acinar cells, starting a vicious circle (Fig. 4.8). ATP and ADP released from dying acinar cells act on purinergic receptors on macrophages generating Ca^{2+} signals in these cells due to activation of CRAC channels [44]. This stimulates secretion of many cytokines, including interleukins and TNF-α, which in turn causes further necrosis of the acinar cells (Fig. 4.8). It is therefore these necrotic amplification loops, dependent on Ca^{2+} influx through CRAC channels that drive the development of acute pancreatitis (Fig. 4.8). The therapeutic and preventive effects of small molecule CRAC channel inhibitors [41–43] are therefore not only due to reduction of Ca^{2+} influx into acinar cells, but also due to inhibition of CRAC channel opening in the neighboring stellate cells and macrophages [4,7,44,45].

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5

Physiology of Duct Cell Secretion

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Introduction

The cardinal function of the pancreatic duct is fluid and HCO_3^- secretion, which determines the volume and electrolyte composition of the pancreatic juice and guards the acinar cells against damage by various stressors. Indeed, ductal fluid and electrolyte transport is compromised in diseases such as cystic fibrosis and pancreatitis, which stress the pancreas [1]. Ductal secretion is coupled to acinar secretion that provides the small volume of isotonic, plasma-like fluid. The ducts then secrete the bulk of the fluid into the pancreatic juice making economical and recirculating use of the electrolytes in primary fluid secreted by acinar cells. Thus, for a better understanding of ductal secretion and physiology, first we have to understand the mechanism of acinar secretion and its regulation. Selective transporters in acinar and duct cells mediate vectorial transport of osmotically active ions to generate and secrete fluid of defined composition. Ductal and acinar cells secretion is highly regulated at both the resting and secreting states by multiple inputs that transmit their signals through the two main second messengers Ca^{2+} and cAMP. The Ca^{2+} and cAMP inputs are integrated into a final response with synergized high fidelity. Other important regulators of the entire secretory process are the transported ions. This is highlighted in the regulation of ductal transporters and secretion by intracellular Cl^- [2]. This chapter discusses the principles of ductal fluid and HCO_3^- secretion and its regulation and how they can be corrected in pancreatic disease states.

Sequential Secretion by Acinar and Duct Cells

Fluid and Electrolyte Secretion by Acinar Cell

Pancreatic fluid and electrolyte secretion is a two-step, sequential process. The acinar cells secrete a small volume of isotonic, NaCl-rich fluid. Whereas, the duct produces most of the fluid and determines the final ion composition of the pancreatic juice [3]. Understanding ductal secretion requires an understanding of acinar cells secretion. The key transporters and the mechanism of fluid secretion by acinar cells are modeled in Fig. 5.1. Vectorial ion transport depends on the Na^+ and K^+ gradients and the membrane potential that are set by the basolateral Na^+/K^+ ATPase pump [4]. The Ca^{2+}-activated K^+ channel at the basolateral membrane Kcnma1 sets the membrane potential near the K^+ diffusion potential of about −60 mV [5]. About 60–70% of acinar cells salt uptake is mediated by the ubiquitous basolateral $Na^+/K^+/2Cl^-$ cotransporter NKCC1 [3]. The remaining salt is absorbed by the basolateral Na^+/H^+ exchanger NHE1 and by a Cl^-/HCO_3^- exchange activity. It is generally assumed that the ubiquitous AE2 mediates the Cl^-/HCO_3^- exchange that supports fluid flux. However, in salivary glands, AE4, which functions as a cation-driven Cl^-/HCO_3^- exchanger [6], mediates part of the Cl^- influx necessary for fluid secretion [7]. NHE1 and AE2 also control the cytoplasmic pH (pH_{in}) to prevent large fluctuations in pH_{in} during the secretion [8,9]. Under resting conditions NKCC1, AE2, and AE4 maintain intracellular Cl^- (Cl^-_{in}) at 40–60 mM [10]. The importance of Cl^-_{in} is

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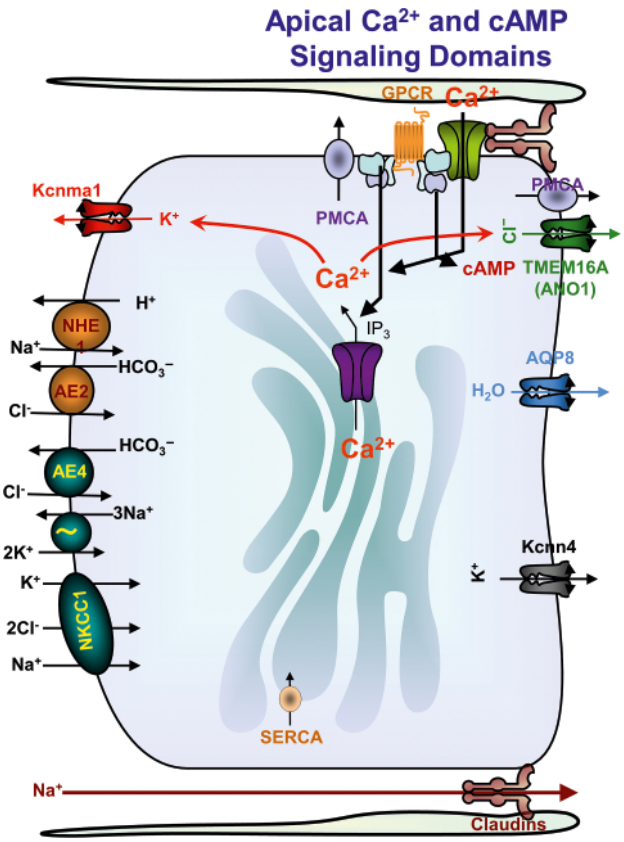


Figure 5.1 Mechanism of fluid and electrolyte secretion by acinar cells. The model shows the key transporters and the relationships between them that mediate the bulk of fluid and electrolyte secretion by acinar cells. Key regulation of acinar fluid and electrolyte secretion take place by assembly of Ca^{2+} and cAMP signaling complexes at the apical pole to control the function of ANO1 and K^+ channels.

discussed below in relation to regulation of the secretory process. Cl^- exits across the luminal membrane through the Ca^{2+}-activated Cl^- channel TMEM16A/Ano1 [11] and water flows through the water channel AQP8 [12]. The tight junction on acinar cells is the main route of paracellular Na^+ flux, which may be mediated by one of the acinar claudins [13].

Acinar cells fluid and electrolyte secretion is regulated by Gq-coupled receptors that increase free cytoplasmic Ca^{2+} ($[Ca^{2+}]_i$) and is enhanced by the cAMP/PKA pathway. To prevent Ca^{2+} toxicity by stronger stimulation, only 1–5% of the Gq pool evoke Ca^{2+} oscillations under physiological stimulation. The Ca^{2+} oscillations initiate and remain confined to the apical pole [14], although they can propagate to the basal pole [15,16]. Acinar cell secretion starts by an increase in apical $[Ca^{2+}]_i$ to activate Ano1 [11], and K^+ channels in the basal [17] and maybe apical poles [18]. This leads to Cl^- efflux into the luminal space and K^+ efflux into the interstitial space. Na^+ transport through the tight junctions results in the net secretion of NaCl and generation of an osmotic gradient that drives water flow through the water channel Aqp8, leading to cell shrinkage. Cell shrinkage reduces $[Ca^{2+}]_i$ and activates the volume-sensitive cotransporters NKCC1 [19], NHE1 [20], AE2 [21], and perhaps AE4 to recover cytoplasmic electrolytes and cell volume. The cycle of Ca^{2+}-regulated water flow is repeated with each Ca^{2+} spike making acinar cells function as a Ca^{2+}-driven ion and water pump.

Fluid and Electrolyte Secretion by Duct Cell

The main transporters mediating ductal fluid and HCO_3^- secretion are shown in Fig. 5.2. Transport is fueled by the Na^+ gradient and the membrane potential set by the Na^+/K^+ ATPase pump [22], the K^+ channels K(Ca^{2+})1.1 [23], and an unknown basolateral K^+ channel. HCO_3^- enters the ducts by basolateral $1Na^+–2HCO_3^-$ co-transport [24,25] mediated by the electrogenic NBCe1-B isoform [26] that accumulates cytoplasmic HCO_3^- and osmolytes. The basolateral Na^+/H^+ exchanger NHE1 [25] and Cl^-/HCO_3^- exchange, likely AE2, control pH_{in} and Cl^-_{in}, which is required for stimulated secretion [27].

The bulk of HCO_3^- exits across the luminal membrane by the interrelated activity of the cAMP-activated Cl^- channel cystic fibrosis transmembrane conductance regulator (CFTR) and the exchanger slc26a6 [3]. Slc26a6, an electrogenic $1Cl^-/2HCO_3^-$ exchanger [28,29], is essential for ductal fluid secretion because it mediates net solute transport in addition to HCO_3^- secretion. Fluid moves osmotically and exits the luminal membrane through AQP1, a process essential for ductal fluid secretion [30]. CFTR has finite HCO_3^- permeability [31] and CFTR-mediated HCO_3^- flux becomes important at the distal portion of the ducts when luminal and cytoplasmic Cl^- are low [3]. Other ductal transporters on the luminal membrane of note are Na^+/H^+ exchanger NHE3 [32] and H^+/K^+ ATPase pump ATP12A [33]. Luminal ATP12A may inhibit H^+ absorption [33], although ATP12A in the airway epithelium actually contributes to the pathology in cystic fibrosis [34], a disease that prominently affects the pancreas. Hence, the role of ATP12A in the pancreatic duct remains to be established. We have suggested that H^+-secreting transporters like NHE3 and perhaps ATP12A function to salvage HCO_3^- in the ductal resting state [32] (Fig. 5.2a).

Ductal secretion is stimulated by the Gs-coupled secretin receptor that transmits its signal by increasing cAMP to activate protein kinase A (PKA) [3]. PKA phosphorylates the R domain of CFTR to activate the channel. CFTR then activates the slc26a6 by interaction of CFTR R domain with the slc26a6 STAS domain [35]. In turn, this interaction further activates CFTR. At the same time, CFTR inhibits NHE3 to prevent H^+ secretion

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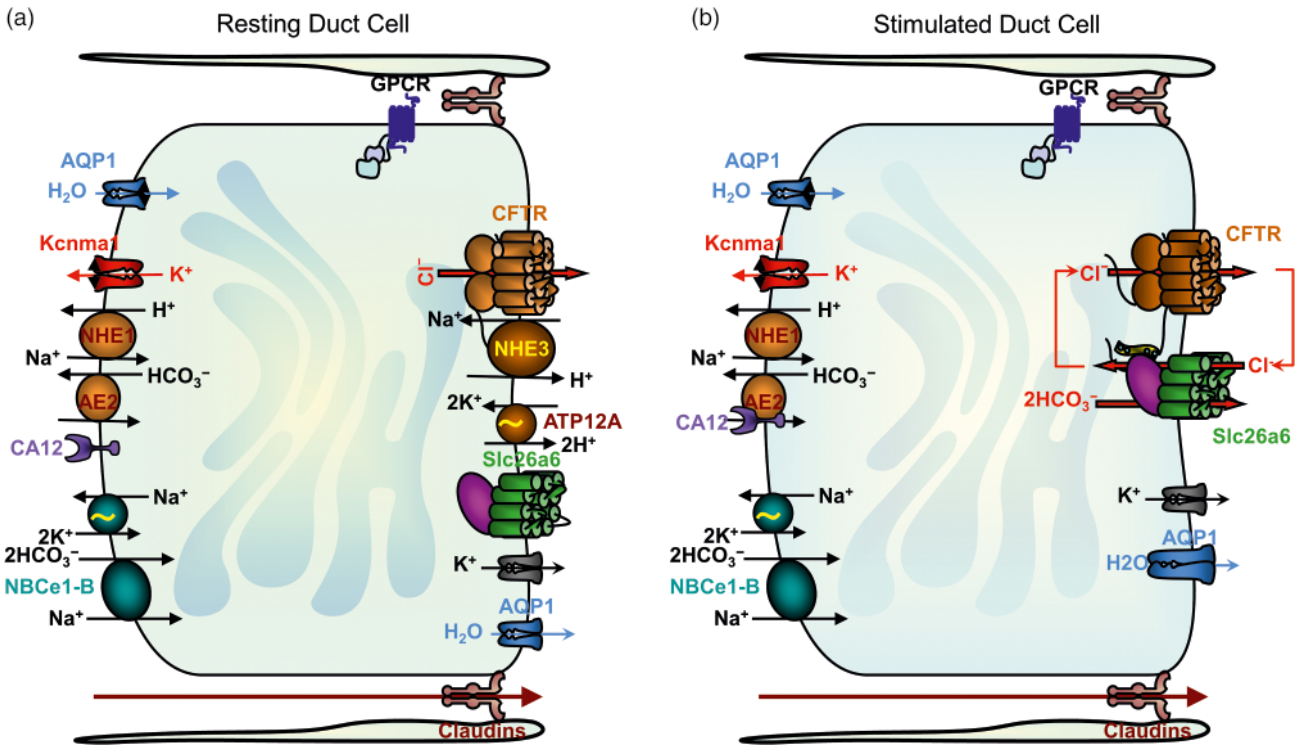


Figure 5.2 Mechanism of fluid and electrolyte secretion by duct cells. The models show the key transporters and the relationships between them in the resting (a) and stimulated ducts (b). The resting duct can secrete H^+ by NHE3 and perhaps ATP12A to salvage HCO_3^-, while slc26a6 is away from CFTR and not active. In the stimulated state the H^+-secreting transporters are inhibited and slc26a6 and CFTR are mutually activated to cause fluid and electrolyte secretion. Osmotic flow of H_2O is through the water channel AQP1.

into the lumen [36]. CFTR recycles the Cl^- absorbed by slc26a6 to maintain HCO_3^- secretion through slc26a6. Net osmolyte secretion by slc26a6 in the form of HCO_3^- together with paracellular Na^+ flow drives osmotic water secretion to generate the final volume of the pancreatic juice.

Regulation of Ductal Secretion

Ductal secretion is dynamically regulated in both resting and stimulated states by kinase and phosphatase pathways and scaffolding proteins. In addition, Cl^-_{in} regulates the transporters that mediate ductal secretion by affecting their activity and selectivity [2]. The resting state is set by the WNK, SPAK/OSR1, and CAMKII kinases [37]. Pancreatic duct cells express CaMKII [38] and mammals have four WNKs [39], with WNK1, WNK3, and WNK4 expressed in the pancreas [3]. The WNKs regulate Na^+, K^+, Cl^-, HCO_3^-, and Ca^{2+} transporters in epithelia by determining their surface expression and activity [39]. SPAK and OSR1 are homologous stress-activated kinases that act downstream of the WNKs, with the WNKs serving as scaffolds to the SPAK/OSR1. The SPAK/OSR1 can affect surface expression, inhibit or activate the ion transporters [40]. Another level of regulation of the WNK kinases is through interaction with kelch-like 3 (KLHL3) and cullin 3 (CUL3), which regulate WNKs level by ubiquitination and degradation [41]. The role of CaMKII in epithelial transport is not well understood, although CaMKII affects the activity of many transporters and channels, such as Ca^{2+} channels [42] and the regulation of NBCe1-B by Cl^- [37].

In the pancreatic duct, the WNK and the SPAK/OSR1 kinases function in the same pathway with the WNKs acting as scaffolds for the SPAK/OSR1 kinases. The WNK/SPAK pathway regulates the ductal NBCe1-B [43], slc26a6 [31], and CFTR [43,44] by inhibiting surface expression and the activity of the transporters. Notably, knockdown of the WNK and of SPAK kinases enhanced stimulated ductal fluid secretion, indicating that the kinases exert tonic inhibition of the secretion [43] to set the basal non-secretory state (see model in Fig. 5.3a). Similarly, by modulating NBCe1-B inhibition by Cl^-_{in}, CaMKII limits HCO_3^- secretion to favor the resting state [37].

The multifunctional protein IRBIT (IP_3 binding protein released with IP_3) regulates the pancreatic duct stimulated, secretory state. IRBIT was discovered as a

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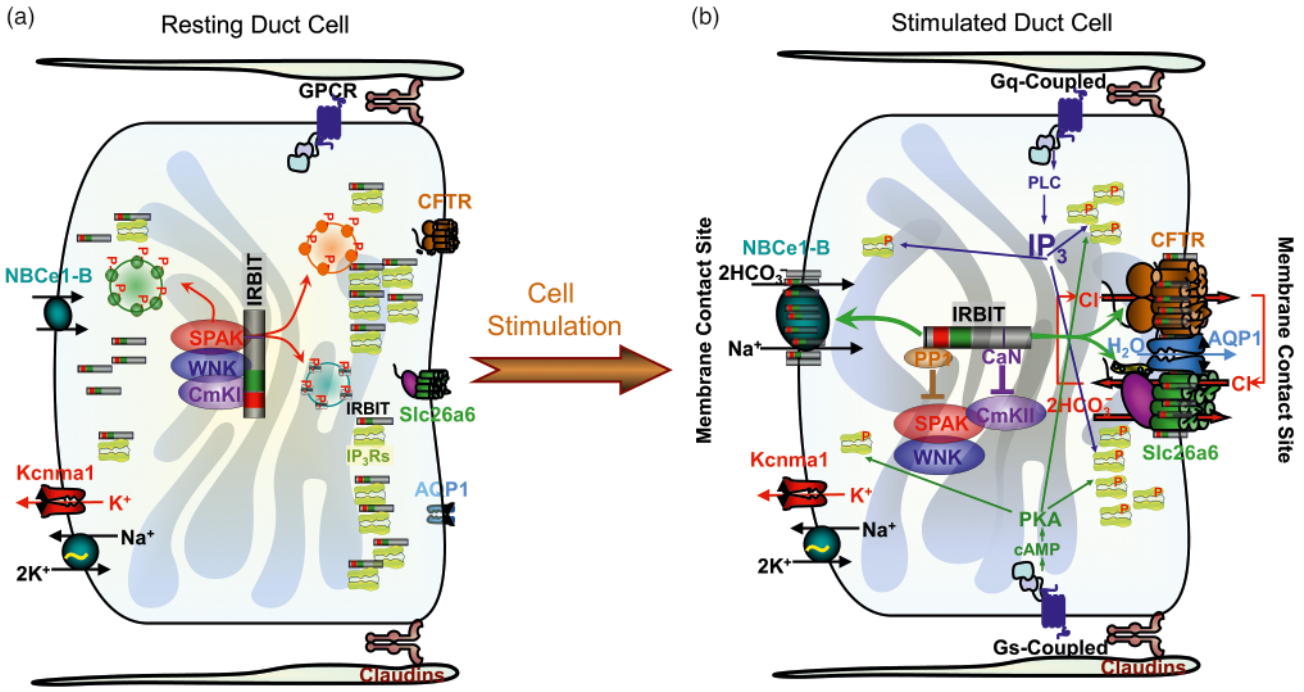


Figure 5.3 IRBIT mediates synergistic activation of the cAMP and Ca^{2+} signaling pathways at membrane contact sites. In the resting state (a), the WNK/SPAK and CaMKII kinases associate with the transporters and SPAK and CaMKII phosphorylate NBCe1-B AID, slc26a6, and CFTR to sequester most of them in intracellular organelles and modulate their regulation by Cl^-_{in}. IRBIT is sequestered by the IP_3 receptors but also aids in association of the kinases with the transporters. When the cells are stimulated (b) with physiological concentrations of IP_3 and cAMP generating agonists, PKA phosphorylates the IP_3R to facilitate release of IRBIT from the IP_3R by IP_3 and IRBIT localizes to membrane contact sites. IRBIT recruits PP1 and CaN to the transporters to dephosphorylate them at the SPAK and CaMKII phosphorylation sites and target them to the plasma membrane at membrane contact sites. IRBIT remains bound to the transporters' autoinhibitory domains and further activates the transporters and ductal secretion.

protein that binds to the IP_3 receptors (IP_3Rs) [45] and as an activator of NBCe1-B [46]. IRBIT has an N terminus protein phosphatase 1 (PP1) binding motif, a PEST domain, a coiled-coil domain, calcineurin (CaN) binding motif and a PDZ ligand at the end of the C-terminus [37,47]. The coiled-coil domain participates in activation of target proteins by IRBIT [48] and the PDZ ligand locates IRBIT close to the HCO_3^- transporters [43] and at membrane contact sites (MCS) [49]. IRBIT activates transporters by two mechanisms, increasing their surface expression and transport activity, and perhaps by assembling them into complexes at MCS. This is best understood with NBCe1-B. The first 85 residues of NBCe1-B form an autoinhibitory domain (AID) [50]. IRBIT interacts with the AID to prevent the NBCe1-B self-inhibition [46]. In addition, IRBIT reverses the inhibition of NBCe1-B by WNK/SPAK and by CaMKII through recruiting PP1 and CaN to the transporter, which dephosphorylates the SPAK phosphorylated Ser65 [37,51].

IRBIT also interacts with and potently activates CFTR [43,48] and slc26a6 [51] by interacting with a sequence similar to the NBCe1-B AID that is present in CFTR R domain and slc26a6 STAS domain [51]. Indeed, IRBIT similarly recruits the PP1 to NBCe1-B, CFTR, and slc26a6 [43,51]. The key role of IRBIT in ductal secretion was established by showing that knockout of IRBIT in mice markedly inhibits ductal fluid secretion. The reduced secretion due to IRBIT knockdown was partially recovered by knockdown of SPAK [43], showing the interplay between the IRBIT/PP1 and the WNK/SPAK pathways in modulating ductal secretion, as illustrated in Fig. 5.3b.

HCO_3^- secretion depends on strict regulation of both intracellular and surface membrane HCO_3^- concentrations that are determined by carbonic anhydrases (CA). CA are either cytoplasmic or membrane anchored with their active site at the extracellular cell surface [52]. The surface CA control the supply or the removal of HCO_3^- at the surface of the plasma membrane and the cytoplasmic CA buffer cytoplasmic HCO_3^-. The plasma membrane localized CA interact with many H^+ and HCO_3^- transporters [53]. We know very little about the role and molecular identity of the CA that are important in ductal secretion. Some information became available from human disease in which mutations in CA12 causes

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salt wasting [54,55]. CA12 is a critical activator of AE2 and ductal secretion. Deletion or mutation in CA12 inhibits its ductal secretion by about 50% and overexpression of CA12 markedly increases ductal secretion [27]. Hence, activation of CA12 is a potential treatment of ductal hypofunction.

Another prominent regulator of ductal function is Cl^-_{in}. Cl^-_{in} has a key role in ductal function by driving HCO_3^- secretion through slc26a6, controlling the luminal membrane potential through CFTR and of pH_{in} through AE2 (Fig. 5.2). Sensing Cl^-_{in} is therefore essential for tuning the secretory process. Cl^-_{in} regulates the function of multiple channels and transporters by functioning as a signaling ion [2]. Cl^- regulates the activity of at least two HCO_3^- transporters, NBCe1-B and CFTR. Cl^-_{in} controls HCO_3^- permeability of CFTR by affecting the function of WNK1 [31,56]. Once Cl^-_{in} is below 8 mM, CFTR becomes the HCO_3^- channel to increase HCO_3^- concentration of pancreatic juice from 120 to 140 mM [57]. A more dramatic regulation by Cl^-_{in} is seen with NBCe1-B. IRBIT-activated NBCe1-B is regulated between 5 and 20 mM Cl^-_{in} [58]. Ductal secretion starts when resting Cl^-_{in} is about 35 mM and decreases to 4 mM toward the latter phase of Cl^- absorption and HCO_3^- secretion [3,59]. At Cl^-_{in} above 20 mM, 70% of NBCe1-B activity is inhibited, which is sufficient to support HCO_3^- secretion at the proximal duct. As demand for cytoplasmic HCO_3^- increases in the face of accumulation of luminal HCO_3^-, Cl^-_{in} is reduced toward 4 mM to increase the activity of NBCe1-B threefold [58], which ensures continued HCO_3^- supply.

The Ca^{2+} and cAMP Pathways Synergize to Activate Ductal Secretion

Synergism between signaling pathways is a fundamental concept in biology that serves to prevent cell toxicity by overstimulation. Signaling pathways function at 1–5% of capacity and synergize to generate the maximal physiological response. The Ca^{2+} and cAMP signaling pathways synergize in a mechanism mediated by IRBIT [51]. At the resting state IRBIT is bound to IP_3 receptors. Physiological stimulation increases ductal cAMP to phosphorylate the IP_3R to increase their affinity for IP_3 and reduce their affinity for IRBIT [51]. A small increase in IP_3 by physiological stimulation with Ca^{2+}-mobilizing receptors releases IRBIT from the IP_3R that then binds to CFTR, slc26a6, and NBCe1-B to activate them and ductal secretion [51]. This important physiological mode of synergism is illustrated in Fig. 5.3.

Ductal Secretion-Associated Pancreatic Diseases

Ductal fluid and HCO_3^- secretion not only wash digestive enzymes to the intestine, but also protect the parenchyma from damage due to stresses to the pancreas. In addition, as a chaotropic ion, HCO_3^- is essential for solubilization of macromolecules like digestive enzymes and mucins and divalent ions in biological fluids [3,60]. The duct is the first line of defense of the pancreas that must be breached before damage to acinar cells takes place. Indeed, damage to ductal secretion occurs in several diseases of the pancreas, including cystic fibrosis (CF) and pancreatitis. CF leads to destruction of the pancreas and pancreatic insufficiency [61] due to inhibition of ductal fluid and HCO_3^- secretion [3]. Moreover, several studies have identified mutations in CFTR that are associated with chronic pancreatitis [62] and specifically inhibit CFTR-dependent HCO_3^- transport [56,63] and permeability [56], independent of Cl^- channel activity [56]. The importance of the duct in protection of the pancreas and of CFTR in ductal function [64] led to the examination of the state of CFTR in chronic autoimmune [65] and alcoholic pancreatitis [65,66], which revealed mislocalization of CFTR in these forms of pancreatitis. Notably, treatment of autoimmune pancreatitis with corticosteroids ameliorated the disease primarily by increasing ductal HCO_3^- secretion [65]. In animal models, induction of acute pancreatitis by cerulein stimulation, bile duct infusion, and alcohol treatment impaired ductal function [67]. Finally, the chronic pancreatitis model NOD mice and the autoimmune pancreatitis model of poly IC in MRL/Mp-Fas mice showed markedly reduced expression of CFTR. Notably, treatment with CFTR correctors restored CFTR expression, ductal function, pancreas integrity, and most notably, acinar cell functions [68]. Similarly, CFTR correctors and potentiators reduced the severity of pancreatitis in a cerulein acute pancreatitis model [69]. These findings suggest that CFTR correctors should be considered as a safe and effective treatment for pancreatitis.

The intimate involvement of the duct in the health of the pancreas and pancreatic diseases suggests that the duct should be a prime target for therapy. There are several potential targets. One could be activators of IRBIT together with inhibitors of the WNK/SPAK/OSR1 kinases. Because of their involvement in renal salt homeostasis and hypertension [41], such drugs may became available in the future. Another potential target is CA12 that affects ductal function [27] and is modified in several cancers [70]. Drugs affecting CA12 activity are being developed in the cancer field and

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may become useful for the treatment of pancreatitis. A very promising option is the use of CFTR potentiators and correctors that are approved for the treatment of CF [71]. These drugs repair CFTR localization and increase ductal secretion to slow progress of the disease in animal models and further improve the function of acinar cells. These drugs are effective in humans and in CF patients by increasing pancreatic and acinar cells function, although they increased slightly the incidents of acute pancreatitis in pancreatic sufficient patients [72,73].

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6

Physiology and Pathophysiology of Function of Sphincter of Oddi

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Introduction

The presence of gallbladder and biliary tract was described in some of the earliest recorded observations of humans [1], but their role in digestion was not appreciated until much later. In the sixteenth century, a membrane near the distal end of the common bile duct thought to impede reflux of duodenal contents into the bile duct was described but it was not until 1887 that this structure was described as a sphincter and named after Rugero Oddi, who published a detailed description of its anatomy as a result of dissections undertaken while studying medicine [2]. The physiological role of the sphincter of Oddi was further appreciated after the hormone cholecystokinin (CCK) was shown to contract the gallbladder and reduce sphincter of Oddi resistance. These and subsequent studies firmly established that an intimate relationship existed between gallbladder contraction, sphincter of Oddi function, and the flow of bile and pancreatic juice into the duodenum.

Anatomy and Morphology

The terminal parts of the common bile duct and pancreatic duct, the common channel, and major duodenal papilla of Vater are invested by varying thickness of smooth muscle that together form the sphincter of Oddi segment (Fig. 6.1). The major part of the human sphincter of Oddi lies within the duodenal wall, and is anatomically and functionally independent of the duodenal muscle.

Distinct sphincters have been described at the terminal end of the common bile duct (sphincter choledochus), pancreatic duct (sphincter pancreaticus), and common channel (sphincter ampullae) [3]. However, studies using a combination of radiologic, duct cast techniques, and histologic sectioning methods did not distinguish separate sphincters [4], and human autopsy studies have concluded that the common bile duct and pancreatic duct become fused in a common connective tissue sheath outside the duodenal wall and pass together through a slit in the duodenal muscle known as the "choledochal window." However, the lumina do not join at this level but are separated by a thick muscular septum. In most subjects, fusion of the two lumina occurs in the submucosal layer of the duodenum to form a common channel that varies in length between 2 and 17 mm. Before entering the duodenum, each duct becomes completely surrounded by circular muscle, some of which forms a figure-of-eight pattern around the two ducts. The point at which the smooth muscle starts on each duct is readily identified radiologically as a notch. Distal to the notch each lumen becomes narrow as it traverses the duodenal wall, this narrowing being associated with a thickening of the duct wall due to smooth muscle, connective tissue, and mucous glands. As the ducts pass through the duodenal wall longitudinal muscle, fibers interdigitate between the circular ductular muscle fibers and the duodenal muscle. The ducts emerge from the duodenal muscle layers and pass through the duodenal submucosa for a variable distance before opening onto the papilla of Vater; throughout this submucosal course, the ducts are ensheathed by circularly oriented smooth muscle. Manometric studies in humans support Hand's description of the sphincter of Oddi in that separate sphincteric zones have not been identified [5].

The mucosa of the human sphincter of Oddi segment is lined by columnar epithelium and contains numerous

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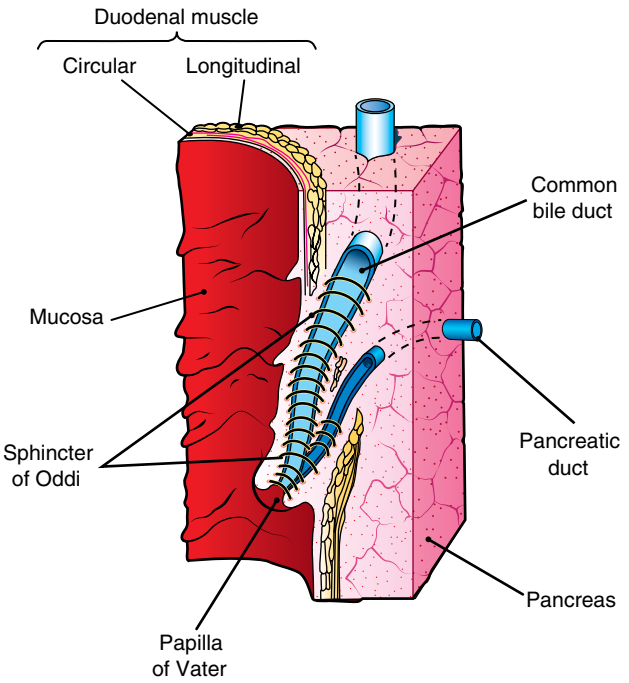


Figure 6.1 Anatomy of the human sphincter of Oddi at the junction of the bile and pancreatic ducts with the duodenum.

mucus-secreting glands. The mucosa is thrown into longitudinal folds likened to mucosal valvules [6]. These folds are least marked proximally and increase distally, becoming maximal in the common channel. The mucosal folds may occasionally be seen projecting through the orifice of the duodenal papilla.

Innervation

The extrahepatic biliary tract is innervated by dense networks of extrinsic and intrinsic nerves that regulate smooth muscle tone and epithelial cell function of the extrahepatic biliary tree. The celiac ganglia contribute both motor and sensory nerves made up of sympathetic fibers that originate in the T7–T10 spinal segments. The hepatic plexus is formed by nerve fibers from both vagi and supplies parasympathetic motor nerves to the extrahepatic biliary system [7].

The wall of the biliary tract is composed of three layers, namely serosal, muscularis, and mucosal. Ganglionated nerve plexuses are located in the subserosal and the subepithelial layers. The sphincter of Oddi has a rich ganglionic plexus. It has a predominance of cholinergic ganglia and a smaller number of adrenergic ganglia. Immunohistochemical studies from our laboratory have demonstrated the presence of a wide range of peptidergic neurons in the sphincter region, including galanin-, substance P-, and somatostatin-containing nerves. In addition, the inhibitory transmitter nitric oxide has been demonstrated in nerves to the sphincter and is thought to have an important function in modulating sphincter relaxation. It has been shown that the nerves in the sphincter region communicate with the proximal biliary tract, the gallbladder, and the duodenum [8,9].

Physiology

Bile reaches the sphincter of Oddi via the common hepatic and common bile ducts. The sphincter of Oddi not only regulates the flow of bile and pancreatic juice into the duodenum, it is also the regulatory structure that prevents reflux of duodenal contents into the pancreatobiliary passages. The role of the common bile duct in the control of bile flow has been confused due to anatomic differences in species studied. Histologic studies in humans have demonstrated only thin longitudinally oriented layers of smooth muscle within the walls of the common bile duct [10]. The major tissue component appears to be elastic fibers. However, in other species such as sheep, the common bile duct is invested with circularly oriented smooth muscle that exhibits peristaltic activity.

The weight of evidence suggests that the human common bile duct does not have a primary propulsile function. However, the elastic fibers and the longitudinally oriented smooth muscle provide a tonic pressure that may help overcome the tonic resistance of the sphincter of Oddi. The diameter of the human common bile duct before and after cholecystectomy has been the subject of controversy. Part of the disagreement is due to the methodology used in determining duct size. It has become evident that duct size as determined by ultrasonography and magnetic resonance cholangiography (MRC) cannot be equated to duct size determined by endoscopic retrograde cholangiopancreatography (ERCP) or intraoperative extraluminal measurements. Ultrasound and MRC record the nondistended lumen, whereas the contrast used during ERCP produces distension. Intraoperative measurements include wall thickness. In general, the normal diameter of the common bile duct as determined by ultrasound is less than 6 mm, by ERCP, less than 10 mm, and by intraoperative extraluminal measurements less than 12 mm. What has become clear is that the common bile duct does not increase in diameter significantly following cholecystectomy [11,12]. The major cause of dilated common bile duct is increased intraluminal pressure, which generally is produced by either primary or secondary obstruction at the sphincter of Oddi.

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Motility of the Sphincter of Oddi

The primary function of the sphincter of Oddi is to control the delivery of bile and pancreatic juice into the duodenum. This is possible because of low pressure within the bile duct. Approximately 800–1500 mL of bile flows through the human sphincter of Oddi. Various studies in animals and humans have tried to evaluate the mechanism by which the sphincter of Oddi controls the flow of bile and pancreatic secretions. These studies have shown that there is anatomic variability between species and that sphincter of Oddi motility differs from one species to another. Thus, while many commonalities exist, one needs to be circumspect in comparing animal data directly with the motility and function of the human sphincter of Oddi.

Sphincter of Oddi Motility Studies in Animals

In vivo studies in dogs, cats, rabbits, and monkeys have demonstrated that the sphincter of Oddi exhibits muscle contractions that are independent of duodenal activity. The common bile duct and pancreatic duct proximal to the sphincter do not demonstrate spontaneous motor activity. Results from the dog studies have suggested that the sphincter of Oddi has a milking effect on bile, thus propelling small volumes of fluid from the common bile duct into the duodenum [13]. Manometric and electromyographic studies of the opossum sphincter of Oddi have demonstrated that the predominant mechanism of common bile duct emptying in the opossum is the antegrade sphincter of Oddi phasic contractions that propagate the entire length from the cephalic to the caudal end [14,15]. However, the frequency of the phasic contractions varies periodically during fasting. In cats, cholecystokinin (CCK) inhibits the sphincter phasic contractions and produces a fall in sphincter tone by stimulation of nonadrenergic noncholinergic inhibitory neurons—this effect overriding a lesser, direct smooth muscle stimulatory action of the hormone [16].

Recent studies have shown that the sphincter may act as a pump or a resistor and that bile duct pressure influences it [17]. This intrinsic activity is controlled by interstitial nerves of Cajal and is modulated by hormones [16], ATP and adenosine [18], and nitric oxide [19].

Neurohistochemical studies have demonstrated both adrenergic and cholinergic neurons within the sphincter of Oddi and experiments in animals have determined the pharmacologic effects of histaminergic, cholinergic, and adrenergic stimulation on the sphincter muscle [14]. However, the physiologic significance of these drug actions on the sphincter of Oddi requires further investigation.

The function of the vagus nerve in sphincter of Oddi physiology remains obscure. Sphincter of Oddi neurons likely receive vagal input and their activity is modulated by release of neuropeptides from sensory fibers, a significant source of excitatory synaptic input to these cells arising from the duodenum. This duodenum–sphincter of Oddi circuit is likely to play an important role in the coordination of sphincter of Oddi tone with gallbladder motility in the process of gallbladder emptying [20]. Studies in dogs have suggested that following vagal transection the resistance to flow across the sphincter of Oddi is decreased [21]. However, in the prairie dog increased resistance to flow through the sphincter of Oddi occurs after truncal vagotomy. Results from vagal stimulation studies have failed to define clearly the role of the vagus in biliary dynamics.

The Australian possum sphincter of Oddi demonstrates activity similar to that of the human sphincter. In this species, inhibition of sphincter phasic contractions promotes flow of bile. It has been shown that this inhibition is mediated by neural release of nitric oxide [16]. There is evidence that nitric oxide mediates the cerulein- and CCK octapeptide-mediated relaxation of the canine sphincter of Oddi [22]. The neuropeptide, galanin, selectively stimulates longitudinally oriented sphincter of Oddi smooth muscle via a direct mechanism, leading to a moderate reduction in trans-sphincteric flow [23]. Table 6.1 illustrates the effects of various bioactive agents on the sphincter of Oddi.

Table 6.1 Effects of various bioactive agents on the sphincter of Oddi.

Stimulators
Morphine met-enkephalin
Galanin
Substance P
Cholecystokinin
Neuropeptide Y
Nitric oxide
Inhibitors
Tramadol
Glucagon
Calcitonin gene-related peptide
Cholecystokinin
Peptide YY
Somatostatin

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Sphincter of Oddi Motility in Humans

Cineradiographic studies of the human sphincter of Oddi exhibit rhythmic contractions that propel contrast into the duodenum [24]. Sphincter of Oddi pressure studies conducted at the time of biliary tract surgery have demonstrated variations in pressure thought to be the manometric equivalent of the cineradiographic contractions [25]. Resistance to outflow of fluid from the common bile duct into the duodenum has also been demonstrated by the intraoperative studies. This resistance was reduced after administration of CCK octapeptide or smooth muscle relaxants such as amyl nitrite [26].

Manometric recordings from within the sphincter of Oddi segment have been made via a pressure-sensitive catheter introduced into the sphincter of Oddi via a duodenoscope (Fig. 6.2) [27].

The manometric recordings have demonstrated that the human sphincter of Oddi is characterized by prominent phasic contractions superimposed on a basal sphincter of Oddi pressure 3 mmHg above the pressure in the common bile duct and pancreatic duct (Fig. 6.3). The amplitude of the phasic contractions is approximately 130 mmHg and the mean frequency is 4/min. Analysis of the direction of propagation of the phasic contractions during a continuous 3-min period demonstrated that the majority of contractions (60%) are oriented in an antegrade direction from the common bile duct toward the duodenum. A smaller number of contractions occurred either simultaneously (24%) or had a retrograde orientation (15%). Intravenous bolus injection of CCK octapeptide (20 ng/kg) normally produces inhibition of the phasic contractions and a fall in the basal sphincter of Oddi pressure.

Table 6.2 shows the pressures recorded from the sphincter of Oddi of normal subjects. Studies from patients with T-tubes inserted in the common bile duct following bile duct exploration [28] have shown that the frequency of sphincter of Oddi phasic contractions

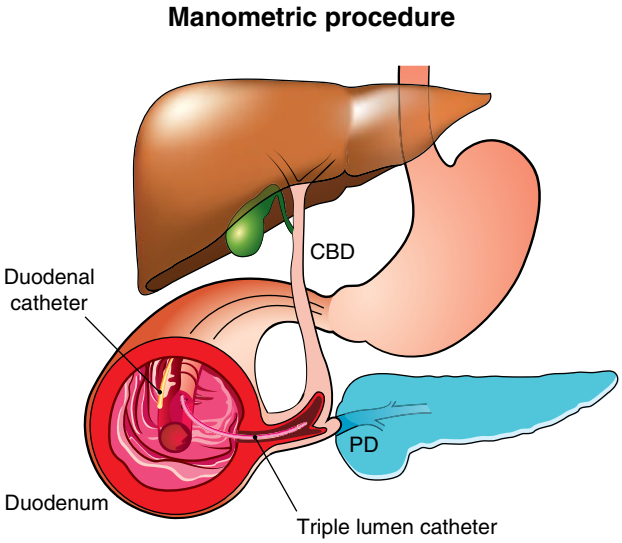


Figure 6.2 Manometric recording from the human sphincter of Oddi. A triple-lumen pressure-sensitive catheter is positioned in the sphincter via the biopsy channel of the duodenoscope. A separate catheter records duodenal pressure. CBD: common bile duct; PD: pancreatic duct.

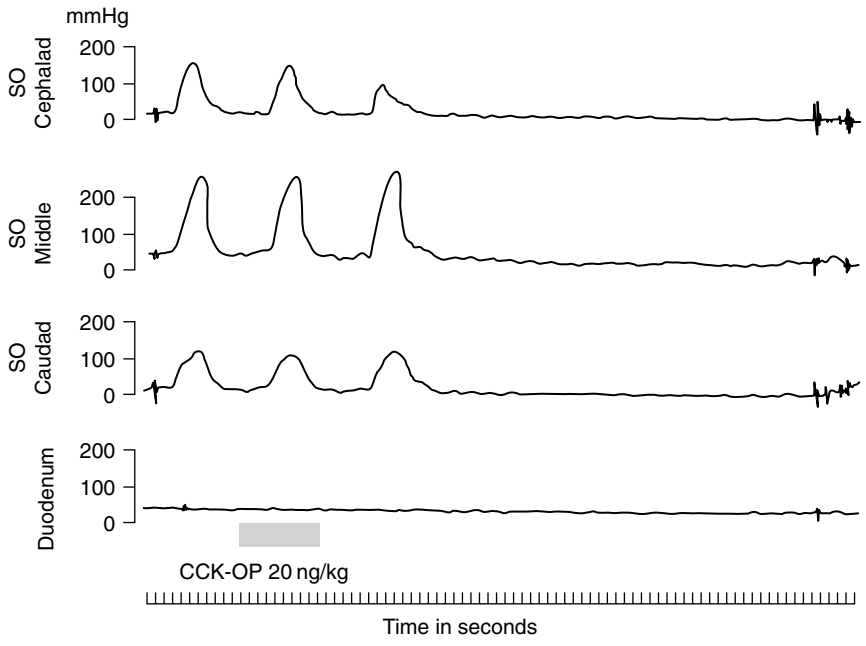


Figure 6.3 Manometric recording from the human sphincter of Oddi (SO) showing prominent phasic contractions, which are inhibited after injection of cholecystokinin octapeptide (CCK-OP).

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during fasting exhibits a periodicity in relation to duodenal migrating motor complexes, similar to that demonstrated in the opossum (Fig. 6.4).

Following the ingestion of a meal, bile flow across the sphincter of Oddi is promoted by inhibition or reduction in the amplitude of the phasic contractions and a fall in the sphincter of Oddi basal pressure. This effect on the human sphincter of Oddi is similar to that following intravenous injection of CCK octapeptide. In humans, bile flow occurs mainly between sphincter of Oddi phasic contractions during the period of diastole. The phasic contractions do propel small volumes of bile into the duodenum, but this is not the major means by which bile flow occurs. The phasic contractions in humans may function to prevent reflux of duodenal contents into either the bile or the pancreatic ducts, and to maintain the ducts free of small debris. In order to promote flow across the human sphincter of Oddi, inhibition or reduction of the phasic contractions and a fall in basal pressure is necessary.

Table 6.2 Pressures recorded from the sphincter of Oddi of normal subjects.

	Normal		
	Median	**Range**	**Abnormal**
Basal pressure (mmHg)	15	3–35	>40
Amplitude (mmHg)	135	95–195	>300
Frequency (/min)	4	2–6	>7
Sequences			
Antegrade (%)	80	12–100	
Simultaneous (%)	13	0–50	
Retrograde (%)	9	0–50	

Pathophysiology of the Sphincter of Oddi Dysfunction (SOD)

The terminology SOD implies motility abnormalities of the sphincter of Oddi associated with pain, elevations of liver or pancreatic enzymes, common bile duct dilatation, or episodes of pancreatitis. The most common presentations of this symptom complex include persistent or recurrent "biliary" symptoms postcholecystectomy (10–20%) [29] or features consistent with idiopathic recurrent acute pancreatitis (abnormal sphincter of Oddi manometry has been recorded in 30.5% [30]).

In 2016, the Rome IV expert consensus [31] updated the diagnostic criteria for sphincter of Oddi disorders [32]. For biliary pain, the Rome IV expert consensus [31] included the criteria listed in Table 6.3, as well as the presence of elevated liver enzymes or dilated bile duct (but not both), in the absence of bile duct stones or other structural abnormalities. The consensus statement also listed supportive criteria the presence of one or more of which, in association with the pain, may help in arriving at the diagnosis. These include abnormal amylase/lipase, abnormal sphincter of Oddi manometry, and abnormal hepatobiliary scintigraphy.

The clinical diagnostic system for SOD is the Modified Milwaukee Classification described for both biliary [33]

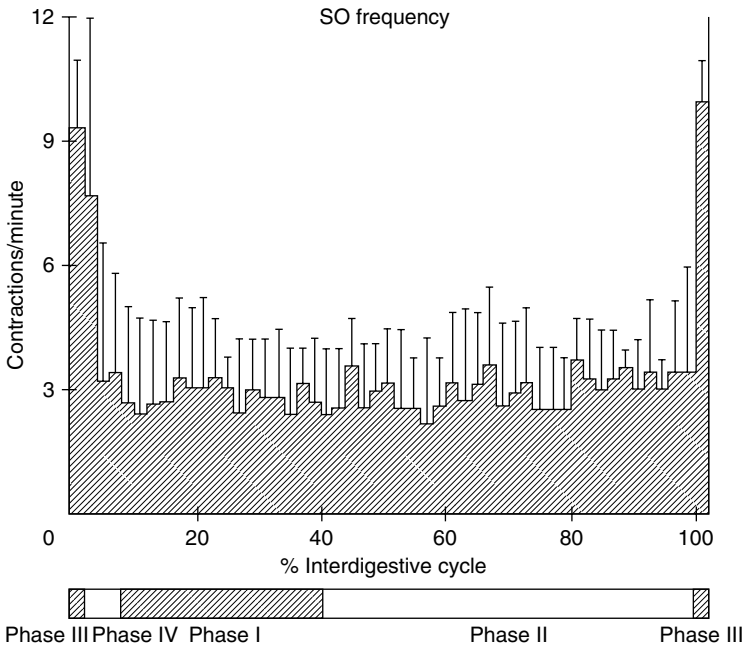


Figure 6.4 Manometric recordings of the human sphincter of Oddi showing changes in frequency of contraction in relation to the duodenal interdigestive motility pattern.

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and pancreatic [34] disorders (Table 6.4). These have been modified from the original Milwaukee Classification proposed by Hogan and Geenen [35]. Pancreatic SOD may be considered in patients with documented acute recurrent pancreatitis, after exclusion of known etiologies for pancreatitis, and documenting elevated pancreatic sphincter of Oddi pressures on manometry [31].

An alternate classification of SOD may be based on manometric recordings. We have previously subdivided SOD into two groups [36], namely, those exhibiting a stenotic pattern (abnormally raised basal sphincter pressure >40 mmHg) and those displaying a dyskinetic pattern including paradoxical response to CCK injection, rapid contraction frequency, high percentage of retrograde contractions, or short periods of raised basal pressure [37]. These patients display an abnormal response to morphine or a fatty meal stimulus. In addition it has been postulated that SOD characterized by a manometric stenosis may contribute to the development of adult choledochal cysts [38,39].

The stenotic subtype of SOD is characterized by pathomorphological changes evident on histological examination of sphincter complexes resected at the time of transduodenal sphincteroplasty for patients with severe postcholecystectomy pain. The changes contributing to the high basal pressure include inflammation of the papilla and its transampullary septum or fibrosis with or without inflammation, papillary cholesterolosis [40], muscle hypertrophy, or mucosal edema [41]. These findings have been reported in 58% of patients undergoing transduodenal sphincteroplasty and transampullary septectomy for postcholecystectomy pain [40] and one possible cause has been postulated to be due to the chronic passage of small gallstones [40]. Another possible cause may be end-stage dyskinetic SOD. The stenotic subtype corresponds to the Modified Milwaukee type 1 and responds best to sphincterotomy (surgical or endoscopic). We have previously demonstrated that surgical sphincteroplasty and septectomy when performed for manometrically confirmed sphincter of Oddi stenosis in patients with recurrent pancreatitis resulted in a good clinical outcome in a majority of patients [42,43].

In a clinical setting, there is no need for manometry prior to ERCP and sphincterotomy for type 1 SOD of either biliary or pancreatic type presentation.

The dyskinetic subtype, conversely, is believed to be the result of a functional or neurohormonal disturbance in the absence of any pathological reproducible abnormalities [36]. Infections such as Cryptosporidium and HIV have also been shown to lead to features of SOD [44]. This subtype corresponds to the type 2 and 3 of the Milwaukee Classification. Sphincter of Oddi manometry is essential to arrive at the diagnosis. The paradoxical response to CCK injection noted by us [41] may be the result of a defect in the enteric nervous system akin to that described for achalasia of the esophagus [45]. While sphincterotomy relieves symptoms of type 1 SOD, it is less effective in alleviating symptoms of this subtype [46]

Table 6.3 Rome IV diagnostic criteria for biliary-type pain
Adapted from [31].

Pain located in the epigastrium and/or right upper quadrant and all of the following:

1) Builds up to a steady level and lasting 30 minutes, or longer
2) Occurring at different intervals (not daily)
3) Severe enough to interrupt daily activities or lead to an emergency department visit
4) Not significantly (<20%) related to bowel movements
5) Not significantly (<20%) relieved by postural change or acid suppression

Supportive criteria: Nausea and vomiting, radiation to the back and/or right subscapular region, and waking from sleep.

Table 6.4 Modified Milwaukee classification for biliary and pancreatic sphincter of Oddi dysfunction.

	Diagnostic criteria	
Classification	**Biliary**	**Pancreatic**
Type 1	A) Biliary-type pain B) Elevated ALT, AST, ALP >1.1 times the upper limit of normal on one occasion C) Bile duct diameter ≥9 mm	A) Pancreatic-type pain B) Serum amylase or lipase level of 1.1 times the upper limit of normal on one occasion C) Duct dilatation of >6 mm in the head and >5 mm in the body of the pancreas
Type 2	A) Biliary-type pain with either B or C in the criteria mentioned in Type 1	A) Pancreatic-type pain with either B or C in the criteria mentioned in Type 1
Type 3	A) Biliary-type pain only without other abnormalities	A) Pancreatic-type pain only without other abnormalities

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase.

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and is associated with a risk of early recurrence of symptoms on follow-up [47]. Following clinical studies over the last decade there has been a change in our understanding of the SOD dyskinetic subtype.

The Rome IV consensus postulates that type 3 SOD is a disorder of "gut–brain interaction" [31]. This view was largely shaped by the findings of the clinical trial entitled "Evaluating Predictors and Interventions of SOD (EPISOD)" [48]. This multicentre randomized controlled trial conducted in seven centers involved the randomization of 214 patient with postcholecystectomy pain and without significant abnormalities on imaging or laboratory studies, with no prior sphincter of Oddi treatment or pancreatitis. Patients either had an endoscopic sphincterotomy or sham therapy irrespective of manometry findings. A significantly higher proportion of patients in the sham-treatment group experienced relief as compared to the sphincterotomy group (37% vs. 23%; $P = 0.01$). These findings persisted at 5-years' follow-up with patients who received a sphincterotomy faring worse-off based on the Patients' Global Impression of Change (PGIC) criteria [49]. The authors recommended that ERCP be undertaken only in patients with a dilated bile duct or significantly deranged liver function tests [50]. This recommendation has been supported by the results of the ERCP for Sphincter of Oddi Disorders (RESPOnD) study [51]. The latter was a prospective longitudinal cohort study that evaluated the benefit of ERCP with sphincterotomy when performed for SOD.

Type 2 SOD is considered a "functional biliary sphincter disorder" by the Rome IV consensus [31] statement and includes those patients who have biliary pain postcholecystectomy with either dilated ducts or elevated liver enzymes. Current data supports the performance of biliary manometry in these patients [46,52] and there remains a role for sphincterotomy in those patients who had demonstrable pre-procedure abnormalities in manometry [53]. The response to sphincterotomy in patients with type 2 SOD is not uniform but demonstrates benefit in a significant number of individuals.

Management of patients with type 3 SOD and those patients with type 2 SOD who do not benefit from a sphincterotomy or in whom manometry findings remain inconclusive is a challenge. Various pharmacologic agents have been used with varying success. These include hyoscine butyl bromide, nifedipine, nitric oxide, octreotide, gabexate mesylate, ulinastatin, trimebutine, amitriptyline, and duloxetine [54–57].

The treatment of pancreatic types 2 and 3 SOD remains speculative. We have elucidated various mechanisms by which galanin may be involved in the pathogenesis of acute pancreatitis [58]. Given the action of galanin on the sphincter of Oddi [23], its contribution to SOD-induced acute pancreatitis [59] is worthy of consideration. Use of galanin antagonists [60–63] may offer a potential therapy in this subgroup of patients.

The causes for pain in SOD remain conjectural. Mechanisms for production of pain may include relative obstruction of flow through the sphincter of Oddi resulting in bile duct or pancreatic duct distension, "ischemic" pain arising from spastic contractions, hypersensitivity of the papilla, and severance of nerves supplying the sphincter of Oddi during cholecystectomy. Other potential explanations may include duodenal-specific visceral hyperalgesia (in type 3 SOD) [64], continuous visceral pain (biliary pain) caused by local inflammatory/sensitizing processes or persistent hyperexcitability of the nociceptive neurons in the central nervous system [65], or other functional gastrointestinal disorders including intestinal dysmotility [66], irritable bowel syndrome (IBS), or non-ulcer dyspepsia.

Summary

The sphincter of Oddi is a small but important complex muscle that modulates flow of bile and pancreatic juice across one of the busiest anatomic junctions of the body. Its motor activity is controlled by an interaction of neuronal and hormonal modulators. In such a complex structure it is not surprising that at times disorders in motility arise and these disorders lead to significant clinical syndromes.

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7

Neurohormonal and Hormonal Control of Pancreatic Secretion

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Introduction

The pancreas, one of the most important organs in the digestive tract, has both exocrine and endocrine functions. The exocrine pancreas secretes digestive enzymes and HCO_3^- to facilitate digestion and absorption of nutrients. The endocrine pancreas releases hormones that regulate metabolism and the disposition of the breakdown products of food.

The human pancreas secretes about 1 liter of juice daily, containing mostly water, electrolytes, and digestive enzymes. Mediation of postprandial pancreatic secretion has been ascribed mainly to the hormones secretin and cholecystokinin (CCK) and to vagovagal reflexes that activate cholinergic postganglionic neurons in the pancreas. In addition to these classical pathways, other regulatory peptide hormones and neurotransmitters may be involved.

Stimulation of Pancreatic Secretion

Hormonal Mechanisms

Secretin

Secretin is the most potent and efficacious stimulant of pancreatic fluid and HCO_3^- secretion in humans and all other species tested. It is synthesized by small intestine S-type enteroendocrine cells and is released postprandially. Duodenal pH is the major regulator of secretin release. A threshold pH of 4.5 triggers secretin release and stimulates pancreatic HCO_3^- secretion [1,2]. Below this pH, pancreatic HCO_3^- output is related to the total amount of titratable acid presented to the duodenum. Secretin levels in humans increase only a few picomolars postprandially because food buffers much of the gastric acid and pancreaticobiliary secretion neutralizes the remaining acid entering the duodenum by [3]. The mechanism by which acid stimulates secretin release is unclear. In rodents it was shown that H^+ may release a secretin-releasing factor into the proximal intestinal lumen to stimulate secretin release [4]. Secretin-producing cells appear to have acid-sensing ion channels belonging to the TRP (transient receptor potential) channel family. Hence, luminal acid likely stimulates secretin release by more than one mechanism.

Nonacid factors may influence postprandial secretin release. Nutrients such as oleic acid and other digestive products of fat can increase plasma secretin levels and pancreatic HCO_3^- secretion [3,5]. Bile in the upper gut can also stimulate secretin release [6]. However, the physiological importance of these nonacid factors in postprandial secretin release is questionable, as the postprandial plasma secretin level does not increase in achlorhydria or in health if meal-induced acid secretion is neutralized with $NaHCO_3^-$.

The pancreas appears highly sensitive to the small amounts of secretin released into the circulation postprandially [3,6]. *In vitro* animal models show that secretin stimulates HCO_3^- secretion by isolated ducts or duct fragments [7,8]. ^{125}I-labeled secretin and autoradiography revealed a secretin-binding site on pancreatic acini and duct cells [3], suggesting that secretin acts directly on the pancreas to stimulate pancreatic secretion. Conversely, *in vivo* studies have shown that the effect of secretin at physiological doses is highly sensitive to atropine [3]. Receptor autoradiography, immunocytochemistry, and electrophysiology demonstrate the presence of secretin receptors in vagal afferent fibers [3,9,10]. Vagal nodose ganglia also contain high-affinity CCK_1 receptors [3]. Injection of a subthreshold dose of CCK-8 (5 pM) significantly enhances the neural response to

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5 pM secretin. This synergistic interaction helps to explain the robust postprandial pancreatic HCO_3^- and enzyme secretion despite a modest postprandial increase in plasma CCK and secretin.

Cholecystokinin

CCK is the other gut hormone that plays an important role in pancreatic secretion. It is synthesized in specific enteroendocrine I cells in the proximal intestine and released by hydrolytic products of digestion such as amino acids and fatty acids [11]. Undigested fat is ineffective, but products of lipolysis such as fatty acids are the most potent stimulants of CCK release [12]. The CCK response to fatty acids is influenced by chain length, saturation, concentration, and total load [13].

Fasting plasma CCK levels are low, averaging about 1 pM in humans [14–16]. Postprandially, plasma CCK concentration increases to 6–8 pM within 10–30 min, then gradually declines to basal levels during the ensuing 3 h [15,16]. Several molecular forms of CCK appear to be released into the circulation postprandially, including CCK-58, CCK-33, CCK-22, CCK-12, and CCK-8 [17]; CCK-58 being predominant in dogs and humans and the only form detected in rats [16–19].

Nutrients may stimulate CCK secretion by a number of mechanisms. In species such as the rat, in which feedback inhibition of pancreatic enzyme secretion occurs, CCK release is mediated by a trypsin-sensitive CCK-releasing peptide [20]. Duodenal peptone stimulates serotonin (5-HT) release from intestinal enterochromaffin cells, which in turn activates submucosal sensory substance P neurons. Signals are then transmitted to cholinergic interneurons and to epithelial CCK-releasing peptide-containing cells by way of cholinergic secretomotor neurons [20]. CCK release may be controlled by the level of active intraluminal proteases [16]. Protein, the major food stimulant of CCK secretion in rats, may bind or inhibit intraluminal endopeptidases, which would otherwise inactivate the CCK-releasing peptide [21] (Fig. 7.1). The mechanisms responsible for the actions of CCK-releasing peptide in humans are unclear, but may be similar to rats as feedback regulation of CCK release by proteases also occurs in humans. Study of CCK secretion from purified CCK-producing cells shows that amino acids stimulate CCK release by binding to the Ca^{2+}-sensing receptor [22], whereas fatty acids bind to specific G-protein–coupled fatty acid receptors [23]. Thus CCK secretion may be mediated by more than one mechanism.

CCK plays an important role in the stimulation of postprandial pancreatic enzyme secretion. The infusion of physiological doses of CCK produces the same level of pancreatic enzyme secretion as during the postprandial state [24]. Furthermore, administration of the potent CCK antagonist lorglumide or MK-329 produces a 50–60% inhibition of meal-stimulated pancreatic secretion in dogs [25] and humans [26]. CCK can also stimulate fluid and HCO_3^- secretion [27]. The effect on HCO_3^- secretion is weak but physiologically relevant because CCK potentiates the action of secretin on the pancreas [28]. In intact dogs and humans, CCK-stimulated pancreatic enzyme secretion is not potentiated by secretin [24,29,30]. The mechanisms by which CCK stimulates pancreatic enzyme secretion remain

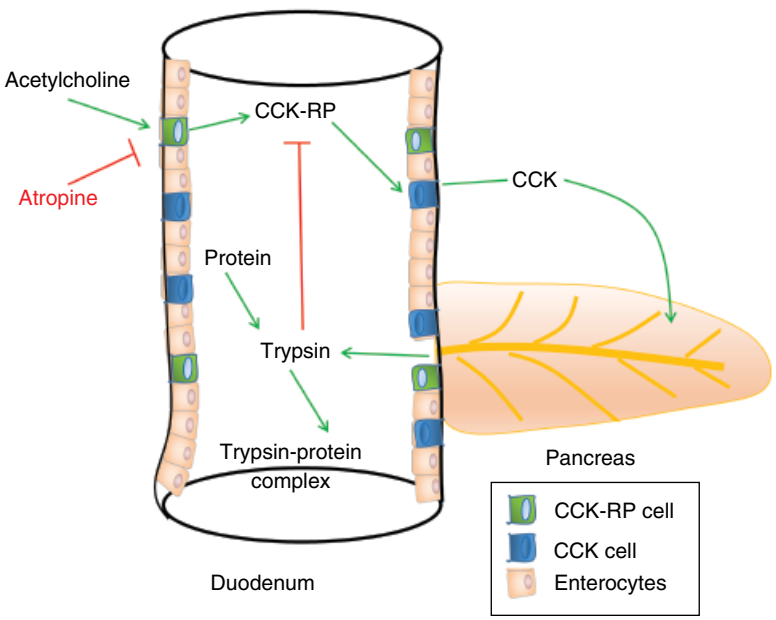


Figure 7.1 Cholecystokinin (CCK)-releasing peptide (CCK-RP) stimulation of postprandial secretion. CCK-RP is secreted into the proximal small intestine under the influence of cholinergic pathway and inactivated by trypsin. When food enters the duodenum postprandially, protein binds to trypsin and prevents the inactivation of CCK-RP. CCK-RP stimulates CCK cells in the duodenum to release CCK into the bloodstream. CCK, in turn, stimulates pancreatic enzyme secretion.

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controversial. *In vitro* studies using dispersed rat pancreatic acini show that CCK-stimulated amylase release is insensitive to atropine or tetrodotoxin, indicating a direct action on pancreatic acini [31]. However, *in vivo* studies of humans and dogs have shown that atropine can block CCK-stimulated pancreatic secretion, implying involvement of cholinergic pathways [31]. Furthermore, enzyme output in response to low-dose CCK is reduced after vagotomy [31]. It appears that CCK can act through atropine-sensitive and atropine-insensitive pathways to stimulate pancreatic exocrine secretion. Human studies have shown that CCK-8 infusions at physiological doses can stimulate pancreatic enzyme output predominately in an atropine-sensitive fashion [31]. Furthermore, studies in rats indicate that physiological doses of CCK act through stimulation of vagal afferent pathways originating from the duodenal mucosa [31] (Fig. 7.2). CCK receptors have been detected in the rat vagus nerve using *in vitro* autoradiography [16]. Vagal CCK_1 receptors exist in high- and low-affinity states [16]. Under physiological conditions, CCK appears to act through high-affinity vagal CCK_1 receptors to mediate pancreatic enzyme secretion [16]. In contrast, the effect of CCK on satiety is mediated by low-affinity vagal CCK receptors [16]. These findings suggest that different affinity states of the vagal CCK receptors mediate different digestive functions. Under physiological conditions, CCK seems to stimulate postprandial pancreatic enzyme secretion through cholinergic pathways rather than through direct action on pancreatic acinar cells. M1 and M3 muscarinic receptors on pancreatic acini appear to mediate these responses [32,33] (Fig. 7.2). The molecular cloning of the CCK receptor gene and subsequent recognition that its expression is virtually absent in human pancreas [16,34] suggests that CCK acts at an extrapancreatic site. One study indicates that human acini do not respond to CCK agonists, although they respond to a muscarinic agonist [16]. In contrast, acini responded to CCK agonists after adenovirus-mediated CCK receptor gene transfer [16]. Quantitative reverse transcription–polymerase chain reaction showed that CCK_1 receptor mRNA expression was ~30-fold lower than that for CCK_2 receptors, and ~10-fold lower than for M_3 muscarinic receptors. In situ hybridization did not detect CCK_1 receptor mRNAs in adult human pancreas, supporting the concept that CCK acts at an extrapancreatic site to stimulate enzyme secretion. By contrast, a study of isolated human pancreatic acini showed that physiological levels of CCK induced Ca^{2+} signaling, activated mitochondrial function, and stimulated enzyme secretion [35]. The physiological relevance of these observations is unclear. CCK_1 receptors are expressed in human pancreatic stellate cells, which lie near acinar cells [36]. Low CCK concentrations (20 pM)

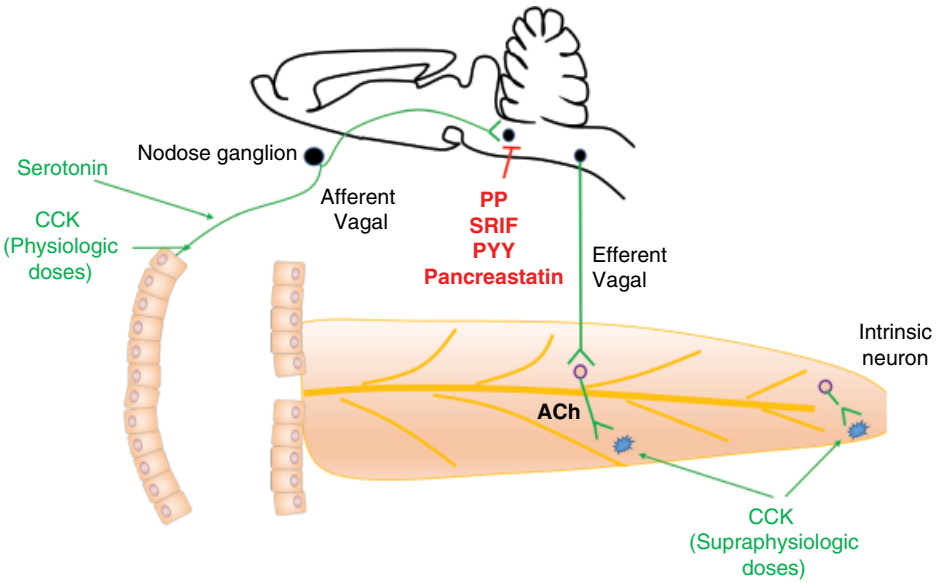


Figure 7.2 Sites and mechanisms of action of stimulatory and inhibitory hormones to modulate pancreatic enzyme secretion. Dosages of cholecystokinin-8 (CCK-8) that produce physiological plasma CCK levels act through stimulation of the vagal afferent pathway, which originates from the gastroduodenal mucosa. In contrast, dosages that produce supraphysiological plasma CCK levels act on intrapancreatic neurons and, to a lesser extent, on pancreatic acini. Serotonin (5HT) another stimulatory hormone also acts via vagal afferent pathway to evoke pancreatic enzyme secretion. In contrast, most of the inhibitory hormones such as PP, SRIF, PYY, and Pancreastatin act at a central vagal site to inhibit pancreatic secretion. ACh: acetylcholoine; PP: pancreatic polypeptide; SRIF: somatostatin; PYY: pancreatic polypeptide YY.

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stimulate acetylcholine release, which evokes enzyme secretion from pancreatic acini. Thus, it appears that CCK may regulate cholinergic stimulation of the pancreas through both neural and nonneural pathways.

Serotonin

Apart from CCK, intestinal serotonin (5-HT) appears to play an important role in mediating postprandial pancreatic enzyme secretion [16]. Although 5-HT is found in the myenteric plexus, the major source of 5-HT in the gastrointestinal tract appears to be mucosal enterochromaffin cells [37]. 5-HT is released in response to various stimuli [37], including duodenal acidification [37], instillation of hypertonic glucose, sucrose, or maltose solutions [16,38], vagal stimulation [39], and mechanical stimulation [40]. 5-HT may increase the discharge of vagal afferent fibers from the stomach and proximal intestine [41,42], which in turn can stimulate pancreatic secretion by way of a vagovagal reflex mediated by a cholinergic afferent pathway [16]. *In vivo* studies show that vagal responses to luminal osmolarity and the digestion products of carbohydrates depend on the release of endogenous 5-HT from mucosal enterochromaffin cells, which acts on 5-HT_3 receptors on vagal afferent fibers [16] (Fig. 7.2).

5-HT and CCK are the principal mediators of postprandial enzyme secretion. A CCK_1 receptor antagonist inhibited 54% of postprandial protein secretion in rats. CCK_1 receptor and 5-HT_3 antagonists combined almost completely abolished exocrine pancreatic secretion [16], suggesting that 5-HT–dependent pancreatic stimulants account for about 50% of postprandial pancreatic secretion. Vagal CCK and 5-HT receptors act synergistically to mediate pancreatic secretion [16], explaining how a small increase in the plasma CCK level is sufficient to produce a robust postprandial pancreatic secretion.

Other Hormones and Stimulatory Factors

Insulin plays a significant role in modulating exocrine pancreatic secretion [43]. Animal studies have demonstrated that insulin potentiates the secretory response of secretin plus CCK [44], and that ouabain, an inhibitor of Na^+,K^+-ATPase activity, abolishes the stimulatory action of insulin. Physiologically, the actions of insulin are important because immunoneutralization experiments in conscious rats showed that pancreatic secretion of water, HCO_3^-, and protein stimulated by a meal or by a combined intravenous infusion of physiological doses of secretin and CCK is markedly reduced when the circulating insulin is neutralized with a rabbit anti-insulin antibody [45]. It is well known that pancreatic enzyme secretion is often reduced in diabetes without overt pancreatic disease [46]. This may be mediated by enhanced activation of the TRESK K^+ channel in the nodose ganglia, observed in rats with diabetes [47] or fed a high-fat diet, reducing the excitability of the nodose ganglia and contributing to decreased pancreatic secretion mediated by the vagovagal reflex [47].

Bombesin (a gastrin-releasing peptide in mammals), a polypeptide isolated from the skin of frogs and also found in the human digestive tract, stimulates pancreatic secretions that contain small amounts of HCO_3^- and high concentrations of enzymes in humans [48,49]. Bombesin can act directly on the pancreas, or indirectly by promoting CCK release from the small intestinal mucosa [50]. In other systems, bombesin reportedly exerts its effect by way of a cholinergic pathway [51]. Hence, bombesin may act through different pathways to stimulate pancreatic secretion. However, the physiological importance of bombesin in pancreatic secretion is uncertain as bombesin receptor antagonists do not influence postprandial enzyme secretion in mammals [52].

Neurotensin appears to stimulate pancreatic enzyme secretion in humans and dogs. In rats, the stimulation appears to be neurally mediated, involving cholinergic vagal afferent pathways. Neurotensin is released by intestinal fatty acids, suggesting a role in mediating fat-stimulated pancreatic secretion. However, exogenous infusion of neurotensin in doses that stimulate pancreatic secretion results in a plasma level much higher than after a normal meal [53,54].

Ghrelin, found in gastric endocrine cells and in neurons of the hypothalamic arcuate nucleus, has been shown to stimulate pancreatic enzyme secretion. It acts as an endogenous ligand for the growth hormone secretagogue receptor, which is found throughout the body, including the hypothalamus and the pancreatic islet and acinar cells. Depending on the animal species, ghrelin acts directly on acinar cells or centrally through the vagal cholinergic pathways [60].

Nitric oxide (NO) is present in pancreatic neurons and vascular endothelium [61], and appears to play a significant role in regulating pancreatic secretion. In humans, L-NAME, an inhibitor of NO production, dose dependently reduces enzyme secretion stimulated by secretin and cerulein [62]. *In vitro*, NO synthase inhibition has no effect on amylase release or intracellular Ca^{2+} concentration in rat pancreatic acinar cells stimulated by carbachol and CCK-8 [63]. L-NAME also reduces CCK-stimulated pancreatic microvascular blood flow and at the same time decreases pancreatic fluid and protein output in rats [64]. This observation may have clinical importance because inadequate blood flow has been associated with clinical pancreatitis. Interestingly, treatment with NO donor L-arginine before and after cerulein injection increases pancreatic blood flow and reduces the severity of cerulein-induced hemorrhagic pancreatitis. These observations

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suggest NO may protect the pancreas from injury, possibly because it increases pancreatic blood flow.

Other peptides with stimulatory effects on enzyme secretion include those with direct effects on acinar cells, including atrial natriuretic factor (ANF), fibroblast growth factor 21 (FGF21), and histamine. Other peptides stimulate pancreatic secretion through neural mechanisms, including C-natriuretic factor (CNP) and melatonin. The effect of amylin on enzyme secretion is unresolved.

Neural Mechanisms

Parasympathetic Nervous System

The pancreas is innervated by parasympathetic and sympathetic nerve fibers. The parasympathetic fibers pass through the pancreas directly through the vagus nerve and indirectly by the celiac ganglion, the splanchnic nerves, and perhaps through the intramural plexus of the duodenum. In humans, the vagus nerve appears to play an important role in mediating pancreatic secretion. Insulin-induced hypoglycemia, which is presumed to stimulate the vagus nerve centrally, augments secretin-stimulated pancreatic protein output [65]. Vagotomy reduces the HCO_3^- secretory response to exogenous hormones. Furthermore, vagotomy also reduces pancreatic enzyme responses to intestinal stimulants and food [31,66]. Exogenous cholinergic stimulation appears to primarily modulate the actions of gut peptides on pancreatic secretion but has no physiologically relevant effect on CCK or secretin release [67].

In humans, stimulation of duodenal volume receptors and osmoreceptors elicits a pancreatic enzyme response mediated by cholinergic neurons [31]. Increased firing in peripheral afferent vagal neurons and in central sites has been recorded after gastric distension and intestinal perfusion with amino acids and HCl [68,69].

Intrapancreatic postganglionic cholinergic neurons regulate enzyme and HCO_3^- secretion. These neurons are activated by central input during the cephalic phase and by vagovagal reflexes initiated by gastric- and intestinal-phase stimulation. Acetylcholine released by pancreatic neurons may act directly on acinar cells or potentiate the action of secretin on HCO_3^- secretion from duct cells *in vitro*. Acetylcholine and CCK interaction is additive. The enteropancreatic reflex may also play a role in mediating postprandial enzyme secretion [31]. This is especially important after chronic vagotomy [70].

Sympathetic Nervous System

Adrenergic innervation of the pancreas occurs mainly through the splanchnic nerves, which are distributed to blood vessels, with a few passing to acini and ducts [28].

Activation of splanchnic nerves usually inhibits exocrine and endocrine pancreatic secretion; splanchnic nerve stimulation decreases and splanchnicectomy increases pancreatic secretion in response to pancreatic stimulants [28,71]. These responses are likely mediated by vasoconstriction caused by stimulation of α-adrenergic receptors on blood vessels. Physiologically, the major role for adrenergic activation appears to be the inhibition of fluid and HCO_3^- secretion, which is mainly mediated by vasoconstriction.

Enteropancreatic Neural Reflex

Functional and anatomic enteropancreatic neural connections have been demonstrated by anterograde and retrograde tracing. Neurons in the ganglia of the myenteric plexus of the stomach and duodenum project directly to the pancreas [72]. Stimulation of duodenal myenteric neurons can influence endocrine and exocrine pancreatic functions in the rat. These enteropancreatic neural pathways have cholinergic and serotonergic components [72,73]. The cholinergic nerves from the duodenum stimulate intrapancreatic neurons through nicotinic synapses. In contrast, stimulation of enteropancreatic serotonergic axons inhibits pancreatic secretion through presynaptic 5-HT_{1P} receptors on cholinergic nerves [72]. The physiological role of the serotonergic enteropancreatic neural pathways is unclear.

Inhibition of Pancreatic Secretion

The regulation of pancreatic secretion depends on the balance between inhibitory and stimulatory influences exerted through hormones and the autonomic nervous system. The inhibitory phase of pancreatic secretion is mediated by many hormones.

Pancreatic polypeptide (PP) is localized in the islets of Langerhans and between the acinar cells of the exocrine pancreas [74]. PP secretion is regulated mainly by a cholinergic mechanism [75]. Postprandial PP release is mediated by a long vagovagal reflex and short local cholinergic pathways [75].

In humans and dogs, infusion of physiological concentrations of PP inhibits basal and stimulated pancreatic secretion [75,76]. *In vivo*, PP appears to act preferentially by inhibiting vagal stimulation [77]. *In vitro*, PP inhibits pancreatic enzyme secretion by way of presynaptic modulation of acetylcholine release [78]. Because its secretion is under cholinergic control and it acts by interfering with cholinergic transmission, PP is an ideal candidate to modulate pancreatic secretion stimulated by the cholinergic enteropancreatic reflex. PP may also act centrally, as suggested by the presence of PP receptors in discrete locations in the hypothalamus, limbic system, brain

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stem, and other central locations [79]. Microinjection of PP into the dorsal motor nucleus (DMV) inhibits CCK-stimulated pancreatic secretion, suggesting that the DMV is an important site for neural feedback inhibition of pancreatic exocrine secretion [80]. Hence, PP acts at multiple brain stem sites to modulate vagal cholinergic efferent output to the pancreas [81].

Glucagon also inhibits pancreatic exocrine secretion stimulated by secretin and CCK or by ingestion of a test meal in dogs, cats, rats, and humans [82–84]. The inhibitory characteristics are reduced flow volume and decreased HCO_3^- and enzyme secretion. Currently, the sites of action are unclear.

Somatostatin, present in the pancreas as well as the upper gastrointestinal tract and central nervous system, may also play a role in the inhibition of pancreatic secretion. Research indicates that somatostatin does not act on peripheral vagal afferent or efferent pathways nor directly on pancreatic acinar; it exerts its inhibitory action at a central vagal site [85]. Somatostatin injected into the DMV significantly inhibits pancreatic exocrine secretion evoked by intravenous administration of CCK-8 or 2-deoxy-D-glucose, suggesting somatostatin acts through a central cholinergic mechanism [16].

Enteroglucagon is an intestinal hormone believed to mediate the inhibitory action of hypertonic glucose infusion into the jejunum. In animal studies, infusion of oxyntomodulin, a 37-amino acid glucagon-containing peptide isolated from porcine lower intestine, inhibits basal and cerulein-stimulated pancreatic secretion of HCO_3^- and enzymes [86]. The inhibitory action of enteroglucagon is 10-fold more potent than that of pancreatic glucagon.

Peptide YY (PYY) is a 36-amino acid peptide found in the distal intestine and colon of humans and experimental animals [87]. It is released by fat and, to a lesser degree, protein in the ileum or colon. PYY infusion in dogs significantly inhibits basal and meal-stimulated pancreatic HCO_3^- and enzyme secretion [88]. Physiological experiments demonstrate that intra-ileal, but not colonic, carbohydrate increases plasma PYY levels and decreases amylase secretion in dogs [89]. In humans, ileal carbohydrate perfusion inhibits exocrine pancreatic secretion. Therefore, PYY may represent a late postprandial event serving as a physiological signal to reduce exocrine pancreatic secretion after completion of digestion and nutrient absorption.

Glucagon-like peptide 1 (GLP-1) is another ileal hormone that is elevated in the circulation during ileal carbohydrate infusion. There is conflicting data on whether GLP-1 has inhibitory vs. stimulatory and direct vs. indirect effects on exocrine pancreatic secretion. Recent studies support a direct stimulatory effect on acinar cells through a cyclic AMP-dependent mechanism. Older studies suggest the opposite. In anesthetized pigs with cut splanchnic nerves, intravenous GLP-1 infusion inhibits hypoglycemia-induced pancreatic HCO_3^- and protein secretion, effects absent in vagally stimulated, isolated, and perfused porcine pancreas [90], suggesting that GLP-1 acts through a central mechanism. Studies in rats indicate GLP-1 inhibitory action depends on intact vagal nerves [91].

Other peptides. Although the list of peptides known to inhibit exocrine pancreatic secretion continues to expand, little is known about the mechanisms through which these and other hormones or neurotransmitters inhibit pancreatic enzyme secretion. Most of these peptides lack direct inhibition of pancreatic acinar cells and most suppress pancreatic enzyme secretion *in vivo* but do not act directly on acinar cells to reduce pancreatic enzyme release. Animal studies suggest that peptides such as PP, somatostatin, calcitonin gene-related peptide (CGRP), enkephalin, and pancreastatin inhibit pancreatic enzyme secretion by modulating cholinergic transmission, and most, if not all, act through a central vagal site [92–98]. Leptin also inhibits pancreatic enzyme secretion through a similar neuro mechanism, but paradoxically increases pancreatic protein output in rats when administered by duodenal perfusion through CCK activation of duodeno-pancreatic reflexes. Less clear are mechanisms of inhibiting pancreatic secretion by adrenomedullin and galanin.

Feedback Regulation of Pancreatic Secretion

A series of observations in rats suggest that intraluminal actions of pancreatic proteases play an important role in regulating pancreatic enzyme secretion [16,99]. It was demonstrated that diversion of pancreatic juice in the duodenum stimulates CCK release and pancreatic enzyme secretion [16]. Conversely, intraduodenal administration of trypsin or chymotrypsin inhibits CCK release and pancreatic enzyme secretion [16]. This phenomenon is specific for activated proteases, not with inactivated trypsin, amylase, lipase, or HCO_3^-.

Feedback regulation of pancreatic secretion by proteases appears to be mediated by a trypsin-sensitive substance secreted by the proximal small intestine, originally designated CCK–releasing factor (CCK-RF) [16,21]. When trypsin is present, this peptide is cleaved and inactivated. CCK-RF may mediate pancreatic enzyme secretion in response to dietary protein intake in rats. Dietary protein in the intestine competes for the trypsin that would otherwise inactivate CCK-RF [16]. The resulting increase of CCK-RF in the intestinal lumen stimulates CCK release and pancreatic enzyme secretion (Fig. 7.1).

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Efforts to demonstrate a protease-sensitive feedback mechanism in humans remain controversial because of technical limitations in removing or blocking intraluminal protease activity. Using a different approach, investigators reported that intraluminal administration of trypsin or chymotrypsin in humans suppresses CCK release and partially reduces the CCK response to intestinal administration of amino acids or oral ingestion of a test meal [16,100]. These observations support the existence of feedback regulation of pancreatic enzyme secretion in humans. Liener and colleagues demonstrated that Bowman–Birk soybean trypsin inhibitor, an inhibitor of chymotrypsin and elastase, strongly stimulates pancreatic enzyme secretion in humans [101].

The existence of feedback regulation of pancreatic enzyme secretion in humans may have important clinical implications. In patients with chronic pancreatitis, decreased pancreatic enzyme secretion may result in elevated plasma CCK levels, reflecting a failure in the feedback modulation of CCK release. This may cause hyperstimulation of the pancreas and produce pain. Effective enzyme replacement therapy may reduce pancreatic stimulation, decrease intraductal pressure, and diminish pain. Large doses of pancreatic extract have reduced pain in some patients with chronic pancreatitis [102,103].

Conclusion

Under physiological conditions, in rodents and humans, cholinergic vagal afferent pathways rather than pancreatic acinar cells represent the primary targets on which CCK may act as a major mediator of postprandial pancreatic secretion. The vagal afferent pathways also transmit sensory information about the mechanical and physiological state of the digestive tract, mediated in part by 5-HT, which in turn influences pancreatic secretion. A synergistic interaction between CCK and 5-HT at the level of the nodose ganglia may explain the robust postprandial pancreatic enzyme secretion despite a modest increase in plasma CCK after a meal. Interestingly, most hormones such as PP, somatostatin, CGRP, and pancreastatin act through a central vagal site. This supports the Pavlovian concept that the neural system is the major regulator of pancreatic secretion.

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8

Regulation of Pancreatic Protein Synthesis and Growth

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Introduction

Regulation of pancreatic protein synthesis and growth allows the exocrine pancreas to provide an adequate supply of digestive enzymes for nutrient assimilation. In young animals, the pancreas grows along with general body growth and thereby provides an increasing amount of digestive enzymes. In the adult, digestive enzyme synthesis is regulated at both transcriptional and translational levels to match the need for both total and specific digestive enzymes. If the need for digestive enzymes is greater than can be met through these mechanisms, the pancreas can grow or regenerate [1]. This can occur either as a result of increased food intake, or because of decreased pancreatic mass due to disease. Some of the same systemic regulatory signals that regulate enzyme secretion, that is, the vagal nerve and gastrointestinal (GI) hormones, also participate in the regulation of pancreatic protein synthesis and growth, although the intracellular regulatory pathways involved are significantly different. An additional regulatory influence is provided by nutrients, especially amino acids, and islet hormones, particularly insulin, which do not directly affect secretion. The purpose of this chapter is to provide a brief overview of the regulation of pancreatic protein synthesis and growth. Not all areas can be covered in depth owing to page limitations. Areas of recent progress are featured with review articles being cited to cover the older literature.

Regulation of Protein Synthesis

Protein synthesis plays a central role in the maintenance of the pancreas and provision of digestive enzymes. Both the mRNA profile and autoradiographs of newly synthesized proteins are dominated by digestive enzymes. Whether the acinar cell can regulate digestive enzyme synthesis independent of the synthesis of cellular structural proteins is unclear. In general, the GI tract, including the exocrine pancreas, atrophies in the absence of food and protein synthesis that occurs in response to food intake helps to maintain normal function. Individual dietary components also regulate protein synthesis. In most cases, as reviewed in the following, this involves transcriptional regulation of digestive enzyme mRNA. By contrast, shorter term meal-stimulated protein synthesis is regulated primarily at the translational level. Finally, increased protein synthesis is necessary for pancreatic growth.

Long-Term Regulation by Diet

Since the original work by Pavlov, the adaptation of the exocrine pancreas to dietary changes has been observed in a variety of species [2,3]. The content and secretion of the major digestive enzymes, proteases, amylase, and lipases change in proportion to the dietary content of their respective substrates, protein, carbohydrate and fat, by stimulation of both, transcriptional and translational mechanisms [4–6]. Various hormones mediate many of these effects and in most cases their release is increased by the nutrients whose digestion they regulate. In some cases the genetic elements regulated in the promoter region have been identified although the full intracellular pathway leading to their regulation is not yet known [2].

Protein

Feeding a high-protein diet to rodents (typically 60–80% casein or other high-quality protein) increases the content of multiple proteases and the mRNA levels of

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trypsinogen, chymotrypsinogen, and proelastase [2,7], with activation of the mTORC1 pathway and can occur independently of cholecystokinin (CCK) [8]. There are, however, differential effects on different isoforms of enzymes such as trypsinogen and this increase is not mimicked by feeding a mixture of amino acids [9–11]. Clinical studies have shown that a severe reduction of protein in the diet causes pancreatic injury, leading to nutrient malabsorption and a state of malnutrition [12,13], which can be especially critical in children and young adults [14]. The pancreas is extremely vulnerable to protein deficiency states, as seen in patients with the *kwashiorkor* syndrome, where the pancreas is one of the most severely affected organs, with reductions in size and secretory capacity [12,15,16]. In an experimental study, feeding mice a protein-free diet for 4 days resulted in a decrease in the relative pancreatic digestive enzyme content and secretion [17]. Other data showed that the stimulation of protease synthesis, by isolated pancreatic lobules following infusion of the CCK analogue caerulein, *in vivo*, was greatly increased compared with a small increase in translatable mRNA, suggesting a post-transcriptional locus for this regulation.

It has also been shown that a high protein (40%) diet can stimulate pancreas growth in mice, independent of CCK [8]. Individual amino acids can increase pancreatic trypsin levels and stimulate pancreas growth [9,18]. The amino acid leucine, specifically, modulates growth responses of pancreatic progenitors, involving mTORC1 [19], and changing the synthetic rates and messenger RNA (mRNA) levels during several days or weeks.

Carbohydrates

The level of carbohydrate in the diet has long been known to have significant effects on pancreatic amylase content and amylase mRNA [2,3]. This is seen when dietary carbohydrate replaces either dietary fat or protein, provided that dietary protein is adequate. Starch and sugars all similarly affect amylase, as does intravenous glucose. The effects of carbohydrate are believed to be primarily mediated by insulin. When animals are rendered diabetic, the amylase content and synthesis and mRNA levels fall dramatically, whereas lipase increases moderately [3,20]. Insulin restores the amylase synthesis and content and mRNA levels in diabetic rats. Similar decreases in amylase have been seen in obese rat and mouse models with insulin resistance. However, insulin administration to normal rats either decreases or does not change amylase, and other evidence suggests a more direct role for glucose in addition to effects on insulin. Amylase is also regulated by glucocorticoids [21], although this may not mediate dietary effects of carbohydrate. A dietary response sequence in the promoter of the amylase *Amy2.2* gene has been identified that mediates dietary adaptation and the effect of insulin [22].

Fat

In response to a high-fat diet (40–70% of calories as triglycerides), the content and synthesis of pancreatic triglyceride lipase increase [2]. This is accompanied by an increase in its mRNA [23,24]. Adaptation of other pancreatic lipases and colipase have been much less well studied. In neonate mice and rats, bile salt-stimulated lipase and pancreatic lipase-related protein 2 are the two predominant lipases [25]. Secretin has been proposed as a mediator of the effect of dietary lipid [26]. Fatty acids can stimulate secretin release and infusion of secretin in conscious rats led to an increase in the relative synthesis of lipase [2]. Gastric inhibitory peptide (GIP) has also been shown to increase pancreatic lipase and colipase content and mRNA levels [27]. Finally, ketones, metabolites of ingested fat, have also been proposed as a mediator of the increase in pancreatic lipase [2].

Meal-to-Meal Regulation of Translation by Hormones and Nutrients

Whereas long-term dietary changes in digestive enzymes may be mediated by changes in mRNA expression, short-term meal-to-meal control needs to be immediate, reversible, and flexible. Such control of protein synthesis is mainly at the translational level [28]. This section reviews the effects of food intake and hormones, especially CCK and insulin, on the exocrine pancreas translational machinery. Translation of mRNA into protein can be divided into three phases: initiation, elongation, and termination. For details on these three mechanisms, the reader is referred to reviews on translation [28–32]. Only a few studies have evaluated the immediate regulation of the pancreatic translational synthetic machinery after food intake. Early studies showed that fasting reduces total protein synthesis in the pancreas and refeeding stimulates it [33,34]. More recent studies showed that feeding a regular meal activates protein synthesis in the mouse pancreas at the translational level without an increase in the mRNA of the digestive enzymes [35]. In humans, feeding increases both the rate of secretion and synthesis of digestive enzymes, although the rate of turnover of zymogens remains fairly constant during feeding and fasting [36]. In rats and mice, feeding stimulates the protein kinase B (PKB/Akt)/mammalian target of rapamycin complex 1 (mTORC1) pathway and the phosphorylation of 4E-BP1 and ribosomal protein S6, downstream of mTORC1, in addition to the formation of the eIF4F complex [35,37] as illustrated in Fig. 8.1.

Dietary protein and amino acids have also been shown to be necessary to stimulate pancreatic protein synthesis

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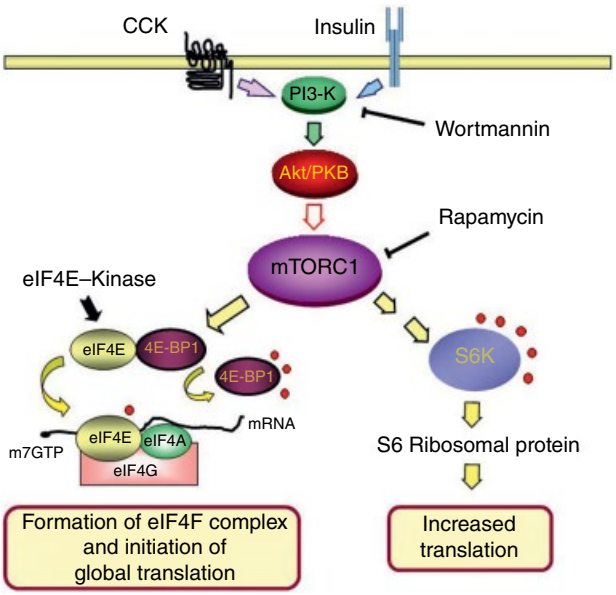


Figure 8.1 CCK and insulin stimulate translational initiation through the P13K-PKB-mTORC1 pathway. mTORC1, which can be inhibited by rapamycin, phosphorylates the eIF4E-binding protein (4E-BP1) that allows the release of eIF4E and the formation of the eIF4F complex necessary for a global increase in translation. mTORC1 also phosphorylates S6K1, which is responsible for phosphorylating S6, thereby increasing the translation of a specific subset of mRNAs. CCK also increases the activity of an eIF4EK, leading to phosphorylation of eIF4E. Together, these effects lead to an increase in protein synthesis Adapted from [28].

at the translation initiation level in mice after 2 h of feeding [38]. When protein or the amino acid leucine are removed from the diet, postprandial pancreatic digestive enzyme synthesis is strongly inhibited, and their deficiency could induce pancreatic insufficiency and malnutrition. The inhibition of protein synthesis and decreased polysomal fraction, caused by the reduction of protein, or only leucine in the diet, has a similar general effect, but it is induced by different mechanisms: protein deficiency causes a partial reduction of the activation of mTORC1 and the guanine nucleotide exchange factor eIF2B; whereas leucine deficiency causes an amino acid imbalance that activates the general controlled nonrepressed (GCN2) kinase, that, in turn, increases eIF2α phosphorylation that blocks protein synthesis [38].

Other studies have shown how dietary protein and amino acids stimulate pancreatic protein synthesis and pancreatic growth in rats [39] and mice [8] fed for several days. Branched-chain amino acids (BCAA), particularly leucine, also stimulate the phosphorylation of 4EBP1 and S6K and the formation of the eIF4F complex in mice and rats, without the need for an increase in the hormones CCK and insulin [40]. A mechanism has been described for a direct stimulation of protein synthesis by amino acids through mTORC1 [35,40–42], and it seems that amino acids are necessary both as a signal and as a substrate for pancreatic digestive enzyme synthesis after a meal [38].

The effects of food can also be mediated by GI and systemic hormones and neurotransmitters. Their stimulatory mechanisms have been mainly studied in isolated pancreatic acini [43]. CCK, carbachol, insulin, and bombesin all stimulate the synthesis of total protein, trypsinogen, chymotrypsinogen, lipase, and amylase in isolated rat acini [44–46]. These *in vitro* studies demonstrate that CCK and insulin, at their stimulatory doses, have an additive effect on protein synthesis after 30 min, and that this effect is mainly at the translational level because it occurs without a change in mRNA levels and in the presence of actinomycin D [46,47]. Increased synthesis of both digestive enzymes and structural proteins was observed, although differences between individual proteins suggested nonparallel translational effects [47].

CCK stimulates protein synthesis in isolated rat acini and in the whole animal [48–50], by increasing the rate of translation initiation [48–51] and elongation [52], at concentrations that stimulate digestive enzyme secretion. Additionally, CCK or its analogue caerulein, activates the S6 kinase (S6K) [53,54] and the phosphorylation of eIF4E [50,51] and activates the formation of the eIF4F complex by stimulating the release of eIF4E from its binding protein 4E-BP1 and increasing the association of eIF4E with eIF4G [35,51]. These actions are summarized in Fig. 8.1. The activation of S6K, the formation of the eIF4F complex, and the activation of the elongation processes and eEF2 appear to be regulated through a rapamycin-sensitive pathway and to be downstream of phosphatidylinositol 3-kinase (PI3K) [49,52,53]. The calcium–calmodulin-activated phosphatase calcineurin is also involved in the activation of CCK-stimulated pancreatic protein synthesis and the regulation of the translational machinery [50]. As mentioned earlier, insulin also stimulates protein synthesis in pancreatic acini *in vitro* [45] by activating the eIF4F complex formation, in a similar manner to CCK [49]. Insulin stimulates pancreatic digestive enzyme synthesis *in vivo*, after a meal. This has been demonstrated with the use of pancreatic acinar cell conditional insulin receptor (IR) knockout mice [54]. The activation of the Akt/mTORC1 pathway is reduced in the pancreas of these mice after 2 h of a meal feeding, and also the translational machinery and polysomal fraction. Additionally, the protein content of the stimulated pancreatic juice is reduced, but not the total pancreatic juice volume, compared with their littermate controls. This demonstrates that insulin is an important physiologic regulator of the pancreatic digestive enzyme synthesis and acinar cell homeostasis that could lead to pancreatic insufficiency during diabetes [28].

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At concentrations of CCK and cholinergic analogues that inhibit secretion [43], protein synthesis is also inhibited [44,48,55]. In minced rabbit pancreas, however, only a decrease in protein synthesis was observed in response to CCK, and this was accompanied by a decrease in the number of polysomes [55].

Inhibition of Pancreatic Protein Synthesis. Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response (UPR)

In vivo, inhibition of pancreatic protein synthesis occurs during the development of acute pancreatitis [56]. This inhibition is accompanied by a reduction in the activity of the guanine nucleotide exchange factor eIF2B, an increase in eIF2α phosphorylation, and a decrease in the formation of the eIF4F complex [48,50,56] (Fig. 8.2). Additionally, this inhibitory effect appears to be calcium related, because the incubation of isolated acini in calcium-free media or with A23187 and thapsigargin to release intracellular Ca^{2+} increases eIF2α phosphorylation and inhibits eIF2B activity. This suggests that pancreatic acinar cells adapt to short-term stress induced by reduction in calcium stores by inhibiting protein synthesis of pancreatic enzymes [48,55]. The ER-resident kinase (PERK) [57] mediates eIF2α phosphorylation in the exocrine pancreas [58,59] and activates the ER stress mechanisms. The inhibition of protein synthesis associated with high concentrations of CCK could therefore be an adaptive or protective mechanism in response to stress localized in the ER [48,56].

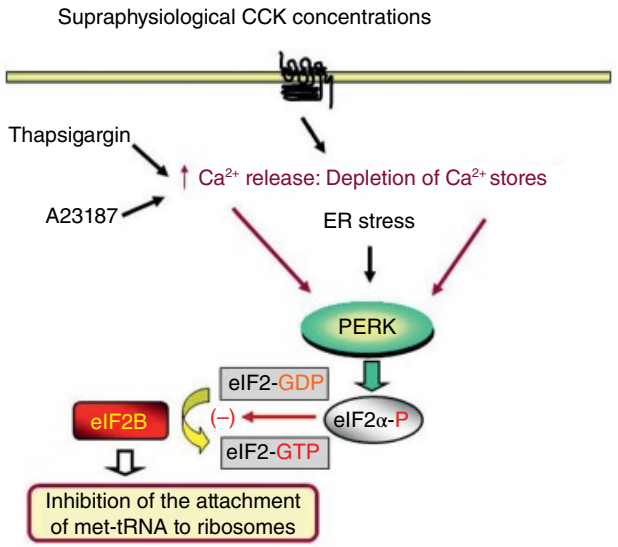


Figure 8.2 Mechanism by which high concentrations of CCK and induction of ER stress inhibit initiation of translation. Depletion of intracellular Ca^{2+} stores or other forms of ER stress activates a kinase (such as PERK), which phosphorylates eIF2α and thereby inhibits eIF2B. This inhibition results in a decrease in protein synthesis Adapted from [28].

ER stress mechanisms are protective cellular responses to stress in the ER, due to an accumulation of unfolded or misfolded proteins in this cellular compartment that trigger the UPR [59]. ER stress and UPR mechanisms have been described in some experimental models of acute pancreatitis [56,60], in pancreatic acinar cell damage *in vitro* [61], and in induced pancreatic acinar cell damage due to alcohol abuse *in vivo* [62].

Regulation of Pancreatic Growth

The pancreas arises embryologically as an outgrowth of the foregut that develops through a relatively undifferentiated duct-like state into acini, islets, and mature ducts under the influence of mesenchyme and a number of transcriptional regulators [63]. By birth, the pancreas has assumed its fully differentiated form and histology but continues thereafter to grow in parallel with body growth. Depending on the species, this can occur by hypertrophy or hyperplasia. A recent study showed that rodent pancreas grows predominantly by hypertrophy, and human pancreas by hyperplasia [64]. During this period, growth of the acinar cell mass is by self-duplication of acinar cells [65]. While all acinar cells can divide, some studies have shown a subset that divides faster in normal growth and regeneration [66]. In the adult animal, acinar and islet cells were originally assumed to be no longer dividing but in fact they both show a small but finite turnover that can be accelerated by hormones and diet. Hence the acinar and beta islet cells are considered to exist in the G_o phase of the cell cycle rather than being terminally differentiated. Whether undifferentiated stem cells remain in the adult pancreas or if small duct cells can function as stem cells remains controversial.

In the exocrine pancreas, enhanced growth in response to hormones or diet can take the form of cellular hypertrophy in which protein increases in excess of DNA resulting in larger cells, or cellular hyperplasia marked by an increase in DNA resulting in more cells. Normally in hyperplasia, protein increases in parallel with DNA, so the endpoint is normal-sized cells. In hypertrophy and hyperplasia, there is usually an increased total digestive enzyme content in the pancreas, although the concentration relative to DNA or total protein may or may not change. Although not as well studied, glandular atrophy can result from loss of cellular protein, as seen with protein-deficient diets [17], or from loss of cells, as seen with some forms of pancreatitis following apoptosis or necrosis. Two distinct types of *in vivo* growth to be discussed are adaptive growth in response to diet and

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hormones and regeneration following the loss of functional cells. The use of cell culture as a model for pancreatic growth will also be reviewed.

Adaptive Growth in Response to Nutrients and Hormones

To ensure adequate nutrient absorption, the amount and composition of digestive enzymes secreted by the pancreas must complement the size and macronutrient composition of a meal. Although the synthesis and secretion of digestive enzymes can increase with consumption of larger and/or more frequent meals, this capacity is finite. Another mechanism whereby the pancreas can adapt to increased feeding is through growth of the acinar cells. Both a high-protein diet and hyperphagia that occurs with cold exposure, pregnancy, and lactation are associated with pancreatic growth [1].

GI hormones released after a meal may contribute to the growth-promoting effects of feeding on the exocrine pancreas as CCK, secretin, and gastrin have all been shown to induce pancreatic growth [67]. The effects of CCK have been studied extensively in rodents and have been reviewed previously [43,68]. Direct administration of CCK or caerulein induces acinar cell growth *in vivo* [1,67,69], and *in vitro* [70]. Feeding a high-protein diet and especially synthetic or naturally occurring trypsin inhibitors, such as those found in raw soy flour, prevents feedback regulation of CCK secretion and culminates in maintained high concentrations of circulating CCK [71], which also stimulates pancreatic growth [72]. Oral trypsin inhibitor-induced pancreatic growth is blocked by coadministration of CCK antagonists [73] and is absent in CCK [74] and CCK-A receptor-deficient mice [75]. In the rat, CCK-stimulated growth is primarily through cellular hypertrophy, but with some hyperplasia, whereas in mice it is primarily through hyperplasia. In both cases, the hyperplasia involves DNA synthesis and replication of mature acinar cells [76]. Although CCK can mediate adaptive growth, it does not appear to be essential for growth during development and CCK or its receptors are not necessary in most studies for maintenance of normal pancreatic size. In contrast to CCK, the hormone secretin had little effect by itself but can potentiate the action of CCK [67].

More recently, information has emerged on intracellular pathways mediating pancreatic growth (Fig. 8.3). CCK is known to activate a number of intracellular pathways potentially related to growth, including an increase in intracellular Ca^{2+}, three MAPK pathways, and the PI3K-mTOR pathway [43]. Most of these pathways are activated in the pancreas in response to endogenous CCK release following feeding of camostat [77]. Pharmacologic and genetic evidence exists for three major intracellular pathways, calcineurin–NFAT, mTORC1, and ERK1/2, playing nonredundant roles in adaptive pancreatic growth. The calcineurin–NFAT pathway can be blocked pharmacologically with the calcineurin inhibitors FK506 and cyclosporin A and genetically by overexpression of *Rcan1* [74,78,79]. The mTORC1 pathway can be blocked with rapamycin [80] or by acinar cell-specific deletion of Raptor, an essential component of mTORC1 (SJ Crozier, MD Sans, and JA Williams, unpublished data). The ERK pathway can be blocked with specific MEK inhibitors active *in vivo* such as PD-0325901 [81]. Blockage of each of these pathways blocks pancreatic adaptive growth induced by feeding camostat. These pathways are important regulators of mRNA transcription and translation, and it is likely through modulation of these processes that CCK affects pancreatic growth by activating the cell cycle.

Polyamines have also been studied as mediators of pancreatic growth induced by CCK and other hormones [82]. The naturally occurring polyamines putrescine, spermidine, and spermine are normal cell components involved in protein and DNA synthesis. Biosynthesis of polyamines is initiated by ornithine decarboxylase and its inhibitor difluoromethylornithine inhibits pancreatic growth in response to CCK. However, there is no clear role for polyamines in pancreatic growth and it may be that they are simply a cellular component necessary for pancreatic growth similar to their role in intestinal adaptation and liver regeneration.

Growth of the pancreas in response to CCK administration is greatly diminished in rats fed a low-protein diet [83]. Conversely, consumption of large amounts of protein induces pancreatic hypertrophy in rodents [84], even in the presence of a CCK receptor antagonist [18] and in CCK-deficient mice [85]. Therefore, it appears that dietary protein both potentiates the effects of CCK on pancreatic growth and also stimulates pancreatic growth via CCK-independent mechanisms. These CCK-independent mechanisms are undoubtedly mediated, at least in part, by amino acids. Purified amino acids do not stimulate CCK secretion, yet ingestion of large quantities of amino acids stimulates pancreatic growth [18]. This action is mediated in large part by the mTORC1 pathway, which is activated by amino acids [8]. Interestingly, growth of the pancreas in mice fed a high-protein diet occurs predominately via cellular hypertrophy [85] whereas that associated with supraphysiologic levels of CCK, such as direct CCK administration and trypsin inhibitor feeding, in mice is primarily hyperplastic [74]. It may be that a threshold level of CCK exists, above which signal transduction pathways are activated that permit cell division following cellular hypertrophy.

Other systemic hormones, including insulin [20], thyroid hormones, and glucocorticoids, can stimulate and regulate pancreatic growth in response to meal feeding [1,86].

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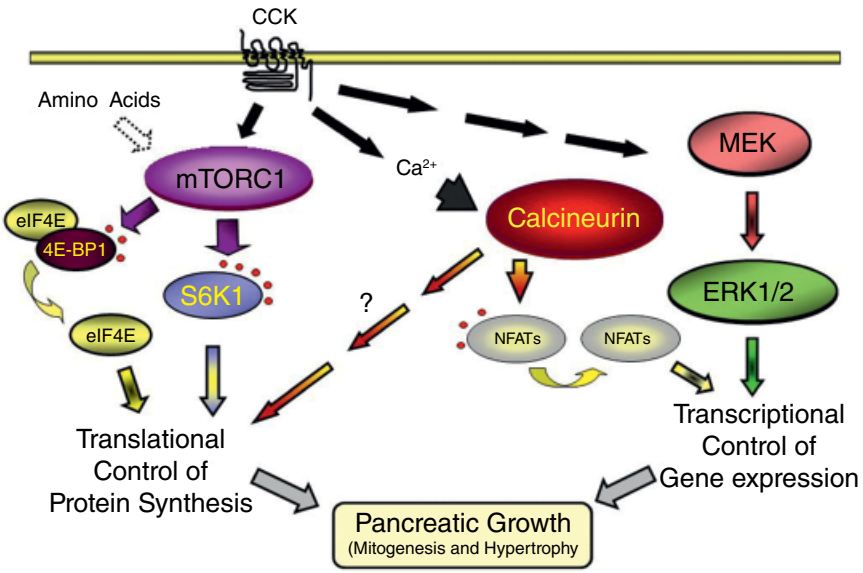


Figure 8.3 Intracellular pathways through which CCK stimulates pancreatic growth. At least three pathways involving calcineurin-NFAT, mTORC1, and ERK1/2 have been shown to be necessary for growth of rodent pancreas either *in vivo* or *in vitro*. Inhibitors of all three pathways can block growth Adapted from [1].

Activation of vagal nerve fibers to the pancreas during feeding stimulates the release of additional peptides associated with secretion of bicarbonate and digestive enzymes. Some of these neuropeptides may also play a role in the regulation of pancreatic growth and their effects have been reviewed previously [87]. In particular, vasoactive intestinal polypeptide (VIP) potentiates the effects of caerulein on pancreatic growth in a manner similar to secretin and gastrin-releasing peptide and bombesin stimulate pancreatic growth, although not as strongly as CCK.

Regeneration

Despite the low rate of cellular turnover normally observed in the adult pancreas, studies in rodents have demonstrated its ability to regenerate in response to tissue injury [88]. This has been studied both after pancreatitis and following surgical resection. Experimental pancreatitis induced by caerulein, arginine, bile salts, or ethionine leads to cell death by a combination of apoptosis and necrosis. The remaining acinar cells dedifferentiate and form tubular complexes that express both acinar and ductal characteristics and some markers of embryonic pancreas. These cells divide and grow and eventually differentiate back into mature acinar cells [89–91]. At present, there is little definitive evidence for regeneration from stem cells.

Following surgical resection of 50–90% of the rat pancreas, the remnant pancreas increases in size and protein and DNA content, with the increase being greater after more complete resection [92]. However, the pancreas never regains its normal size and islets appear to regenerate to a greater extent than exocrine tissue. In some reports differentiated acinar cells are said to incorporate thymidine or show mitotic figures, whereas in other studies regeneration is reported to occur in the injured margin and show tubular complexes and express embryonic markers [93]. In mice, a 75% resection was followed by growth of the remnant by 40%, with evidence for proliferation of differentiated acinar cells [94].

Similarly, to adaptive growth, dietary protein, CCK, and insulin play a significant role in the regeneration of exocrine cells following pancreatic injury. The pancreas is incapable of regeneration in rats fed a protein-free diet. Both exogenous and endogenous CCK enhance and CCK receptor antagonists slow the rate of pancreatic regeneration following pancreatitis [95]. There is also a significant decrease in the rate of pancreatic regeneration in mice lacking the CCK-A receptor in the pancreas [96]. The importance of insulin is shown by the fact that in diabetic rats, CCK administration fails to induce pancreatic regeneration following pancreatitis unless exogenous insulin is also administered [97]. Pertinently, it has been demonstrated that the expression of IGF-1 mRNA is significantly increased following pancreatitis and resection, indicating that both insulin and IGF may be important in pancreatic regeneration.

The expression of cellular oncogenes that regulate the cell cycle and thereby control cellular proliferation rates is significantly increased in models of pancreatic regeneration [98,99]. Many genes associated with embryonic development, and whose expression is normally repressed in the adult, are re-expressed during pancreatic regeneration following pancreatitis [90]. Only a little is known of signal transduction pathways that mediate these changes in gene expression. The p42/p44 MAPK pathway, which modulates the expression of cell-cycle

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regulators, is activated in the regenerating pancreas [100]. Activation of the PI3K pathway has been shown to be necessary for pancreatic regeneration following resection, as inhibition of the pathway via pharmacologic inhibitors or siRNA severely diminished regeneration [94]. Moreover, the PI3K pathway activation in response to resection decreased with age and may contribute to the reduced regenerative capacity of the aged pancreas. Further identification of the signal transduction pathways, and also the factors modulating these pathways, will be important for improving our understanding of pancreatic regeneration.

Growth of Pancreatic Cells in Culture

In vitro culture of differentiated or immortalized cells can be used as models for cell growth. Most pancreatic cancer cell lines, however, are undifferentiated and will not be considered here. Primary dissociated pancreatic cells, although not dividing, can be maintained in suspension culture under conditions such that they retain the differentiated phenotype or where they dedifferentiate and adopt a more plastic phenotype. When isolated acinar cells or acini are placed on an extracellular matrix such as collagen or matrigel, the cells will initiate division and remain viable for several weeks but almost invariably lose their differentiated appearance. CCK or its analogue caerulein can stimulate cell division and growth, as do insulin, epithermal growth factor (EGF), and other growth factors [70,101]. This model has been applied to evaluating which intracellular pathways mediate growth, with evidence for participation by Ras [102], PI3K/Akt [94], and MAPK pathways [103]. The dedifferentiated phenotype of cultured acinar cells was originally reported as duct like [104,105]. Subsequently, they were characterized as similar to precursor cells that can transdifferentiate into insulin-containing islet cells [106] and that the dedifferentiated cells can simultaneously express acinar, ductal, or beta-cell proteins. Another report showed retention of acinar cell phenotype with an altered medium containing a high amino acid level [107]. In a similar manner, pancreatic duct cells have been grown in monolayer culture. They retain their ion-transporting phenotype and have been used to study duct function. Their growth in culture is stimulated by EGF, TGFα, and insulin, inhibited by TGFβ, but not affected by secretin or other GI peptides [108].

Although no real differentiated pancreatic acinar cell line exists, considerable research has been carried out with AR42J cells, a rat cell line derived from an azoserine-induced tumor which under the influence of glucocorticoids assumes a more acinar phenotype [109]. However, these cells were subsequently shown also to have neuroendocrine properties and can even be driven toward an islet phenotype such that they appear more like an undifferentiated ductal epithelium. Their growth can be stimulated by CCK, gastrin, PACAP, and other peptides, but only to 25–30% and not after exposure to dexamethasone, which induces acinar differentiation but inhibits growth [109].

In summary, all the cultured pancreatic cells studied to date, although dividing and regulated by hormones, possess a relatively undifferentiated phenotype. Hence, they are more a model for regenerating pancreas after pancreatitis than they are a model for diet- or hormone-driven acinar proliferation.

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9

Fibrogenesis in the Pancreas: The Role of Pancreatic Stellate Cells

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Introduction

Fibrogenesis is defined as the development or production of fibrous tissue. In the healthy pancreas, fibrogenesis is a well-controlled, regulated process that is essential for regular turnover of extracellular matrix (ECM) in the parenchyma, thereby maintaining normal pancreatic architecture. In diseased states, however, this process is hijacked such that the fine balance between production and degradation of fibrous tissue is disrupted, leading to the deposition of excessive amounts of ECM proteins in the organ, eventually resulting in pathologic fibrosis.

Elucidation of the cellular and molecular mechanisms involved in pancreatic fibrogenesis began in earnest in 1998, when methods were developed to isolate and culture pancreatic stellate cells (PSC), now established as key cells in the fibrogenic process, from rodent and human pancreas [1–3]. Interestingly, the presence of these cells in the pancreas was first reported by Watari et al. [4] in Japan a decade and a half earlier (in 1982), and confirmed by Ikejiri [5] in 1990. However, little was known of their function at the time. It was the subsequent development of techniques to isolate viable PSC from the pancreas that provided the much-needed *in vitro* tool that enabled researchers to interrogate the functions of these cells both in health and in pancreatic disease.

Pancreatic Stellate Cells (PSC)

PSC in Health

PSC comprise 4–7% of total parenchymal cells in the normal pancreas. They are found around the basolateral aspects of acinar cells (Fig. 9.1a), blood vessels, and small pancreatic ducts [1,2] and also around pancreatic islets [6].

In their native, quiescent (non-activated) state, PSC store abundant vitamin A (retinoids) in their cytoplasm and belong to a larger "stellate cell system" in the body, comprising retinoid storing cells in several other organs, including the liver, lungs, intestine, kidney, spleen, and adrenal glands [7]. The specific density imparted by the stored lipid enabled Apte et al. [1] to develop the density gradient centrifugation method for the isolation of quiescent PSC from the pancreas. This method has since been refined and further customized by several groups to suit their experimental purposes. The presence of cytoplasmic vitamin A droplets (Fig. 9.1b), and the expression of selective markers such as the intermediate filaments desmin, glial fibrillary acidic protein (GFAP) and nestin, and the neuroectodermal proteins neural cell adhesion molecule and nerve growth factor differentiate PSC from fibroblasts. Due to the expression of neural markers, PSC were initially thought to be of neuroectodermal origin. However, lineage tracing studies with hepatic stellate cells (counterparts of PSC in the liver) have confirmed a mesenchymal origin for these cells [8]. The fact that a proportion of PSC are replenished from bone marrow further supports a mesenchymal origin for PSC [9].

Islet stellate cells (ISC) are similar to but differ in certain aspects from PSC. ISC have fewer vitamin A-containing droplets and undergo a more rapid activation than PSC. Upon activation, ISC express more α-SMA but have reduced rates of proliferation and migration compared with exocrine PSC [6].

Initial studies were focused on the ability of PSC to maintain normal extracellular matrix turnover in health, by not only synthesizing ECM proteins such as collagen,

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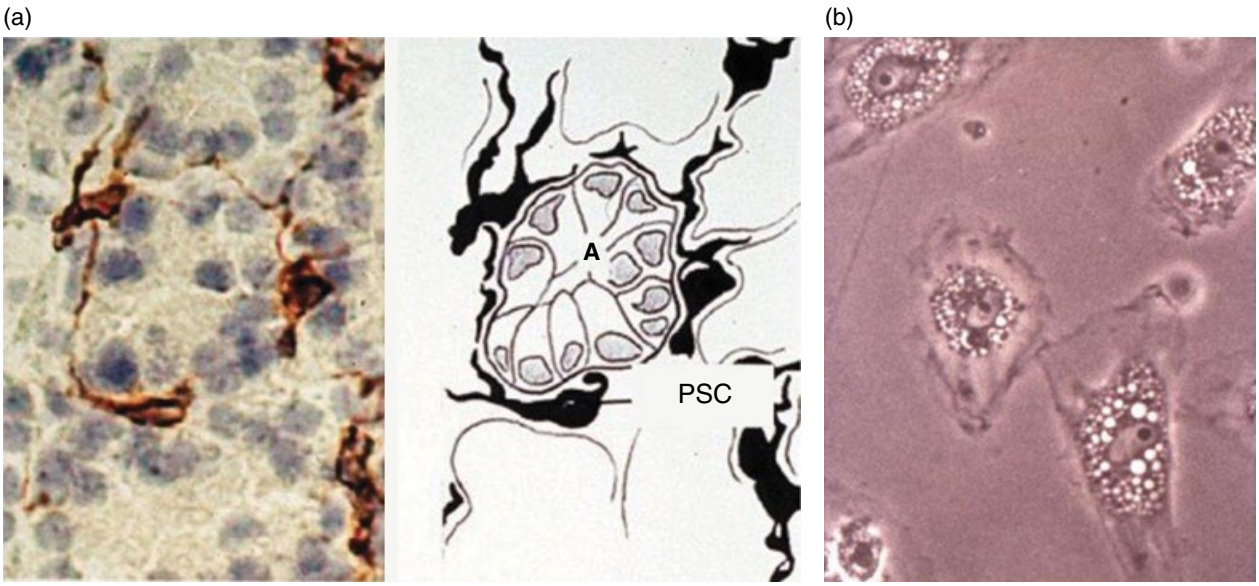


Figure 9.1 (a) Expression of the cytoskeletal protein desmin in pancreatic stellate cells (PSC): a representative photomicrograph of a normal rat pancreatic section immunostained for the stellate cell selective marker desmin is shown on the left with a corresponding line diagram on the right. Desmin-positive (brown) PSC with long cytoplasmic projections can be seen along the basolateral aspects of acinar cells. (b) PSC in early culture exhibiting a typical flattened polygonal shape. The nucleus is surrounded by numerous vitamin A-containing lipid droplets in the cytoplasm. *Source:* Apte et al. (1998) / Reproduced with permission from BMJ Publishing Group Ltd.

fibronectin, and laminin, but also the enzymes (matrix metalloproteinases [MMP] and their inhibitors [TIMP]) that degrade ECM [10]. Evidence has now emerged to indicate that PSC may serve several other functions in the healthy pancreas, including (i) a role in innate immunity and first-line defense (since they express toll-like receptors, TLR 2, 3, 4, and 5 [11], which recognize PAMPs, DAMPs, and alarmins), as well as their ability to phagocytose cell debris and neutrophils [12]; (ii) as mediators of cholecystokinin-induced pancreatic enzyme secretion (since they respond to CCK via CCK receptors by secreting acetylcholine), which in turn acts on muscarinic receptors on acinar cells to stimulate enzyme secretion [13]; and (iii) progenitor-like capabilities since they express several stem cell markers, including CD133, SOX9, nestin, and GDF3 [14,15]. They can differentiate into other cell types including insulin-secreting cells under the influence of relevant growth factors.

PSC in Disease

During pancreatic injury, PSC are activated, i.e., they transform from their quiescent state to a myofibroblast-like phenotype characterized by loss of vitamin A stores, expression of alpha smooth muscle actin (αSMA), fibroblast activation protein (FAP), fibroblast specific protein (FSP1), and fibrinogen [16] (Table 9.1). Activated PSC synthesize and secrete excessive amounts of ECM proteins, overwhelming their ability to degrade these proteins, eventually causing fibrosis of the gland. PSC can be activated by a wide range of factors, each of which is pertinent to pancreatic pathophysiology either as a factor that is upregulated/modulated during pancreatic disease

Table 9.1 Characteristics of quiescent and activated pancreatic stellate cells (PSC).

Characteristic	Quiescent PSC	Activated PSC
Vitamin A lipid-containing droplets	Abundant	Absent
Alpha smooth muscle actin	Not expressed	Expressed
Proliferation	Basic	Enhanced
Ability to migrate	No	Yes
Collagen production	Limited	Increased
Activity of matrix metalloproteinases (MMP) and tissue inhibitors of matrix proteinases (TIMP)	In equilibrium	TIMP > MMP
Cytokine production	Limited	Increased inflammatory cytokines (PDGF, TGFβ, CTGF, IL-1, IL-6, IL-15)
Ability for phagocytosis	No	Present (CD6-mediated)
Protein expression	Basal expression	Differential expression

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Table 9.2 Factors causing pancreatic stellate cell activation.

Angiotensin
Cyclooxygenase 2 (COX-2)
Endothelin-1
Endotoxin
Ethanol and its metabolites (acetaldehyde, fatty acid ethyl esters)
Fibrinogen
Galectin-1
Hyperglycemia
Hypoxia
Inflammatory mediators (cytokines, growth factors, complement)
Lipopolysaccharide
Nicotine
Oxidant stress
Parathyroid hormone-related protein (PTHrP)
Pigment epithelium-derived factor
Proteases

Table 9.3 Signaling pathways involved in pancreatic stellate cell (PSC) activation.

Factor	Pathway involved	Outcome
Oxidative stress	Nrf2 antioxidant pathway	PSC activation and pancreatic fibrosis
Nicotine	α7nAChR-mediated JAK2/ STAT3 signaling pathway	PSC activation, proliferation, α-SMA expression, and ECM formation
LPS	NLR family pyrin domain-containing 3 inflammasome	Activation of PSC
TGF-β1	SNHG/miR-34b/ LIF pathway	Proliferation, migration, and ECM accumulation
siRNA	Notch3	Inhibits the activation, proliferation, and migration of cancer cells
CCG-222740	Rho/MRTF pathway	Reduces PSC activation and modulates immune cells
Tissue injury/ pathogens	Sonic hedgehog/ Smo/Gli pathway	PSC activation and perineural invasion
Ethanol and growth factors	MAPK pathway	PSC activation and fibrosis
Thiazolidinediones	PPR γ pathway	PSC activation inhibition
IL-6	JAK2/ STAT3 pathway	PSC activation and immune modulation
siRNA	transcription factor NF-κB pathway	PSC activation, proliferation, apoptosis

or as a compound that is directly injurious to the gland (listed in Table 9.2). Notably, in addition to being activated by exogenous cytokines (released by surrounding acinar or inflammatory cells) via paracrine routes, PSC are capable of producing their own cytokines, which act on the cells via corresponding receptors (autocrine pathways) resulting in a state of perpetual activation thus further facilitating pathological fibrosis.

Signaling pathways that mediate activation of PSC are being increasingly identified (summarized in Table 9.3). Furthermore, close interactions between several of these pathways have now been characterized, implying that there is considerable redundancy when it comes to modulation of PSC activation [17–20]. Interestingly, several studies have shown that a number of the above signaling pathways converge to a common downstream mediator of PSC activation, namely a sustained increase in intracellular calcium [21]. In recent years, attention has been focused on microRNA, (small noncoding RNA) in PSC because they are now recognized as important factors in numerous cell functions including proliferation, differentiation, apoptosis, and protein synthesis. Several miRNA have been shown to be differentially expressed between quiescent and activated PSC [22]. MicroRNA 15b and 16 (reported to regulate PSC apoptosis) [23] and miR21 are postulated to be cofactors in connective tissue growth factor (CCN2)-mediated PSC activation [24]. MicroRNA are often transported by small extracellular vesicle (exosomes) secreted by a variety of cell types. A recent study has shown that exosomes from acinar cells carrying miR-130a-3p can fuse with PSC membranes, with consequent transport of miR130a into PSC where it binds to and inhibits PPARγ leading to PSC activation [25]. In addition to the identification of factors causing PSC activation, in recent times attention has been turned toward signaling pathways and factors that maintain PSC quiescence or reverse activated PSC to their quiescent state. These are discussed in more detail in the context of development of therapeutic approaches to inhibit/reverse pancreatic fibrosis under the section titled "Reversal of Pancreatic Fibrosis."

Over the past decades several major advances have been made in our understanding of the role of PSC in the diseased pancreas. It is clear that PSC are critical to the process of regeneration and repair in acute pancreatitis (usually a self-limiting inflammatory condition), but also play a central role in disease progression in recurrent acute and chronic pancreatitis as well as pancreatic cancer.

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Acute Pancreatitis (AP)

In the majority of cases, acute pancreatitis is a self-limiting condition, with restitution of pancreatic structure and function to normal within a few weeks. Early in the disease process and in response to acinar cell-derived trypsin [26] as well as the chemokines/cytokines released by damaged acinar cells and the infiltrating inflammatory cells, PSC become activated and proliferate rapidly. While most of the increased PSC numbers comprise proliferating resident cells, a small proportion (7–18%) are derived from circulating bone marrow cells [9]. Activated PSC are thought to play a role in the progression of AP via synthesis of nitric oxide, which in turn further damages acinar cells [26,27]. However, they also play a major role in recovery from AP. The ECM proteins produced by these activated PSC provide a supportive lattice and a scaffold that supports the regeneration of acinar and ductal cells during recovery from acute pancreatitis. Notably, the ECM regulates the critical integrin-mediated interactions between cell membranes and the surrounding matrix, which in turn are important controllers of cell proliferation and differentiation. In the absence of integrin receptors (as demonstrated by studies using β1-integrin knockout mice [28], ECM synthesis by PSC is inhibited. This is associated with increased apoptosis and decreased proliferation of acinar cells, thereby delaying the process of pancreatic repair.

PSC also play an important role in aiding regeneration and remodeling after severe necrotizing acute pancreatitis. In a seminal study using pancreatic tissue from patients with severe acute pancreatitis, Zimmerman et al. [29] found outgrowth of "pilot ductules" from islands of granulation tissue (comprised of remnant acini, ductules, and stellate cells). These ductules exhibited a mantle of stellate cells which are thought to support growth and differentiation of ductal cells into mature duct and acinar cells. Thus, PSC may be critical to the reconstitution of pancreatic parenchymal cells after acute injury. Additionally, the MMPs and TIMPs secreted by the cells may help in the remodeling process by removal of excess ECM via fibrinolysis, while activated PSC are removed through processes such as apoptosis, senescence and/or reversion to quiescence.

Chronic Pancreatitis (CP)

Chronic necroinflammation of the pancreas (chronic pancreatitis) is characterized histologically by abundant fibrosis that surrounds islands of atrophied acini and distorted pancreatic ducts. Notably, fibrosis is also detected within and around pancreatic islets despite the absence of obvious necroinflammation of the islet cells [30]. Studies involving dual staining for collagen and the PSC activation marker αSMA (using Sirius Red stain and immunohistochemistry, respectively) combined with immunostaining for selective PSC markers have conclusively demonstrated the presence of activated PSC in fibrotic areas (Fig. 9.2) around acini and ducts as well as around islets; more importantly, dual staining for αSMA and procollagen mRNA has established that activated PSC are the predominant source of collagen I in the fibrotic pancreas [31]. As with AP, the increased numbers of PSC in CP are sourced mainly from the resident PSC population, with a small proportion being derived from pluripotent circulating bone marrow cells [32]. Interestingly, activated PSC are known to cause beta-cell dysfunction (decreased insulin secretion and apoptosis), and these effects are further aggravated by hyperglycemia [33]. These findings indicate that PSC-mediated islet cell dysfunction may be a factor in the diabetes of chronic pancreatitis.

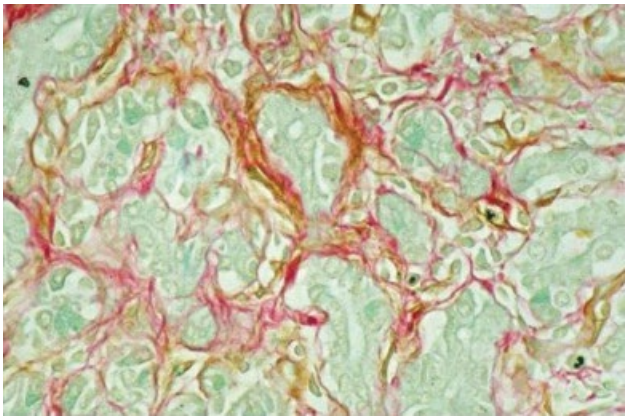


Figure 9.2 Activated pancreatic stellate cells (PSC) in chronic pancreatitis: a section from a patient with chronic pancreatitis showing colocalization of staining for the PSC activation marker alpha smooth muscle actin (αSMA, brown) and collagen using Sirius Red (red) (dual staining) in fibrotic areas of the pancreas. *Source:* Haber et al. (1999) / Reproduced with permission of Elsevier.

The role of PSC in CP has been studied using human CP tissue (which usually only allows point-in-time assessments) and experimental models of CP (which allow examination of chronological events during fibrosis development and progression). Space restrictions preclude a detailed discussion of the current (predominantly rodent) models of CP noted in Table 9.4. Each model has its advantages and deficiencies, but possibly the most physiologically relevant model (particularly for alcoholic chronic pancreatitis) involves chronic ethanol administration followed by endotoxin challenge (given the well-demonstrated increase in serum endotoxin levels in heavy drinkers) [34]. With the recent focus on the role of smoking in chronic pancreatitis and the knowledge that smoking aggravates alcoholic CP, models have been developed whereby alcohol-fed, endotoxin challenged rats or mice

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Table 9.4 Rodent models of chronic pancreatitis.

Repeated injections of caerulein
Pancreaticobiliary duct ligation
Intraductal injection of trinitrobenzene sulfonic acid (TNBS)
Tail vein injection of dibutyltin chloride (DBTC)
Chronic alcohol administration with additional challenge/intervention
• Pancreatic duct ligation
• Free fatty acids
• Caerulein
• Endotoxin/LPS
• Smoke exposure

are exposed to tobacco smoke [35]. These studies support the concept that smoke exposure significantly increases the severity and progression of alcohol-induced pancreatic injury and fibrosis.

Mechanistic insights gained from the above work indicate that during CP, PSC are activated by numerous factors/pathways including (i) the profibrogenic growth factor TGFβ, which is found to be highly expressed in spindle-shaped cells and in infiltrating M2 macrophages within fibrotic areas and also in acinar cells adjacent to areas of fibrosis (but not in acinar cells away from fibrotic areas), supporting the notion that TGFβ induces PSC activation via paracrine and autocrine pathways [31]; (ii) platelet-derived growth factor (PDGF) acting via the PDGF receptor known to be upregulated in fibrotic areas, thereby providing a possible mechanism for the observed increase in proliferation and migration of PSC to injured areas during pancreatic necroinflammation [31]; (iii) nerve growth factor (NGF), demonstrated to be expressed in PSC in areas of fibrosis, and implicated in the pain of chronic pancreatitis via its ability to induce neurite growth [36]; (iv) oxidative stress, as evidenced by increased staining of oxidant stress marker 4-hydroxynonenal [37]; (v) cigarette smoke compounds (via activation of the α7nicotinic acetylcholine receptor [α7NACh receptor]) expressed on PSC [35]. Notably, a positive feed-forward loop is set up between PSC and macrophages, whereby the interleukins IL4 and IL13 produced by activated PSC promote further transformation of macrophages to the M2 phenotype, which, in turn secrete IL22, TGFβ, and PDGF to cause further PSC activation and progression of fibrosis [38].

Reversal of Pancreatic Fibrosis

Our improved understanding of the biology of PSC and their role in the fibrosis of chronic pancreatitis has led to a dramatic increase in efforts in the field to develop targeted therapies to prevent/inhibit/retard the fibrogenic process. It must be acknowledged, however, that the efficacy of most approaches has largely only been demonstrated in animal models and translation of these findings to clinical settings is awaited. The potentially useful strategies suggested by pre-clinical studies are itemized in Table 9.5 and include:

1) *Modulation of growth factors*: Inhibition or degradation of profibrogenic growth factors TGFβ and tumor necrosis factor alpha (TNFα) and their downstream signaling [38–43], histone deacytylase (HDAC) inhibitor [44], heat shock protein (HSP90) inhibitor [45].
2) *Antioxidants*: Vitamin E [46], ellagic acid, a plant polyphenol [47], salvianolic acid, a herbal medicine [48]; and irisin, an exercise-induced hormone [49], N-acetylcysteine [50].
3) Protease inhibitors [51].
4) *Modulation of signaling pathways*: Troglitazone and miR-130a-3p binding to the peroxisome proliferator receptor gamma, PPARγ [12,25]; retinoic acid-

Table 9.5 Reversal of pancreatic fibrosis.

Mechanism	Compounds
Modulation of growth factors	Inhibitors of TGFβ, TNFα, HDAC, HSP90
Antioxidants	Vitamin E, ellagic acid, salvianolic acid, irisin, N-acetylcysteine
Protease inhibitors	Camostat mesylate, dasatinib, CP734
Modulation of signaling pathways	Troglitazone and miR-130a-3p binding to PPARγ; Retinoic acid – Wnt–catenin pathway; miR-200a –TGF-β1/PTEN/Akt/mTOR pathway; 3-methyladenine (3-MA) – PI3K pathway
Inhibition of collagen synthesis	Collagen siRNA
Anti-inflammatory approach	Prostacyclin analogue ONO-1301; amygdalin; indomethacin; isoliquiritigenin
Behavioral modification	Alcohol withdrawal
Plant compounds	Rhein, apigenin, curcumin, saikosponin A, date palm fruit extract
Vitamins	Vitamin D – isoforms D2 and D3, vitamin A (retinol) or its metabolites such as retinoic acid
Induction of quiescence of activated PSC	Melatonin, bone morphogenic protein, troglitazone, kinase inhibitors – sorafenib, sunitinib, trametinib, dactolisib, and dasatanib, coenzyme Q10

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induced PSC quiescence via suppression of the Wnt–catenin pathway [52]; miR-200a-mediated inhibition of TGF-β1-induced PSC activation and extracellular matrix formation through inhibition of the PTEN/Akt/mTOR pathway [53]; 3-methyladenine (3-MA), a PI3K inhibitor causing decreased fibrosis by decreasing autophagy in PSC [54].

5) *Inhibition of collagen synthesis*: Collagen siRNA [55].
6) *Anti-inflammatory approach*: A prostacyclin analogue ONO-1301, which inhibits proinflammatory and profibrogenic cytokine production [56]; amygdalin, which inhibits PSC activation and attenuates fibrosis by decreasing production of profibrotic cytokines in a rat CP model induced by injecting dibutyltin dichloride (DBTC) [57]; inhibition of cyclooxygenase by indomethacin, an anti-inflammatory drug that results in decreased activation of PSC [58]; isoliquiritigenin, a component of licorice which decreases macrophage infiltration and attenuates caerulein-induced pancreatic fibrosis [59].
7) *Behavioral modification*: Alcohol withdrawal in alcohol-induced pancreatitis [60].
8) *Plant compounds* exerting a range of effects that inhibit PSC activation: An anthraquinone derivative rhein and a flavonoid, apigenin; curcumin (a polyphenol found in turmeric) reported to inhibit activation of PSC through the inhibition of IL1β, which decreases TNFα-induced activation of activator protein-1 (AP-1) and mitogen-activated protein (MAP) kinases (ERK, c-Jun N-terminal kinase [JNK], and p38 MAP kinase) [61]; conophylline, a plant alkaloid, which decreases fibrosis through the inhibition of ERK1/2 in PSC [62]; resveratrol, a natural polyphenol, which decreases oxidative stress-induced activation and glycolysis in PSC, mediated by ROS/miR-21 [63]; genestein, a natural isoflavone, which decreases fibrosis in human PSC transfected with let-7d to express thrombospondin 1, a marker of fibrosis [64]; saikosponin A, the active component of the Chinese medicine chaihu, which decreases PSC activation, viability, proliferation, and migration, and promotes apoptosis by inhibiting autophagy and the formation of NLRP3 inflammasome via the AMPK/mTOR pathway [65]; date palm fruit extract, which decreases fibronectin-1 and αSMA, markers of fibrosis in PSC activated by TNF-α [66].
9) *Vitamin D* and its isoforms D2 and D3 decrease *in vitro* PSC activation by decreasing IL-6 [67]. Notably, *in vivo* studies with the vitamin D ligand calcipotriol have shown significant attenuation of the fibrosis of chronic pancreatitis in mice [68]. Based on these findings, a clinical trial is under way (NCT02965898, Laukkarinen J, Tampere University Hospital) to assess if vitamin D supplementation can prevent progression of recurrent AP to chronic pancreatitis. Since storage of vitamin A is associated with PSC quiescence, administration of vitamin A (retinol) or its metabolites such as retinoic acid, has been assessed in models of chronic pancreatitis. In this regard, vitamin A-containing liposomes combined with TLR4-silencing shRNA has been reported to inhibit pancreatic fibrosis in mouse models of chronic pancreatitis [69]. Interestingly, vitamin A deficiency was seen to promote islet stellate cell activation and dysregulation of glucose metabolism in mice, an effect that was mitigated by supplementation of vitamin A [70].
10) *Induction of quiescence of activated PSC*: Melatonin, the anthraquinone derivative rhein [71], bone morphogenic protein [72], troglitazone (a ligand for the peroxisome proliferator activated receptor PPARγ) [25,73]; kinase inhibitors (sorafenib, sunitinib, trametinib, dactolisib, and dasatanib), which have been shown to inhibit PSC proliferation and ECM synthesis [74–76]. Interestingly, trametinib also decreases the expression of two autocrine mediators of PSC activation, IL6 and TGFβ [75]. Coenzyme Q10 suppresses PSC activation by inhibiting autophagy through PI3K/ATK/mTOR signaling [77].

Pancreatic Cancer

It is now well established that the abundant collagenous stroma of pancreatic cancer is produced predominantly by PSC (discussed in more detail below). It is also increasingly clear that PSC play a much wider role to aid cancer progression via active crosstalk not only with cancer cells but also with other stromal cells. Consequently, the development of novel approaches to interrupt this crosstalk is considered a critical addition to currently available treatment strategies for pancreatic cancer.

The fibrotic stroma of pancreatic cancer comprises extracellular matrix proteins including collagen type I, fibronectin, and laminin, noncollagenous factors such as glycosaminoglycans (e.g., hyaluronan), glycoproteins, and proteoglycans, and several cell types, including stellate cells, endothelial cells, neural elements, and immune cells [78].

Studies with human pancreatic cancer sections, involving dual staining for PSC-selective markers and *in situ* hybridization for collagen mRNA, have established that PSC are the major source of the fibrosis of pancreatic cancer [79] (Fig. 9.3). Activated PSC have been identified surrounding the earliest (premalignant) lesions of pancreatic cancer, such as pancreatic intraepithelial neoplasms (PanIN) and intraductal papillary mucous

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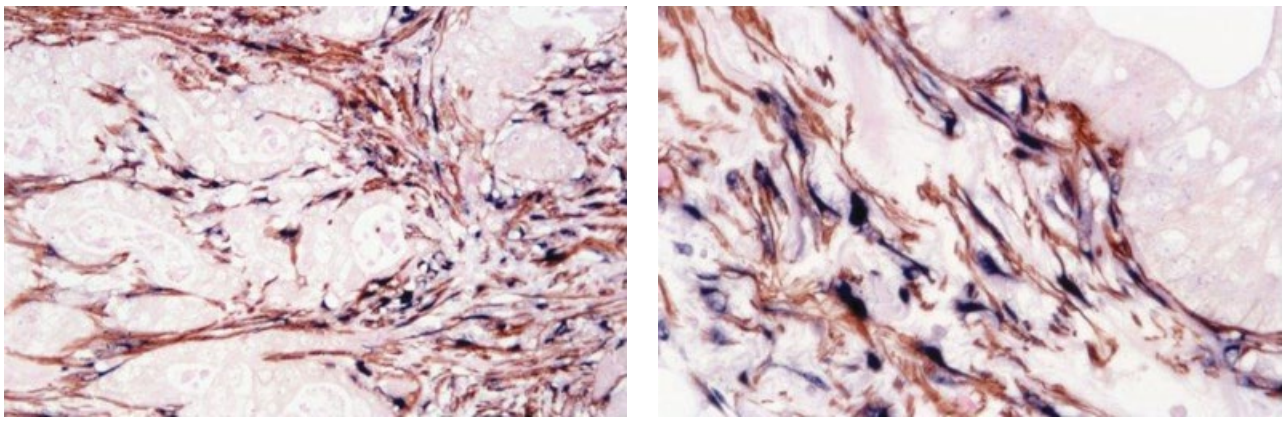


Figure 9.3 Low- and high-power views of a human pancreatic cancer section dual stained for alpha smooth muscle actin (αSMA) and collagen mRNA: immunostaining for αSMA (brown) combined with *in situ* hybridization for collagen mRNA (blue) reveals colocalization of the two stains in stromal areas of the section with no staining in tumor cells. This pattern of staining indicates that pancreatic stellate cells are the main source of collagen in pancreatic cancer stroma. *Source:* Apte et al. (2004) / Reproduced with permission from Wolters Kluwer Health.

neoplasms (IPMN), indicating that PSC activation is an early feature in carcinogenesis [80,81]. While PSC may act to restrain early-stage cancer growth, it is now widely accepted that eventually cancer cells subvert PSC function to their own benefit [82,83]. Indeed, a positive correlation has been reported between the extent of activated PSC in the stroma and poor clinical outcome as assessed by overall survival [84,85].

Recent studies have prompted a recognition of the significant inter- and intra-tumoral heterogeneity exhibited by PSC in pancreatic cancer tissue. Ikenaga and colleagues [86] first reported identifying two populations of PSC based on positive or negative staining for the membrane metalloproteinase CD10, with patients with CD10+ve PSC exhibiting worse outcomes. Subsequently, subtypes of cancer-associated fibroblasts (CAFs) were described by Ohlund et al. [87]—those at a distance from neoplastic cells showing an inflammatory phenotype (high expression of interleukin 6 [IL6] and relatively low expression of αSMA), termed inflammatory CAF or iCAF; and those adjacent to malignant cells showing a myofibroblastic phenotype (high αSMA expression) termed myofibroblastic CAF or myCAF [87]. Since then, a study by Neuzillet et al. [88] using transcriptomic analyses, has reported the presence of four subtypes of CAF (A, B, C, and D) in pancreatic cancer. Each of these subtypes demonstrates specific functional and molecular features and appears to exert different effects on disease prognosis. The authors found that PSC exhibited features mainly of subtypes B and C (prominent expression of myosin II and podoplanin, respectively).

As noted earlier, the role of PSC in pancreatic cancer extends well beyond merely producing the fibrotic stroma. Using *in vitro* (cocultured PSC and cancer cells) and *in vivo* (subcutaneous xenografts, orthotopic implants, genetically engineered models) approaches, a close bidirectional interaction between PSC and cancer cells has been identified, which facilitates local tumor growth and distant metastasis [82,89]. Pancreatic cancer cells induce PSC activation, as evidenced by increased proliferation, ECM production, and migration. In turn, PSC significantly increase pancreatic cancer cell proliferation, while at the same time inhibiting their apoptosis, thereby increasing cancer cell survival. PSC also stimulate cancer cell migration (an effect associated with enhanced epithelial–mesenchymal transition [EMT]) and stemness of cancer cells. Interestingly, cancer cells have been found to induce autophagy in PSC leading to release of alanine, which acts as an alternative carbon source for the TCA cycle and lipid synthesis in cancer cells, thus improving cancer cell survival in the nutrient-poor and hypoxic environment of PDAC [90]. The transport of alanine between PSC and cancer cells is reported to be mediated by the SLC1A4 transporter, which is upregulated on cancer cells and may serve as a novel therapeutic target to inhibit cancer cell metabolism [91]. The factors/signaling pathways that mediate the interactions of PSC and cancer cells are being increasingly elucidated. A detailed discussion of these is out of the scope of this chapter, but the major factors are summarized in Table 9.6. Interactions of PSC with other cells in the tumor microenvironment are covered in Chapter 123.

A known characteristic of pancreatic desmoplasia is its ability to interfere with the delivery of chemotherapeutic agents to cancer cells. Hessmann et al. [92] demonstrate that PSC/cancer-associated fibroblasts are not only resistant

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Table 9.6 Signaling pathways mediating interactions between pancreatic stellate cells and cancer cells.

Mediator	Signaling pathway	Functional role
PSC-derived CXCL12 (SDF-1)	CXCL12 (SDF-1) signaling	Immunosuppression
PSC-derived SDF-1	Galectin-1	Proliferation of PSC and chemokine production facilitating PCC metastasis
Smo, Gli	Hedgehog pathway	PSC activation, ECM synthesis, migration, desmoplasia, angiogenesis; PCC proliferation, migration, and chemoresistance
HGF	HGF/c-MET pathway	PSC promote proliferation and metastasis of tumor cells
CCL2	Hypoxia inducible factor 1 (HIF-1)	PSC activation, Macrophage recruitment
IL-6	IL6/JAK/STAT	PSC activation and proliferation
Kindlin-2	Integrin	Cytokines production in PSC facilitating progression and migration of PCC
MAPK	Mitogen-activated protein kinase (MAPK) signaling pathway	PSC proliferation, TIMP-1 production
Periostin	Periostin pathway	Periostin secreted by PSC promoting PCC proliferation, EMT, and resistance to nutrient deprivation and hypoxia
PPAR-γ ligands	Peroxisome proliferator-activated gamma (PPARγ)	Inhibition of PSC activation, proliferation, and collagen synthesis Increased phagocytosis
PDGF	PI3-Kinase pathway	PSC migration and proliferation
Hyperglycemia	Protein kinase C	PSC proliferation, α-SMA, collagen-I production, angiogenesis
Suppression of miRNA-21	Reactive oxygen species (ROS)	PSC activation and induction of glycolysis
Rho-associated protein kinase	Rho-ROCK pathway	Activation of PSC, collagen I synthesis, and fibrosis
SMAD-2,3	SMADS	PSC activation, proliferation, ECM deposition, transdifferentiation, TGF-β1 expression
TLR9	Toll-like receptor (TLR) signaling	Immunosuppression; PSC-derived cytokine production
Vitamin D	Vitamin D receptor	PSC quiescence; decreased chemoresistance
β-catenin	Wnt/β-catenin signaling	Invasion of PCCs
Caveolin-1 (Cav-1)	Cav-1-ROS signaling	Promotes tumor growth and induces stroma–tumor metabolic coupling
NGF	PI3K/AKT/GSK signal pathway	Cancer cell proliferation and invasion

α-SMA: alpha smooth muscle actin; c-MET: tyrosine-protein kinase of Met; CCL: chemokine ligand; CXCL: chemotactic cytokine ligand; ECM: extracellular matrix; JAK/STAT: Janus kinase/signal transducers and activators of transcription; HGF: hepatocyte growth factor; NGF: nerve growth factor; PCC: pancreatic cancer cells; PDGF: platelet-derived growth factor; PSC: pancreatic stellate cells; SDF: stromal-derived factor; SMAD: small worm mothers against decapentaplegic.

to gemcitabine themselves but can convert gemcitabine into an inactive metabolite 2′,2′-difluorodeoxyuridine thus decreasing the availability of active agent to destroy tumor cells. PSC may also directly modulate the response of cancer cells to chemotherapeutic agents. In an autocrine response to stromal-derived factor 1α (SDF-1α) secreted by PSC, the cells secrete IL6, which in turn exerts a protective effect on cancer cells from the apoptotic effect of gemcitabine [93]. In addition, post-chemotherapy, PSC may facilitate proliferation of residual cancer stem cells leading to recurrence [94].

In view of the emerging strong evidence of the importance of the microenvironment to pancreatic cancer outcomes, there is general agreement in the field that targeting cancer cells alone will remain an inadequate treatment approach and that modulating the microenvironment in addition to chemotherapy represents an essential element of future novel therapies. New high-throughput screening

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modalities have the potential to allow faster identification of potentially useful compounds that target stromal–tumor interactions [95].

Conclusion

In summary, it is now unequivocally established that the cells responsible for fibrogenesis in the pancreas are pancreatic stellate cells (PSC). In health, PSC maintain a fine balance between ECM production and degradation, thereby ensuring normal ECM turnover in the gland. PSC may also have additional roles in the healthy pancreas as progenitor cells, immune cells, and intermediary cells in CCK-regulated pancreatic exocrine secretion. In diseased states, PSC are transformed into an activated myofibroblast-like state, producing excessive amounts of ECM proteins. When the activation of PSC is limited, as in resolving acute pancreatitis, PSC can aid the regenerative/repair process. However, perpetuated activation of the cells, as seen in chronic pancreatitis and pancreatic cancer, ultimately leads to pathologic fibrosis. Notably, it is now becoming increasingly evident that PSC have functions beyond the fibrotic process in both chronic pancreatitis and pancreatic cancer. In chronic pancreatitis, PSC have been shown to facilitate acinar cell injury, interact with M2 macrophages and to promote islet (beta) cell dysfunction. In pancreatic cancer, PSC display heterogeneity facilitating both inflammation and fibrosis and they interact closely with cancer cells and other stromal cells such as endothelial cells, immune cells, nerve cells as well as the ECM itself to influence cancer progression. Understanding the biology of these multifunctional PSC will underpin the development of novel therapeutic approaches for difficult-to-treat fibrotic diseases of the pancreas such as chronic pancreatitis and pancreatic cancer.

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10

Pancreatic Endocrine–Exocrine Relationship

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Introduction

The adult pancreas is composed of two functional tissue components. One is exocrine pancreatic tissue, in which acinar cell clusters are connected to the pancreatic ducts and secrete digestive enzymes into the duodenum. The other is the islet, an endocrine cell mass that secretes hormones into the bloodstream to maintain blood glucose homeostasis. Though the functions of exocrine and endocrine pancreas are separately conducted by independent functional tissues in mature pancreas, both tissues are anatomically in intimate contact. For example, a capillary microvascular network that connects islets and acini is reported in humans and other mammals. Until very recently, it has long been believed that arterial blood is separately supplied to the islets and acini but the outflow from the islet is drained into the surrounding acini through the microvascular network, known as the insuloacinar portal system. As a result, acinar cells are exposed to high concentrations of islet hormones and potentially receive signals from islet cells. It has been shown that insulin receptors are expressed in acinar cells and that insulin stimulates digestive enzyme secretion [1–4], leading to the concept of an insulin–pancreatic acinar axis. Similarly, other islet hormones are involved in regulating acinar function directly or indirectly, expanding the concept of the islet–acinar axis. For example, somatostatin from islets shows an inhibitory effect on exocrine pancreatic secretion [5,6]. Glucagon and pancreatic polypeptide also regulate exocrine function indirectly via insulin and somatostatin action [7–11]. Considering new information on intra-islet crosstalk among α, β, δ, γ, and ε cells [12], acinar function is regulated by orchestrated outputs from the heterogeneous cell types of the islet.

More recently, however, Dybala et al. performed real-time imaging of individual red blood cells *in vivo* and showed that blood flow in the microvascular network is bidirectional between islet and exocrine pancreas in mice, indicating that blood supply into the islet is not isolated from the microcirculation of exocrine tissue [13,14] (Fig. 10.1). Along with the microvascular network, the lack of capsule or basement membrane, which separates islets from the exocrine acinar compartment, enables intercellular communications between exocrine and endocrine tissues via secreted factors or direct cell-to-cell contact signals [14]. Indeed, the accumulation of abnormal proteins secreted by exocrine acinar cells impairs β-cell function in maturity-onset diabetes of the young type 8 (MODY8) [15]. Thus, endocrine and exocrine pancreas tissues are not only in anatomically intimate contact, they functionally regulate each other through bidirectional communications.

In this chapter, pancreatic endocrine–exocrine interactions are discussed by introducing clinical evidence, phylogenetic comparisons of the pancreas, and a brief overview of murine pancreas development. Further, new information on intercellular signals are reviewed, focusing on the regulation of embryonic islet development by acinar products and intra-islet crosstalk for regulating cell function and the maintenance of cell identity.

Clinical Evidence that Supports the Endocrine–Exocrine Relationship

Exocrine Dysfunction in Diabetic Patients

Exocrine dysfunction in diabetic patients was reported in studies that showed reduced amylase secretion by the secretion-pancreozymin test. Hardt et al. conducted a multicenter analysis and reported that 22.9% of 1021 diabetic patients showed lower concentrations of fecal elastase-1 and a higher prevalence of reduced elastase-1 in

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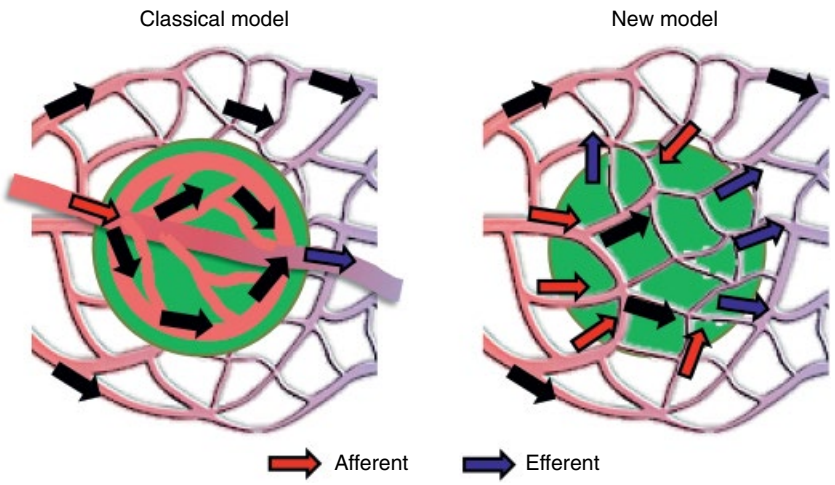


Figure 10.1 Islet microcirculation models. Left panel: the classical model, or "insulo-acinar portal system," assumes independent afferent vasculature (red arrow) to the islet and unidirectional blood flow Adapted from [1–4]. Right panel: the new model by Dybala et al. Adapted from [13] shows connecting capillaries and bidirectional blood flow between exocrine and islet tissues.

T1D than T2D patients (51% and 35%, respectively) [16]. Furthermore, fecal elastase-1 was reported to be inversely correlated with HbA1c levels and duration of the disease [17]. Andriulli et al. reported a meta-analysis of prospective studies involving 2891 patients (921 of them with T1D and 1970 with T2D) [18]. They showed that fecal elastase-1 was low in 921 patients (31.8%). The prevalence of the low elastase-1 level was 37.7% in T1D and 26.2% in T2D patients. Collectively, almost one in three patients with diabetes exhibited impaired exocrine function by testing for fecal elastase-1.

Despite exocrine dysfunction in the majority of diabetic patients being clinically mild, the pancreatic size in T1D patients is reported to be 45% smaller than healthy controls [19,20]. Because acinar cells constitute more than 90% of total pancreatic epithelial cells, this finding indicates the involvement of an endocrine–exocrine relationship, though no clear mechanism is known [19,20].

Diabetes in Patients with Chronic Pancreatitis

Seventy percent of patients with chronic pancreatitis have diabetes mellitus. It is naturally imagined that chronic inflammation in exocrine tissue affects islets and causes β-cell loss, but the pathogenesis has proven not to be so simple. While the majority of patients with chronic pancreatitis show insulin deficiency, only 16% show hypoglucagonemia [21]. Intriguingly, oral glucose intake stimulates glucagon secretion, resulting in hyperglycemia in patients. In addition, Larsen et al. reported that meal-induced somatostatin secretion was elevated in these patients and potentially suppresses insulin secretion [22]. Though the precise mechanism that causes the impaired secretion of these islet hormones in the patients is unknown, Pierzynowska et al. reported that the intravenous administration of amylase decreased insulin levels in a pig model [23]. Considering the leaked digestive enzymes into the pancreatic parenchyma in human chronic pancreatitis, a direct inhibitory effect of acinar products on β-cell function has been an attractive hypothesis.

Maturity-Onset of Diabetes of the Young Type 8 (MODY8)

More direct evidence on the acinar–islet axis was recently shown in the pathogenesis of MODY8 [15]. These patients develop juvenile-onset exocrine dysfunction, followed by glucose intolerance during young adulthood. The causative gene of this disease is carboxyl ester lipase (CEL), which is expressed specifically in pancreatic acinar cells. Mutant CEL protein, which is produced in the acinar cells of MODY8 patients, is up-taken by β cells via endocytosis, and accumulated mutant protein impairs the function of β cells and reduces their proliferation, resulting in glucose intolerance.

Endocrine and Exocrine Pancreas: Phylogenetic Comparison and Embryonic Organogenesis of Mammalian Pancreas

Evolution of Vertebrate Pancreas

To understand the molecular mechanisms functioning in the endocrine–exocrine crosstalk of human pancreas, an understanding of the evolution of vertebrate pancreas in the phylogenetic tree and the machineries of embryonic organogenesis of mammalian pancreas is useful. Invertebrates do not have a pancreas, but islet hormone-producing cells are dispersed within the gut epithelium of

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Cephalochordate [24]. The first animal that showed an endocrine cell cluster, i.e., a primitive islet, is Lamprey, but its islet is not surrounded by exocrine tissue [25]. Interestingly, insulin-producing cells are first found in the gut of ammocoetes, a larva stage, and divided into two clusters in adults; one cluster expands in the gut subepithelial layer and the other enters the liver. Similarly, somatostatin-producing cells are detected first in the gut epithelium but then move to the subepithelial layer, where they form the islet structure with insulin-producing cells. Glucagon-producing cells exist within the gut epithelium throughout life and do not join the islet [26]. As evolution progressed, Gnathostomata acquired exocrine pancreas tissue [27]. The acquisition of a jaw, it seems, required a new digestive organ to meet increased masticatory substances. In Chondrichthyes such as sharks, the pancreas is detected as a solid organ that contains endocrine and exocrine tissue, but the pancreas of Osteichthyes is not uniform. In some fish, including eels and catfish, the pancreas is detected as an independent organ, but in others it exists in the liver as a hepatopancreas [27]. In other vertebrates, including amphibians, reptiles, birds, and mammals, the pancreas is basically detected as an independent solid organ that possesses endocrine and exocrine tissues [24]. Considering the tight connection between the digestion/absorption of nutrients and regulation of blood glucose levels, the coexistence of the two tissues in one organ and the mutual regulation of their function would be a purposeful change during evolution.

Organogenesis of Mammalian Pancreas during Embryonic Stages

As stated above, the pancreas originated from the gut and became an independent organ during vertebrate evolution. A similar process is conserved in the embryonic organogenesis of the mammalian pancreas. Previous studies showed both exocrine and endocrine cells originate from a pool of multipotent precursor cells in the pancreatic buds that evaginate from the primitive gut tube in mice [28]. Within the pancreatic buds, epithelial cells gradually form the ductal plexus and undergo remodeling to form a branched duct structure composed of a Cpa1- and Ptf1a-expressing tip domain and a Nkx6.1-positive trunk domain [28]. During segregation of the tip/trunk regions, the differentiation ability of epithelial cells is spatiotemporally regulated; $Pdx1^{+}Ptf1a^{+}c Myc^{high}Cpa1^{+}$ progenitor cells are multipotent at first but lose their ability for endocrine differentiation after embryonic days 13–14, whereas $Nkx6.1^{+}$ cells in the trunk region can differentiate into endocrine and duct cells [28]. In endocrine lineage, $Ngn3^{+}$ endocrine precursor cells bud out from the lining of the $Nkx6.1^{+}$ ductal trunk and differentiate into all cell types of the islet, including glucagon^{+} α cells, insulin^{+} β cells, somatostatin^{+} δ cells, and pancreatic polypeptide^{+} γ cells. Acinar cells are formed in the Cpa1- and Ptf1a-expressing tip domain [28].

Gene knockout studies have identified several crucial transcription factors in murine pancreas development. For example, *Pdx1* knockout results in pancreatic agenesis, while *Ngn3*-null mice lack differentiated endocrine cells [29]. The inactivation of *NeuroD* causes a significant reduction in endocrine cell numbers and impaired islet formation [30]. Further, *Ptf1a*-null mice completely lack exocrine acinar cells but have a small number of endocrine cells [31,32].

Regulation of Endocrine Development by Exocrine Cells during Embryonic Stages

Kodama et al. reported that the exocrine-specific inactivation of *Pdx1* by Elastase-Cre causes not only hypoplastic exocrine formation but also substantial endocrine defects resulting in a diabetic phenotype [33]. Defects in endocrine development include impaired tip/trunk patterning of the developing ductal structure, accelerated apoptosis, reduced number of Ngn3-expressing endocrine precursors, and ultimately fewer β cells. In addition, postnatal expansion of the endocrine cell content was extremely poor. These findings indicate the existence of several exocrine-driven factors that regulate proper endocrine development and function. Using microarray-based analysis of the same mutant mice and an *in vitro* explant culture of embryonic pancreatic tissue, Hirata et al. identified Trefoil factor 2 (TFF2) as a novel exocrine factor that supports the survival of endocrine cells in the multiple stages of organogenesis through distinct receptors: TFF2 prevents the apoptosis of insulin-producing cells and $Nkx6.1^{+}$ endocrine precursors via CXCR4 receptor and an unknown receptor for TFF2, respectively [34] (Fig. 10.2). Future study warrants the identification of other exocrine-driven factors that regulate endocrine development, and it may be possible that the same embryonic machinery is reactivated in the pathogenic situation in adult organ.

Intra-Islet Crosstalk for Cell Function and Identity

Recent advances in islet biology include the molecular mechanism of intra-islet communications that orchestrate hormone secretion and govern cell state plasticity.

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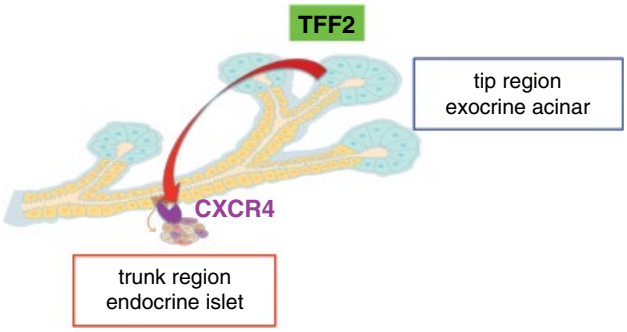


Figure 10.2 Exocrine–endocrine crosstalk in the developmental stage. TFF2, an acinar product, acts on insulin-producing cells to prevent apoptosis through CXCR4 receptor. TFF2: trefoil factor 2; CXCR4: C-X-C motif chemokine receptor 4.

Intra-Islet Communication in Hormone Secretion

Pancreatic islets are composed of five major cell types secreting different hormones: glucagon$^+$ α cells, insulin$^+$ β cells, somatostatin$^+$ δ cells, pancreatic polypeptide (PPY)$^+$ γ cells, and ghrelin$^+$ ε cells. Inside the islet, these endocrine cells have heterogeneous contacts with each other and establish intra-islet crosstalk via paracrine signals, and all play critical roles in the maintenance of blood glucose hemostasis in the body. It should be noted that not only major pancreatic hormones but also several proteins secreted from α and β cells are involved in transmitting intra-islet crosstalk. These transmitters include α-cell-derived glucagon-like peptide 1 (GLP-1) and acetylcholine (Ach), β-cell-derived serotonin (5-HT), and urocortin3 (UCN3) secreted from α and β cells in humans (Fig. 10.3).

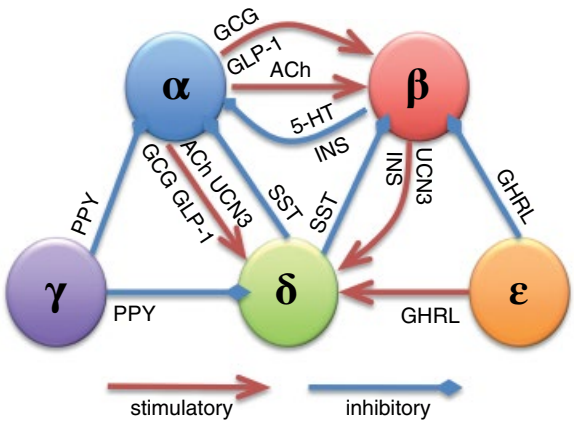


Figure 10.3 Intra-islet crosstalk regulates hormone secretion. Note the reciprocal regulation among endocrine cells to determine the amount of hormone secretion. Ach: acetylcholine; GCG: glucagon; GHRL: ghrelin; GLP-1: glucagon-like peptide 1; INS: insulin, PPY: pancreatic polypeptide; SST: somatostatin; UCN3: urocortin 3; 5-HT: serotonin.

In detail, signaling molecules from α cells, including glucagon and GLP-1, enhance insulin secretion through glucagon and GLP-1 receptors by increasing intracellular cyclic AMP levels [35–37]. Furthermore, ACh released from α cells regulates insulin secretion both positively and negatively; it directly acts on β cells to stimulate the secretion and indirectly suppresses the secretion via δ cells [38,39]. In turn, β-cell signaling molecules, including insulin and 5-HT, suppress α-cell secretion, establishing a paracrine feedback loop between α and β cells [40]. Delta cells are powerful inhibitory modulators of α- and β-cell signaling. Somatostatin secreted from δ cells predominantly functions as a paracrine suppressor to glucagon and insulin secretion in response to stimulatory cues from α or β cells (such as insulin, UCN3, glucagon, GLP-1, and ACh), providing negative feedback loops [38,39,41,42]. Additionally, PPY secreted from γ cells potentiates insulin secretion by inhibiting somatostatin secretion and directly suppressing glucagon secretion [10,11]. Recent studies showed that ghrelin secreted from ε cells suppresses insulin secretion directly and indirectly through enhanced somatostatin secretion [43,44].

The aforementioned mutual communication among islet cells seems to serve as a safety valve to maintain glucose homeostasis for the disease condition; however, intra-islet crosstalk itself is reported to be disturbed in diabetes. Accumulating evidence has shown that α-cell functions and gene expressions are compromised in T1D [45], indicating an impaired counterregulatory response to hypoglycemia [46]. Further, β-cell destruction in T1D decreases intra-islet UCN3 levels, which could lead to the attenuation of somatostatin inhibitory circuits and thus result in exaggerated hyperglycemia via α-cell-derived glucagon action [41]. Therefore, further investigation of impaired intra-islet signaling is required for developing new therapeutic strategies [47,48]. Of note, the islet microenvironment contains non-endocrine cells, including vasculatures, neurons, and immune cells, all of which play significant roles in controlling hormonal outputs from the islet [49,50]. The involvement of these cells in the impaired intra-islet crosstalk in diabetic patients should be clarified.

Intra-Islet Crosstalk for Cellular Identity

Previous studies showed that murine islet cells possess a plasticity to transdifferentiate into other cell types in response to cellular stress or cell death. Talchai et al. demonstrated that murine β cells stop insulin expression under severe metabolic stress and a subset of them dedifferentiate into neurogenin3-expressing endocrine precursor-like cells [51]. In addition, α cells can convert into insulin-producing cells upon near total β-cell loss in mouse diabetic models [52]. However, it was reported

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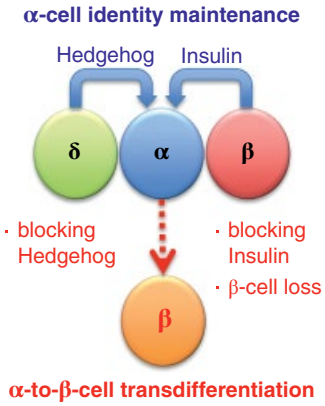


Figure 10.4 Intra-islet crosstalk maintains cell identity. Murine α-cell identity is maintained by insulin and hedgehog signals secreted by surrounding β and δ cells, respectively.

that the percentage of α cells that can transdifferentiate is only 1–2%; thus, the majority of cells are refractory to the cell fate change.

Recent studies have shown that intra-islet crosstalk also plays important roles in maintaining the identity of islet cells (Fig. 10.4). Cigliola et al. revealed that, even without β-cell ablation, blockade of the insulin pathway in α cells, either by insulin receptor knockout or by treatment with insulin receptor antagonists, caused α-to-β-cell transdifferentiation [12]. In addition, the inhibition of δ-cell-driven hedgehog signaling in α cells promotes α-cell conversion into insulin-producing cells [12]. These findings clearly show that α-cell identity is maintained by paracrine permissive signals derived from proximate β and δ cells in mice. As to the plasticity of human islet cells, the first evidence was provided when α and γ cells were observed to transdifferentiate into insulin-producing cells upon Pdx1 and MafA overexpression *in vitro* [53]. However, it is still an open question if transdifferentiation to other cell types upon cellular stress occurs, or if similar intra-islet crosstalk functions to maintain cellular identity in human islets *in vivo*. Future study is warranted.

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Section 3

Acute Pancreatitis

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11

Epidemiology and Etiology of Alcohol-Induced Pancreatitis

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Introduction

Alcoholic pancreatitis represents a clinical paradox. On the one hand, the risk of developing the disease increases with the amount of alcohol consumed, suggesting direct toxic effects of alcohol on the pancreas. On the other hand, only a minority (5% or less) of heavy drinkers develop the disease, suggesting a role for individual susceptibility factors. (Note: In this text, the words "alcohol" and "ethanol" are used interchangeably.)

Epidemiology

In Western society, alcohol ranks with gallstone disease as a major cause of acute pancreatitis, and is the major cause of chronic pancreatitis. There has been variation in attribution rates amongst different studies [1–4]. This variation most likely relates to the background alcohol consumption of the population under study, the types of institutions surveyed (e.g., private facility vs. county or Veterans Affairs facilities in the United States), the difficulties associated with eliciting an accurate alcohol consumption history, and the growing awareness of possible cofactors in the disease (e.g., smoking). There is evidence that the incidence of acute episodes of alcoholic pancreatitis is rising in many Western countries [5].

For a long time, acute alcoholic pancreatitis and chronic alcoholic pancreatitis were considered separate diseases [6]. It is now generally recognized that they are a part of the same continuum. There is good clinical [7,8] and experimental evidence [9,10] that repeated attacks of pancreatic necroinflammation lead to chronic pancreatitis (the necrosis-fibrosis sequence).

With respect to the amount of alcohol consumption required to produce pancreatitis, there has been confusion. Episodic binge drinking or the isolated alcoholic debauch rarely, if ever, causes pancreatitis [11]. However, with regard to the common situation of chronic alcohol intake, an early study suggested that the risk of developing pancreatitis was linear, even at relatively low (social) levels of consumption [12]. Later studies have suggested that there is a threshold above which pancreatitis is more likely to occur [2,13,14]. A recent meta-analysis found that the risk of chronic pancreatitis increased 2.5-fold at 50 g/day consumption and approximately sixfold at 100 g/day consumption [15].

Most clinicians, basing their views on clinical experience, would agree that the diagnosis is not made in the absence of chronic heavy alcohol consumption (80–100 g of alcohol per day for at least 5 years). However, alcoholic pancreatitis is now emerging as a polyfactorial/polygenic disease, so that lesser amounts of alcohol consumed may also be responsible for the phenotype.

Pathogenesis

Large Duct and Small Duct Theories

Historically, studies of pathogenesis of alcoholic pancreatitis centred first on the sphincter of Oddi and the large pancreatic ducts and subsequently on the small pancreatic ducts. The "large duct" theories gradually lost support because of a failure of consensus on the effects of alcohol on sphincter of Oddi motility, the effect of alcohol on pancreatic secretion and other factors. The "small duct" theory lost support over failure to establish the primary role of protein plugs in small pancreatic ducts in the pathogenesis of the disease. These "duct" theories have been dealt with in greater detail elsewhere [16].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Direct Cellular Effects of Alcohol on the Pancreas

From the 1980s, attention focused on the direct effects of alcohol on pancreatic acinar cells; from around 2000, on pancreatic stellate cells and, most recently, on pancreatic duct cells. The results of these studies, conducted largely in rodents, are depicted in Fig. 11.1.

It should be emphasized that there is no satisfactory model of alcoholic pancreatitis. In experimental animals, alcohol by itself induces a number of changes that predispose the pancreas to autodigestion, acinar injury, and stellate cell activation, but which are insufficient to cause overt pancreatitis. However, co-administration of an additional "hit" such as bacterial endotoxin produces pancreatitis (necroinflammation and fibrosis) as delineated in greater detail below.

The recently described Gao-binge model [17] results in pancreatic damage but involves pair feeding of liquid diets followed by a single gavage of diet equivalent to 5 mg/kg ethanol, which equates to 35 standard drinks in a 70 kg male. Although the mortality of this model is reported to be zero, one must query whether the changes reported represent an effect of ethanol per se or perturbation of cardiovascular and other systems.

Metabolism of Alcohol by the Pancreas

Many of the direct effects of alcohol on the pancreas are a consequence of the metabolism of alcohol (ethanol) by the gland via oxidative and nonoxidative pathways.

The oxidative pathway of alcohol metabolism involves sequential oxidation by alcohol dehydrogenase (ADH) to acetaldehyde and then to acetate via acetaldehyde dehydrogenase (ALDH). Catalase in peroxisomes can also metabolize ethanol to acetaldehyde but its activity is thought to be low as it is determined by the availability of its substrate hydrogen peroxide (H_2O_2). Additionally, cytochrome P450 2E1 (CYP2E1) can metabolize ethanol, at high concentrations, to acetaldehyde and this is enhanced by enzyme induction following chronic ethanol exposure [18]. Both ADH and CYP2E1 have been identified in pancreatic tissue (catalase is ubiquitous) [19–21]. The oxidative pathway results in depletion

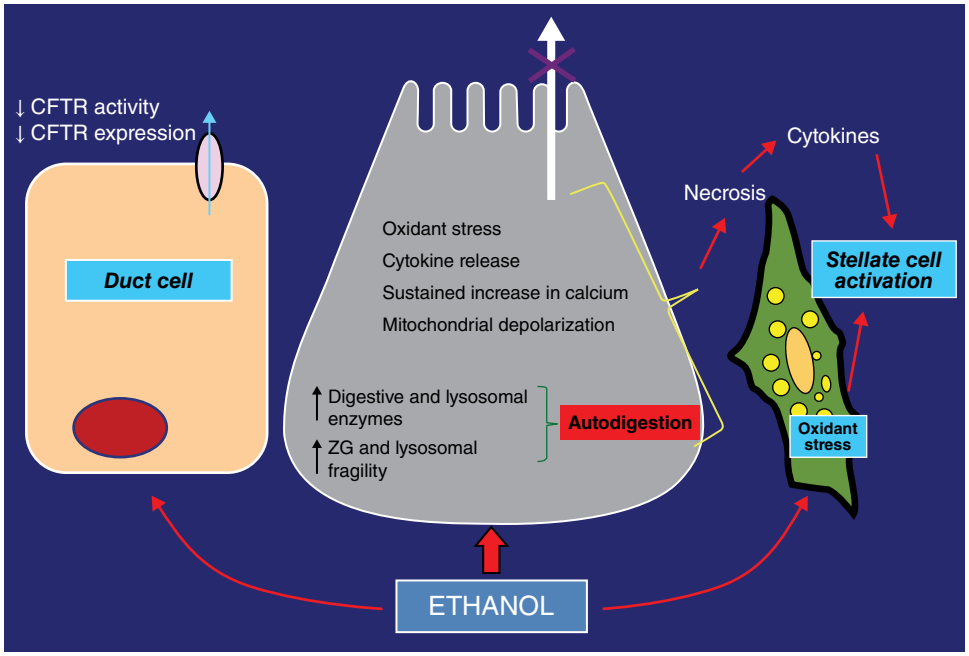


Figure 11.1 Effects of alcohol and its metabolites on the acinar cell, duct cell, and stellate cell of exocrine pancreas. Ethanol induces an increase in digestive and lysosomal enzyme synthesis in the acinar cell, while at the same time, decreasing exocytosis and impairing organelle stability. These effects predispose the cell to premature intracellular enzyme activation and autodigestion. Ethanol metabolism within the cell leads to oxidant stress which damages subcellular membranes, proteins, and nucleic acids. In addition, ethanol causes a sustained increase in intracellular calcium leading to mitochondrial depolarization and cell death. The ethanol-induced injury to the acinar cell also results in the release of cytokines by the cell, which can subsequently damage neighboring cells. Ethanol impairs duct cell function by decreasing CFTR expression and activity. With regard to the pancreatic stellate cell, ethanol and its metabolites and oxidant stress activate PSC leading to production of excessive amounts of extracellular matrix proteins. Cytokines released from acinar cells can also activate PSC via paracrine pathways, while cytokines synthesized by PSC themselves can further activate the cells in an autocrine manner, leading to progressive fibrosis, even in the absence of the initial trigger. *Source:* Pancreatic Research Group, UNSW Sydney.

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of antioxidant defences (mainly glutathione) and the production of reactive oxygen species capable of disruption of membranes, proteins, and DNA.

The nonoxidative pathway involves esterification of ethanol with free fatty acids (FFA) to form fatty acid ethyl esters (FAEE). The enzymes catalyzing this reaction are fatty acid ethyl ester (FAEE) synthases. There appears to be no one enzyme responsible for this reaction, and carboxyl ester lipase (CEL) and triglyceride lipase have been implicated. It has been reported that the pancreas has the highest FAEE synthesizing capacity of any parenchymal organ [22].

FAEE are believed to exert toxicity via:

- direct perturbation of biological membranes following intercalation, and
- a transport shuttle mechanism with local release of FFA resulting in disturbance of intracellular membrane function with decreased lysosomal stability (*vide infra*) and altered intracellular calcium homeostasis with resultant calcium overload, mitochondrial dysfunction and cell death.

The pancreatic acinar cell possesses the enzymatic machinery for both oxidative and nonoxidative ethanol metabolism, with the former representing the major pathway for alcohol metabolism [19–21] in rats. Kinetic studies using rat pancreatic acini suggest that ethanol is metabolized in acinar cells predominantly by Class III (high Km) ADH [19,20]. However, Chiang et al. reported that the predominant class of ADH in human pancreatic acini is ADH I, with ADH III contributing little to pancreatic alcohol oxidation [23]. These disparate findings may reflect species differences and the relative magnitudes of the oxidative and nonoxidative pathways in human pancreatic tissue remain to be determined. However, even in rat pancreatic acinar cells, where oxidative metabolism of ethanol seems to dominate, the contribution of the nonoxidative pathway cannot be discounted because FAEE are produced in sufficient amounts to produce local injury [24]. Interestingly, pharmacological inhibition of the FAEE synthase CEL ameliorates alcohol-induced pancreatic damage in mice [25]. A recent study suggests that circulating FAEE levels may be useful as a specific biomarker for acute alcoholic pancreatitis (as distinct from nonalcoholic acute pancreatitis) [26].

Rat pancreatic stellate cells (PSC) can also oxidize alcohol to acetaldehyde via a pyrazole–sensitive (Class I) ADH [27]. These observations are well supported by a study reporting activity of an ADH Class I isozyme, namely ADH1C, in quiescent human PSC, which was inhibited by pyrazole [23]. Interestingly, this study also showed that the expression of ADH1C was increased in activated human PSC in chronic pancreatitis [23]. The capacity of PSC for nonoxidative ethanol metabolism is yet to be determined.

Effects of Ethanol on Pancreatic Acinar Cells

Chronic alcohol administration to rodents results in a number of changes in acinar cells which may predispose the cells to injury.

In vitro and *in vivo* approaches have now established that ethanol and its metabolites exert multiple effects on acinar cells including:

- an increase in intracellular levels of digestive enzymes (trypsin, chymotrypsin, and lipase) mediated, at least in part, by increases in their respective mRNA levels [28] and possibly also by decreased secretion secondary to acetaldehyde-induced apical microtubule disruption [29] and inhibition of binding of secretagogues to their receptors [30];
- an increase in lysosomal enzyme content [28,31];
- decreased stability of lysosomes mediated by accumulation of FAEE and cholesteryl esters (transesterification products of FAEE) in the cells [24,32];
- decreased zymogen granule (ZG) stability [33], possibly mediated by an ethanol-induced reduction of GP2 [34], the predominant protein in ZG membranes that is responsible for ZG shape and membrane stability.

Taken together, the effects of alcohol on lysosomes and ZGs create a situation whereby there is an increased potential for contact between trypsinogen and lysosomal hydrolases with subsequent generation of active trypsin, thus activating an intracellular digestive enzyme cascade and autodigestion.

- FAEE cause a sustained rise in intracellular calcium levels by (i) inducing calcium release from endoplasmic reticulum following stimulation of IP_3 receptors, and (ii) inhibiting Ca^{++}ATPase pumps in plasma membrane and endoplasmic reticulum (ER) resulting in defective clearance of cytosolic calcium. The sustained rise in calcium levels causes mitochondrial overload and cell death [35].
- Transcription factors NF-κB and AP-1 (which are important regulators of cytokine expression) are induced by alcohol and acetaldehyde as well as by FAEE [19].

The unfolded protein response/ER stress and autophagy are two homeostatic mechanisms for maintaining cellular integrity in all cells. Recent studies have demonstrated that chronic alcohol consumption induces ER stress [36,37] and impairs autophagy [17,38] in pancreatic acinar cells.

Effects of Ethanol on Pancreatic Stellate Cells

PSC are the principal source of collagen and other extracellular matrix proteins in the fibrosis of chronic alcoholic pancreatitis. PSC are directly activated upon exposure to

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ethanol [27,39]. This activation is thought to be mediated via the metabolism of alcohol to acetaldehyde and the subsequent intracellular generation of reactive oxygen species [27].

PSC are also activated by inflammatory cytokines (released during pancreatic necroinflammation) and, in turn, produce their own inflammatory cytokines resulting in an autocrine loop allowing perpetuation of activation even after removal of the initial insult [40–44].

Effects of Ethanol on Pancreatic Duct Cells

Inspired by the original observations of Sarles et al. [6] on pancreatic intraductal abnormalities and sweat electrolytes in patients with chronic alcoholic pancreatitis, Maleth et al. [45] have recently examined the effect of ethanol on CFTR function. This was impaired (as determined by sweat chloride concentration) in recently abstinent alcoholics and in acutely drinking alcoholics with very high blood alcohol concentrations but not in normal individuals consuming alcohol acutely. In addition, it was found that in duct cells isolated from alcoholic pancreatitis tissue, CFTR expression was decreased at both mRNA and membrane protein levels, with evidence of impaired posttranslational processing. In *in vitro* experiments using duct cell lines and tissue from mice and guinea pigs, ethanol decreased CFTR mRNA as well as membrane CFTR levels and stability; these effects were reported to be mediated by nonoxidative metabolites of ethanol.

Regulation of Gene Expression in Alcoholic Pancreatitis

Chhatriya et al. [46] in a preliminary study involving analysis of serum from a small number of patients ($n = 4$) with alcoholic pancreatitis or alcoholics without pancreatitis ($n = 4$, controls "normal") and pancreatic tissue from patients with alcoholic pancreatitis (data from existing datasets) have identified 14 miRNA differentially expressed between index and controls, in both serum and pancreas. Network analysis was performed to identify the differentially expressed genes regulated by these miRNA as well as the transcription factors that influence the expression of the selected miRNA. The findings indicate that both inflammatory and anti-inflammatory pathways are modulated in alcoholic pancreatitis patients, but given the limitation of sample sizes and lack of experimental validation of the functional consequences of the miRNA/gene changes, the study does not provide any conclusive insights into the pathogeneis of alcoholic pancreatitis. Clearly, much more work is required in this area.

RNA Seq methodology has been employed using tissue derived fom human pancreatic transplantation involving subjects with idiopathic, hereditary, and alcoholic pancreatitis. With respect to alcoholic pancreatitis the number of patients ($n = 2$) is too small to draw meaningful conclusions [47].

Individual Susceptibility to Alcoholic Pancreatitis

Despite the substantial experimental evidence supporting direct toxic effects of alcohol and its metabolites on the pancreas, it is well established that only a minority of alcoholics develop clinically evident pancreatitis [48,49], suggesting that additional factors are required to induce the disease in heavy drinkers. The search for these cofactors has prompted many studies, as summarized in Table 11.1.

Ideally, studies into individual susceptibility to alcoholic pancreatitis should compare alcoholics *with* the disease and alcoholics *without* the disease so that the index and the control groups differ in only one variable, i.e., the presence or absence of pancreatitis. This has not always been the case, with several studies using only the healthy population as a control group.

Environmental Factors

Dietary Factors

There is no clear evidence that dietary factors play a role in individual susceptibility to alcoholic pancreatitis [50] especially with respect to macronutrients. Properly controlled studies of dietary micronutrients, antioxidants and other micronutrients are yet to be performed.

Beverage Type and Periodicity of Drinking

Similarly, there is no evidence that the type of alcoholic beverage consumed plays any part in susceptibility to alcoholic pancreatitis [50], although the congeners of alcoholic beverages have not been studied exhaustively.

Additionally, it has not been established that the periodicity of drinking is a susceptibility factor in this disease [50]. Although there have been occasional reports implicating binge drinking, most patients imbibe alcohol at high levels constantly, prior to the initial presentation.

Smoking

The role of smoking as a trigger factor for alcoholic pancreatitis has been a particularly contentious subject [51,52]. The vast majority of heavy drinkers are also smokers, making it difficult to demonstrate unequivocally an independent role for smoking in the initiation of pancreatitis. Law et al. [53] concluded that smoking is independently associated with chronic pancreatitis, after adjusting for alcohol and other risk factors. However, the retrospective nature of the study made it difficult to

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Table 11.1 Individual susceptibility to alcoholic pancreatitis.

Factor	Association	
Drinking pattern	No	Wilson et al., 1985 [50]
Beverage type	No	Wilson et al., 1985 [50]
	Yes	Nakamura et al., 2003 [102]
Diet	No	Wilson et al., 1985 [50]
Smoking	Yes	Lowenfels et al., 1987 [103]
	No	Haber et al., 1993 [104]
	Yes	Maisonneuve et al., 2005 [54]
Obesity	Yes	[a]Ammann et al., 2010 [56]
Inherited factors		
HLA	No	Wilson et al., 1984 [93]
α1-antitrypsin deficiency	No	Haber et al., 1991 [94]
Cystic fibrosis genotype	No	Norton et al., 1998 [105]
Cytochrome P4502E1 polymorphism	No	Frenzer et al., 2002 [98]
ADH genotype	No	Frenzer et al., 2002 [98]
	Yes	Shimosegawa et al., 2008 [69]
	Yes	Maruyama et al., 1999 [70]
	Yes	Matsumoto et al., 1996 [71]
	Yes	Maruyama et al., 2008 [72]
	Yes	Zhong et al., 2015 [73]
Anionic trypsinogen gene mutation	Yes	[a]Witt et al., 2006 [79]
	Yes	[a]Whitcomb et al., 2012 [80]
	Yes	Derikx et al., 2015 [81]
PSTI/*SPINK1* mutations	Yes	Witt et al., 2001 [83]
Claudin 2	Yes	[a]Whitcomb et al., 2012 [80]
	Yes	Derikx et al., 2015 [81]
TNFα, TGFβ, IL10, IFNϒ polymorphisms	No	[a]Schneider et al., 2004 [95]
Detoxifying enzymes		
• Glutathione *S*-transferase	No	Frenzer et al., 2002 [98]
• UDP-glucuronosyl transferase	Yes	[a]Ockenga et al., 2003 [96]
Carboxyl ester lipase (CEL) polymorphism	Yes	Miyasaka et al., 2005 [75]
	No	[a]Ragvin et al., 2013 [76]
Hybrid allele of CEL (CEL-HYB)	Yes	[a]Fjeld et al., 2015 [77]
Calcium sensing receptor gene (CASR)	Yes	[a]Muddana et al., 2008 [99]
	No	[a]Takats et al., 2021 [100]

[a] Studies that did not include alcoholics without pancreatitis as controls.

stratify accurately the extent of smoking and alcohol use. Furthermore, the study population included patients with chronic pancreatitis with a variety of etiologies; only a small proportion of the study subjects were heavy drinkers.

While the role of smoking as an *initiating* factor in alcoholic pancreatitis remains uncertain, there is evidence to suggest that it may *facilitate the progression* of the disease as evidenced by the accelerated development of pancreatic calcifications and endocrine dysfunction in

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patients with alcoholic pancreatitis who smoke [54]. To study the possible mechanisms of this, Lugea et al. [55] exposed mouse and human acinar cell lines to cigarette smoke extract and/or ethanol. Cigarette smoke and ethanol, but neither agent alone, induced oxidative stress and cell death. The authors also reported that in a rat model of ethanol feeding plus LPS, exposure to cigarette smoke promoted cell death and features of pancreatitis by suppressing the adaptive unfolded protein response signaling pathway and increased ER stress pathways in acinar cells.

Obesity

Another putative risk factor for alcoholic pancreatitis is obesity. Using a prospectively recruited cohort of patients with alcoholic chronic pancreatitis and age- and sex-matched healthy subjects as controls, Ammann et al. [56] reported that obesity prior to onset of chronic pancreatitis, defined as body mass index greater than 30 was fivefold more frequent in patients with alcoholic chronic pancreatitis compared to healthy controls, but had no effect on disease progression. However, as obesity is highly prevalent in asymptomatic alcoholics compared to the general population [57], the lack of an appropriate control group (alcoholics without pancreatitis) in the Ammann study [56] precludes any definitive conclusions regarding obesity as a susceptibility factor for the development of alcoholic pancreatitis.

Lipid Intolerance

Alcohol abuse can cause hypertriglyceridemia and hypertriglyceridemia (at exceptionally high levels of serum triglycerides) is a known cause of acute pancreatitis. These facts have led to speculation that those alcoholics who develop pancreatitis do so via the development of hypertryglyceridemia. However, when postprandial lipid tolerance was studied in patients with alcoholic pancreatitis (index group) no difference was found compared with a control group comprising alcoholics without pancreatitis [58]. This study emphasized the importance of appropriate controls in studying susceptibility to alcoholic pancreatitis.

Endotoxin

Serum endotoxin levels are increased in alcoholics, even after a single binge, most likely due to an alcohol-induced increase in gut permeability permitting translocation of gram-negative bacteria (such as *E. coli*) across the mucosal barrier and decreased clearance of endotoxin by Kupffer cells in the liver [59,60]. Forsyth et al. [61] have shown that alcohol increases the permeability of Caco-2 intestinal epithelial cell monolayers via CYP2E1-induced oxidant stress, which in turn induces the circadian clock proteins, CLOCK and PER2.

Experimental studies support the concept of bacterial endotoxin (lipopolysaccharide, LPS) as a promising susceptibility factor for alcoholic pancreatitis. Vonlaufen et al. [62] reported evidence that endotoxin (LPS) challenge in alcohol-fed rats initiates overt pancreatic injury and also stimulates progression to chronic disease manifesting as acinar atrophy and fibrosis. Importantly, this effect was abrogated in TLR4 (Toll-like receptor 4, LPS receptor) knockout rodents [63], demonstrating the specificity of the effects of LPS on pancreatic cells). These studies were corroborated by the findings of Li et al. [64] of increased LPS levels in the portal blood of ethanol-fed rats accompanied by evidence of pancreatic injury, increased pancreatic expression of collagen I (mRNA and protein), increased expression of TLR4 (mRNA and protein), increased numbers of PSC and increased TLR4 protein expression in pancreatic macrophages and stellate cells.

Further work is needed to determine whether genetic polymorphisms pertinent to the alcohol-induced hyperpermeability/endotoxin paradigm may explain individual susceptibility to alcoholic pancreatitis (*vide infra*).

Hypophosphatemia

Recently, Farooq et al. [65] demonstrated that mice on a low phosphate diet and given alcohol developed pancreatitis reversible with phosphate supplementation. Hypophosphatemia impairs ATP production and mitochondrial function, and has been reported to occur in several acute illnesses including acute pancreatitis [66]. Acceptance of such a hypothesis would require a comparison of alcoholics with and without pancreatitis.

In summary, in terms of environmental factors, a clear and single susceptibility factor for alcoholic pancreatitis remains to be identified.

Hereditary Factors

There have been major advances in documenting hereditary factors in the pathogenesis of pancreatitis. However, these have not translated widely into the management of alcoholic pancreatitis. This may be because abstinence remains the mainstay of treatment and because of the current costs of genetic testing. A large study by Gurakar et al. [67] showed that the percentage of patients initially diagnosed as idiopathic pancreatitis can be reduced by genetic testing but the authors did not test their patients diagnosed as alcoholic pancreatitis.

Polymorphisms of Alcohol Metabolizing Enzymes

Alcohol toxicity is most likely to depend on its metabolism generating toxic metabolites such as acetaldehyde, FAEE, and reactive oxygen species. Increased or decreased activities of alcohol metabolizing enzymes (ADH, ALDH, CYP2E1, FAEE synthases) may result in

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the accumulation of toxic metabolites and tissue damage (*vide supra*).

ADH and ALDH are the major enzymes of oxidative alcohol metabolism in the body. There are multiple ADH and ALDH enzymes encoded by different genes which can exist as several allelic variants. These variants can influence rate of metabolism and their distribution varies between ethnic groups as well as different tissues in the body [18].

Based on amino acid sequence and structural similarities, human ADH enzymes are now classified into five classes. The three Class I enzymes (ADH1A, ADH1B, and ADH1C) are the major contributors to ethanol clearance in the liver [18].

There are two main groups of ALDH enzymes, cytosolic ALDH 1 and mitochondrial ALDH2. ALDH2 is the major enzyme responsible for the oxidation of acetaldehyde to acetate [18].

Most attention to ADH-mediated metabolism/damage in alcoholic pancreatitis has been centered on the *ADH1B* gene. In Asian populations, the *ADH1B*2* allele predominates and encodes for the more active β2-ADH subunit that produces acetaldehyde at a much faster rate than the more common *ADH1B*1* allele (wild type) [68,69]. Several Japanese studies have demonstrated that the frequency of the *ADH1B*2* allele is increased in patients with alcoholic pancreatitis compared to alcoholics without pancreatitis [69–71]. In the Japanese population, a decreased frequency of the *ADH1B*1* allele has also been reported suggesting that this allele "reduces vulnerability" [71,72].

A recent meta-analysis of eight case-control studies evaluating the association of ADH1B, ADH1C, and ALDH2 variants in alcoholic pancreatitis found a higher risk for carriers of the *ADH1B*2* allele and a lower risk for the *ALDH2*2* allele (coding for a metabolically nearly inactive protein) in Asian patients [73]. In non-Asian subjects, the *ADH1C*2* allele was associated with decreased risk [73].

Genetic polymorphisms have been described in the promoter region as well as in intron 6 of the *CYP2E1* gene, some of which are associated with altered function [74]. However, no polymorphism has been associated with alcoholic pancreatitis, in studies of alcoholics without pancreatitis as controls.

Mutations of FAEE Synthase Enzymes

One study reported a positive association between the risk of developing alcoholic pancreatitis and a polymorphism of the gene for one of the candidate FAEE synthase enzymes, CEL, in Japanese subjects [75]. The investigators employed alcoholics without pancreatitis as controls. The functional significance of this polymorphism has not yet been elucidated, and the study findings have not been corroborated in a study involving European subjects [76]. A more recent study has reported an association between a hybrid allele of the CEL gene (*CEL-HYB*) and alcoholic chronic pancreatitis [77]; however, the controls used were healthy subjects and not alcoholics without pancreatitis. Based on *in vitro* studies using HEK293 cells, the authors report that the resulting CEL-HYB protein may cause cell injury by impairing autophagy [77].

Trypsinogen Gene Mutations

The landmark report of Whitcomb et al. [78] in 1996 implicating a mutation in the cationic trypsinogen gene (R122H) in hereditary pancreatitis greatly strengthened the notion that trypsin may be central to the pathogenesis of pancreatitis. Certainly this discovery inspired a great amount of work into the pathogenesis of hereditary pancreatitis with a number of other mutations subsequently described.

Using a similar candidate gene approach, studies in alcoholic pancreatitis largely have been negative. A protective variant (G191R) of the anionic trypsinogen gene *PRSS2*, resulting in an easily degraded form of trypsin, was reported to be significantly less common in patients with alcoholic chronic pancreatitis compared to healthy controls, but the prevalence of this variant in alcoholics without pancreatitis was not tested [79].

The results of two large genome-wide association studies (GWAS), one from North America [80] and the other from Europe [81] have been published. A significant association in the *PRSSI*/*PRSS2* locus at 7q34 was detected (rs10273639). This single nucleotide polymorphism (SNP) rs10273639 is located in the 5′ promoter region of *PRSS1* and may affect expression of the trypsinogen gene. Both investigating teams found a decrease in alcoholic pancreatitis risk with rs10273639. This association was not observed in nonalcoholic chronic pancreatitis nor in patients with alcoholic liver disease, although there was no control group of alcoholics without pancreatic or liver disease. The functional significance of rs10273639 awaits clarification.

Claudin 2 Mutations

A second association of alcoholic pancreatitis was revealed by the aforementioned GWAS [80,81], involving the *CLDN2-RIPPLY1-MORC4* locus (Xp23.3, SNPs rs7057398, and rs12688220). *CLDN2* encodes claudin 2, a tight junction protein. The authors again found a decreased risk of alcoholic pancreatitis associated with the *CLDN2* locus SNP rs12688220. The functional significance of this *CLDN2* SNP remains unclear.

In chronic pancreatitis tissue sections, claudin 2 is expressed in duct cells and acinar cells and there is aberrant expression along the basolateral membrane of acinar cells in the presence of the high-risk SNP [80]. There is an intriguing possibility that the SNP reported influences the function of claudin 2 in the intestine, influencing

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intestinal permeability and the possibility of endotoxemia in those alcoholics susceptible to pancreatitis (*vide supra*). Upregulation of pore-forming claudin 2 has been implicated in increased intestinal permeability in Crohn's disease [82].

SPINK 1 Mutations

An association between mutated *SPINK1* and alcoholic pancreatitis has also been described. The N34S mutation, a c.101A>G transition leading to substitution of asparagine by serine at codon 34, was found in 5.8% patients with alcoholic pancreatitis, compared to 1.0% alcoholic controls without pancreatitis [83]. A more recent study on Romanian patients has reported that 5% of patients with ACP had the N34S mutation compared to 1% of healthy controls [84]. A meta-analysis found a significant association of the N34S mutation with alcoholic pancreatitis with an odds ratio of 4.98 (95% confidence interval: 3.16–7.85) but the association was the weakest among categories analyzed including tropical pancreatitis, idiopathic chronic pancreatitis, and hereditary pancreatitis [85]. Since the N34S mutated human *SPINK1* does not show any altered trypsin inhibitor capacity, the functional consequences of this mutation are unclear.

Chymotrypsin Gene Mutations

Chymotrypsin C (CTRC) is a minor isoform of chymotrypsin. In a German study, in individuals with idiopathic or hereditary chronic pancreatitis, various CTRC variants have been found and the two most frequent variants were detected in 3.3% of pancreatitis patients but only in 0.7% of controls [86]. In individuals with alcoholic pancreatitis both variants have been detected more often (2.9%) than in patients with alcoholic liver disease (0.7%) [86]. In a Chinese population more CTRC variants were detected in chronic pancreatitis patients but the overall frequency of mutations was 2.3% and thus lower than in the European study [87].

CFTR Mutations

CFTR mutations have been implicated in a subset of patients with idiopathic pancreatitis [88,89]. In addition, it has been demonstrated, in both animal and human studies, that CFTR expression and function are impaired by alcohol [45]. However, there is an overall lack of evidence implicating CFTR mutations in the pathogenesis of alcoholic pancreatitis. A small study from Brazil showed that patients with alcoholic pancreatitis showed a higher frequency of the T5/T7 genotype in the noncoding region of thymidines in intron 8, suggesting reduced transcription of the *CFTR* gene [90]. Clearly additional and larger studies are needed.

Other Hereditary Factors

A number of other hereditary factors have also been examined as possible triggers for alcoholic pancreatitis. These include blood group antigens [91,92], HLA serotypes [93], alpha-1-antitrypsin phenotypes [94], genotypes of the cytokines transforming growth factor beta (TGFβ) [95], tumor necrosis factor α (TNFα) [95], interleukin 10 [95], and interferon gamma [95], and genotypes of detoxifying enzymes such as UDP glucuronosyl transferase (UGT1A7) [96,97] and glutathione *S*-transferase [98], and calcium sensor receptor genotypes [99,100]. Most studies have failed to show any association with alcoholic pancreatitis, although one recent study has reported a positive association between the risk of developing alcoholic pancreatitis and fucosyl transferase (FUT2) non-secretor status as well as with ABO blood group B status [101]; further work is awaited.

Summary

Since the first association of alcohol excess with pancreatitis more than 200 years ago, understanding of the disease "alcoholic pancreatitis" has undergone considerable conceptual refinement. Although alcohol excess remains a central and definitional component of the disease phenotype, it is clear that the disease is multifactorial/polygenic and that further work is needed to tease out the various pathogenetic components and their inter-relationships.

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12

Epidemiology and Etiology of Biliary Acute Pancreatitis

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Introduction

Acute biliary pancreatitis (ABP) is caused by a primary common bile duct stone (CBDS) or a CBDS that has moved from the gallbladder. Common channel, duodenal reflux, and ductal hypertension hypotheses for the etiology of ABP are posited. CBDS passage or impaction at the common channel can cause ABP. The treatment strategies for ABP differ from those of other types of acute pancreatitis (AP).

Endoscopic biliary drainage may improve the outcome, and differential diagnosis is important for patients with AP. Abdominal ultrasound, CT, MRI/MRCP, and endoscopic ultrasound (EUS) can be used to diagnose CBDS. EUS has the highest detectability among these modalities but requires an expert endoscopist and is relatively invasive. The standard of care of ABP is treatment of AP with/without endoscopic treatment following cholecystectomy when gallstones are detected. The timing of endoscopic and surgical treatment of ABP is controversial. Here, we summarize recent advancements in the etiology, epidemiology, clinical features, diagnosis, and treatment strategies (including endotherapy and cholecystectomy) of ABP.

Etiology

Biliary pancreatitis is caused by stone passage from the common bile duct to the duodenum through the papilla, including the sphincter of Oddi and common channel. Acosta and Ledesma analyzed the feces of patients with gallstones and pancreatitis and found gallstone in the feces of 94%. By contrast, only 8% of patients with simple gallstone attacks without pancreatitis had gallstones in their feces [1]. Passage of a CBDS through the papilla may cause gallstone pancreatitis; however, the underlying mechanism is unclear. There are three hypotheses as to the mechanism by which gallstones cause acute pancreatitis: (i) common channel, (ii) duodenal reflux, and (iii) ductal hypertension.

Common Channel Theory

Opie et al. reported that a patient who died of acute pancreatitis had a stone lodged in the major duodenal papilla of the common duct of the bile and pancreatic ducts [2]. He proposed that the reflux of bile acids into the pancreatic duct caused the pancreatitis. Moreover, Opie injected bile acids into the dog pancreatic duct, which caused inflammation in the pancreas; other studies have yielded similar results [3]. It has become apparent, however, that no more than two-thirds of the population have such a common ductal channel [4,5] and, in many cases, this is so short that a stone obstructing the common bile duct would also obstruct the pancreatic duct.

The common duct is more frequently found in cases of acute biliary pancreatitis [6]. Passage of stones can cause stenosis of the major duodenal papilla, which may lead to functional obstruction of the common duct [7]. Because the pancreatic duct pressure is two- to threefold higher than that of the normal bile duct, pancreatic secretions flow into the bile duct more easily than bile flows back into the duct. The common channel hypothesis is supported largely by the results of the abovementioned studies [8,9].

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Duodenal Reflux Theory

The second hypothesis is that pancreatitis is caused by the influx of duodenal contents into the pancreatic duct due to the passage of a stone. This mechanism was proposed in an animal study involving obstruction of the duodenum. Because ligation of the pancreatic duct did not cause pancreatitis, reflux of the contents was considered the main cause [10]. This phenomenon is rarely observed in humans and can cause acute pancreatitis due to obstruction after gastrectomy and duodenal or small bowel reconstruction [11,12].

However, the oblique course of the duct, the sphincter of Oddi, and the mucosal folds around the opening suggest that this is not the mechanism of pancreatitis. Although the sphincter may be injured immediately or shortly after the passage of gallstones, leading to reflux of duodenal contents, it is not thought that EST in ERCP (endoscopic retrograde cholangiopancreatography) causes gallstone pancreatitis or the development of pancreatitis due to reflux of duodenal contents [13]. In a study in rats, isotonic saline inflow into the pancreatic duct caused pancreatitis, suggesting that pancreatitis associated with duodenal obstruction may be related not only to reflux of duodenal contents but also to increased intestinal pressure.

Ductal Hypertension Theory

Learch et al., using opossums [14], compared the severity of pancreatitis in three groups: pancreatic duct alone ligated, pancreatic duct and bile duct separately ligated, and common duct ligated. The results showed no difference in disease severity among the groups, suggesting that bile reflux is not essential for the development or exacerbation of pancreatitis. Other studies have shown that continuous stimulation of secretion in the presence of pancreatic duct obstruction worsens pancreatitis [15]. When the obstruction of the pancreatic duct was released, the pancreatitis improved [16].

When pancreatic secretion is stimulated by obstruction of the pancreatic duct, it causes an increase in intraductal pressure. Although rare, increased intraductal pressure can also be caused by, for instance, duodenal papillary tumors, parasitic infections, and ERCP. Injections of various compounds into the pancreatic duct at high pressure can cause pancreatitis, and the injection pressure is more related to the development of pancreatitis than the absence of injected material [3]. The mechanism is thought to be rupture of the branched pancreatic duct and leakage of secretions into the interstitium or inhibition of secretion of pancreatic juice into the ductal lumen.

After ligation of the pancreatic duct, changes first occur within the glandular cells rather than in the stroma or around the pancreatic duct. High pressure in the lumen of the gland causes exocytosis of zymogens and inhibits the release of Ca ions from the gland cell membrane [17]. Disruption of the cell membrane and its transporter channels inhibits the recovery of Ca ion concentration that occurs after stimulation of CCK. An increase in calcium ion concentration in the entire glandular cell leads to intracellular activation of trypsin, which in turn activates various proteases, leading to self-digestion by pancreatic enzymes. CCK stimulation compounds the effect of ductal obstruction [16,18]. Disruption of acinar Ca^{2+} signaling is a key early event in the initiation of intra-acinar enzyme activation [19]. Experimentally, pancreatic duct obstruction causes inhibition of calcium ion signaling [20,21].

These three hypotheses are considered to be related in a complex way, as opposed to one being considered most likely. The development of acute pancreatitis may involve a combination of factors, because obstruction alone often causes biliary complications rather than pancreatitis. When gallstone passage occurs in patients with common ducts, pancreatitis is induced. However, once the stones are cleared, the activated pancreatic enzymes are drained and the pancreas recovers. As a result, only mild pancreatitis occurs clinically. Most cases will be mild, but in rare cases the flow of pancreatic juice, which is rich in digestive enzymes, may become obstructed, causing severe pancreatitis. Even if the stone is passed, severe disease typically develops.

Secondary obstruction may be due to edema of the pancreatic head or papillae after the passage of gallstones. Temporary obstruction of the pancreatic duct by multiple small stones has been reported. Large stones falling into the distal bile duct or papillary region can cause obstruction of the pancreatic duct. If this occurs in stages, it suggests that there is a possibility of preventing further obstruction in the early stages and preventing severe pancreatitis.

Epidemiology

Alcohol and gallstones are the two major causes of acute pancreatitis. In a 2016 survey in Japan, alcoholic was the most common cause (42.8%), followed by gallstone (19.8%) and idiopathic (16.2%) pancreatitis in males. In women, cholelithiasis was the most common (37.7%), followed by idiopathic (24.8%) and alcoholic (12.0%) pancreatitis. Alcoholic pancreatitis was more common among those in their 40s, and gallstone pancreatitis was more common among older adults [22]. Regarding the size of the stones, small stones have a higher risk of pancreatitis. Diehl et al. reported a fourfold increase in the incidence of pancreatitis if the stone diameter was less than 5 mm [23].

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In the Japanese report, about 60% of patients had passed stones and only about 25% had bile duct stones of 6 mm or more in diameter. Elevated serum pancreatic enzymes were common in patients with small stones. Also, about 70% of severe pancreatitis was due to naturally passed stones. These factors suggest that small bile duct stones are more likely to induce pancreatitis. Large stones are more likely to obstruct the bile duct before falling into the anatomically common duct, whereas small stones are more likely to fall into the common duct and cause pancreatic duct obstruction.

Clinical Features

It has been reported that 15% of acute pancreatitis develops into severe acute pancreatitis [24]. Gallstones and alcohol are the most common causes of acute pancreatitis, and there are various reports on the differences in severity and mortality. Gallstone pancreatitis is reportedly associated with more severe disease and mortality [25,26]. By contrast, ABP caused by alcohol is thought to be more severe, and the mortality rate is higher [27–29]. Some studies found no clear difference in clinical course between the two groups, and no definite conclusion has been reached [30–32]. In severe pancreatitis, intestinal bacteria migrate out of the intestinal tract at an early stage and cause pancreatic and peripancreatic infections. In the clinical course of acute pancreatitis, such complications of infection are thought to worsen the prognosis. Riity et al. reported differences in the bacterial flora of alcoholic and gallstone infections. A higher percentage of microbes is detected in gallstone pancreatitis, with Gram-positive bacteria being more common in alcoholic pancreatitis and gram-negative bacteria in cholecystic pancreatitis (80% vs. 20%) [33]. A case of severe acute biliary pancreatitis that progressed to walled-off necrosis is presented in Fig. 12.1 (Fig. 12.1a, b, c). This case required endoscopic drainage and necrosectomy because of infection.

Diagnosis of Acute Biliary Pancreatitis

Acute pancreatitis is treated differently depending on the etiology. ERCP improves the prognosis of ABP complicated by cholestasis/cholangitis, though ERCP is contraindicated for other types of acute pancreatitis. Therefore, it is important to distinguish ABP from other forms of pancreatitis because of the need for different treatment strategies.

Blood Tests

Bilirubin, AST, ALT, ALP, and gamma GTP levels should be measured in all patients to differentiate ABP from other-cause acute pancreatitis [34]. If the blood ALT level is more than 150 IU/L (sensitivity 48–93%, specificity 34–96%, positive Eudox ratio 1.4–12.0, negative Eudox ratio 1.8–4.9) [35,36], or if three or more of the five items (bilirubin, ALP, γGTP, ALT, and ALT/AST ratio) are abnormal (sensitivity 85%, specificity 69%, positive likelihood ratio 2.7, negative likelihood ratio 4.6), ABP is highly suspected. When combined with abdominal ultrasonography, it is possible to identify the cause of acute biliary pancreatitis with a sensitivity of 95–98%, specificity of 100%, positive likelihood ratio of ∞, and negative likelihood ratio of 20.0 to 50.0 [37].

Because trypsinogen 1 in blood is specifically elevated in acute biliary pancreatitis, the ratio of trypsin-2-alpha1-antitrypsin complex to trypsinogen 1 in blood is reportedly useful for identifying the etiology of ABP [38].

Abdominal Ultrasonography

If combined with blood tests, it is possible to diagnose the etiology of acute pancreatitis with gallstones in most cases. The probability of detecting a CBDS by abdominal ultrasonography varies from 20% to 90%. The absence of biliary stones or bile duct dilatation on abdominal ultrasonography does not rule out ABP [39–41]. If the initial examination does not reveal biliary stones but gallstone pancreatitis is suspected, it is necessary to perform repeatedly ultrasonography or MRCP.

Computed Tomography

In many cases, biliary stones are not detected by CT (sensitivity 40~53%), and CT is not suitable for the diagnosis of acute biliary pancreatitis [37,41]. Calcium bilirubinate gallstone is the most frequent CBDS, which cannot be detected by CT because of radiolucency. If the etiology is unclear, CT should be performed because pancreatic cancer or intraductal papillary mucinous tumor may be the cause of acute pancreatitis.

MRI/MRCP

The sensitivity of MRI/MRCP to detect CBDS is 80%, compared with 20% and 40% for abdominal ultrasonography and CT, and MRI/MRCP is recommended to determine the indication for endoscopic papillary procedure (ERCP/EST) [42]. Compared to ERCP, it can be used at an earlier stage of pancreatitis because it is noninvasive and does not require EST/EPBD, thus there is no risk of worsening

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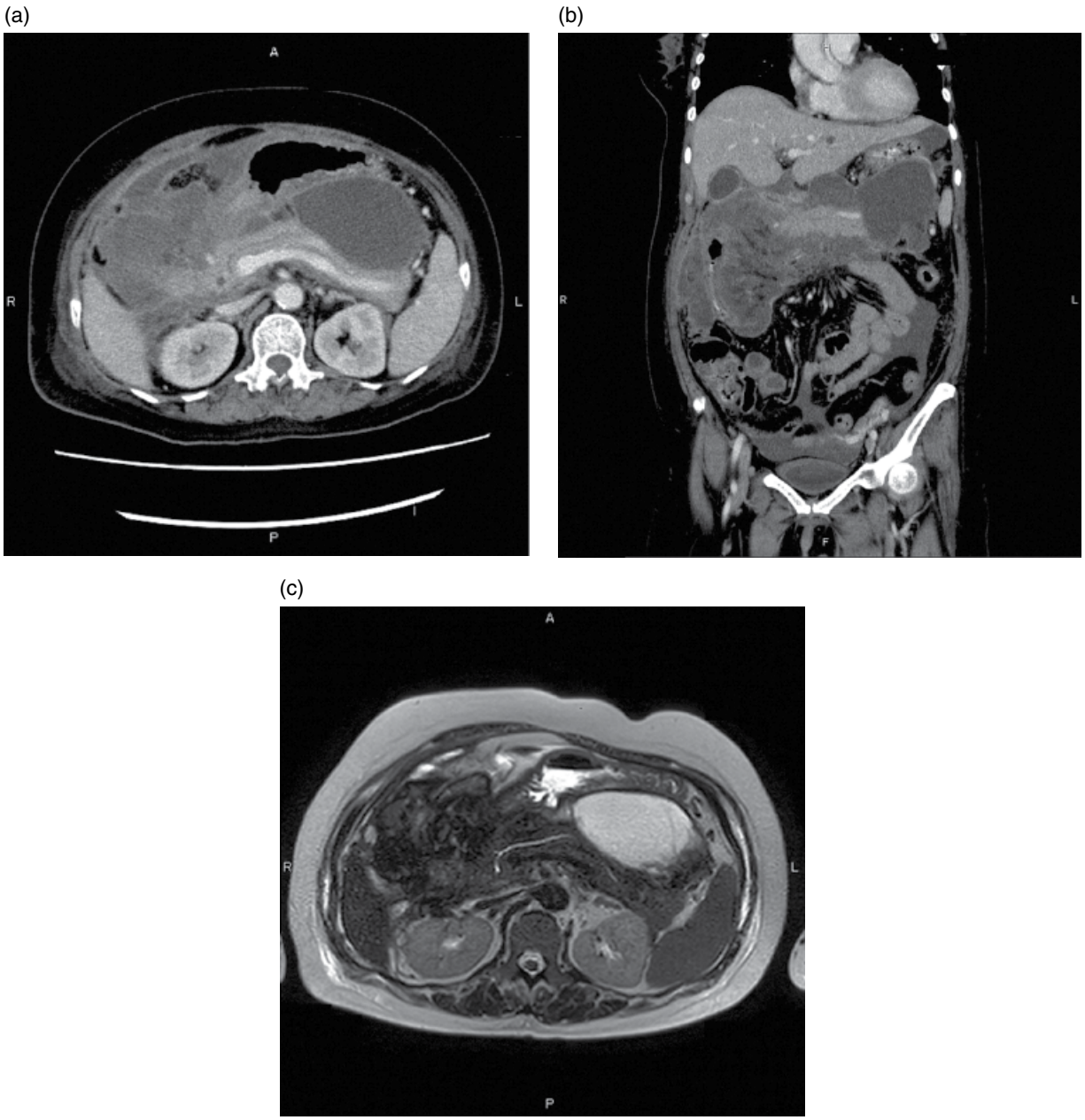


Figure 12.1 A 59-year-old woman presented with severe acute biliary pancreatitis. The inflammatory response remained high. Contrast-enhanced computed tomography (CT) showed an irregularly shaped fluid collection with a contrast-enhancing film (a, b), and MRI T2 showed a fluid collection with mixed high and low signals (c).

acute pancreatitis (Fig. 12.2). However, if the diameter of the bile duct is large, if there is ascites, or if the patient is not holding their breath well, the image quality may be low, and small stones of less than 5 mm may be missed.

Endoscopic Ultrasonography (EUS)

EUS is superior to abdominal ultrasonography in its ability to detect the common bile duct (Fig. 12.3). When the etiology is not clear on abdominal ultrasonography, EUS can detect common bile duct stones in 59–78% of cases [43–45]. Although ERCP and EUS are considered the gold standards for the examination of biliary stones, there is an RCT, which showed that ERCP sometimes failed to detect CBDS (14%), whereas EUS was able to detect CBDS in all patients [46]. In a prospective study of the simultaneous diagnostic performance of EUS, MRCP, and CT cholangiography for the detection of CBDS, their diagnostic sensitivity was 100%, 88%, and 88%, respectively [47]. ERCP during an attack of acute pancreatitis

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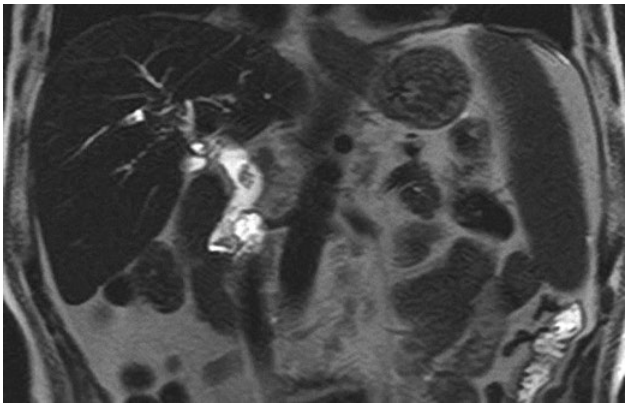


Figure 12.2 MRCP shows a shade defect in the dilated common bile duct that may be a stone.

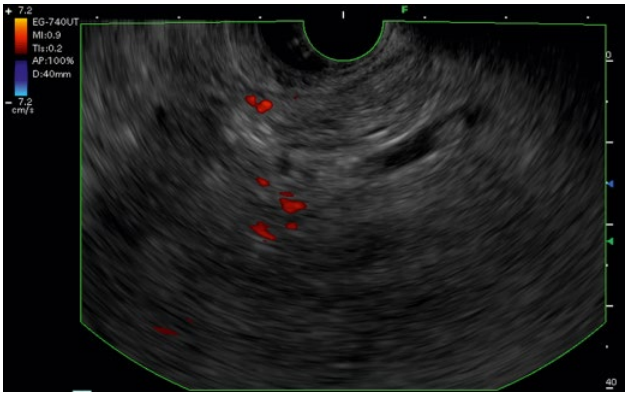


Figure 12.3 EUS shows a stone with acoustic shadow in the common bile duct.

may worsen the inflammation. In cases of suspected ABP, Liu et al. compared whether to perform EUS or diagnostic ERCP for the diagnosis of gallstones and CBDS. Although there were no statistically significant differences in mortality rate, complication rate, hospital stay, or need for intensive care, the complication rate was lower in the EUS group (7.1%) compared with the ERCP group (14.3%) [46]. Therefore, compared with diagnostic ERCP, EUS is safer because it avoids unnecessary ERCP. In addition, in mild-to-moderate acute pancreatitis, the detection rate of gallstones and CBDS does not differ between EUS and MRCP [48]. In terms of invasiveness, MRCP or CT cholangiography (MRCP is more noninvasive in terms of contrast media allergy) should be performed first. If no stone is found on MRCP/CT, confirmation of small stones by EUS may avoid unnecessary ERCP and contribute to a lower incidence of incidental disease.

ERCP

ERCP is not always necessary for diagnosis of ABP but is performed for its treatment. The British Society of

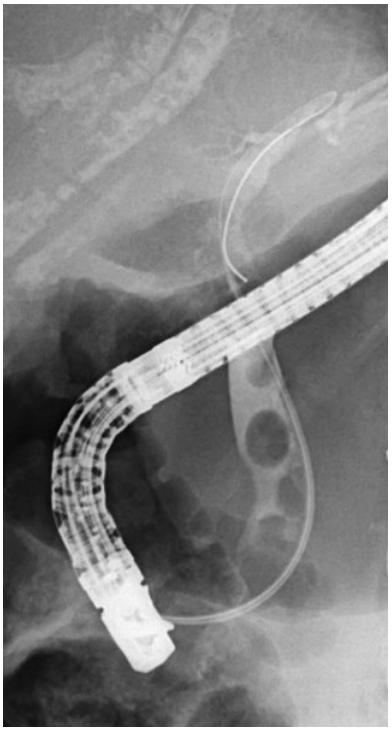


Figure 12.4 ERCP shows multiple shade defects in the common bile duct and common bile duct stones.

Gastroenterology guidelines recommend ERCP in the presence of jaundice, liver damage, dilatation of the common bile duct, and strong suspected presence of CBDS or repeated attacks of acute pancreatitis [49] (Fig. 12.4). Early ERCP in gallstone pancreatitis, which is expected to be severe, does not significantly affect the reduction of fatality, but does affect the reduction of complications of acute pancreatitis [50].

Other indications for diagnostic ERCP were aspiration and analysis of the bile juice to detect sludge/crystal in the bile juice. Biliary sludge/crystal was difficult to detect by other diagnostic imaging modalities including EUS and analysis of bile juice was mandatory. Biliary sludge is almost certainly not a cause of pancreatitis but is a common finding in patients with acute pancreatitis due to reduction in gallbladder motility. As with gallstones, the essential pathophysiologic mechanism is obstruction to the pancreatic duct at the level of the ampulla of Vater. Biliary sludge is a mixture of particulate matter that precipitates from bile, generally consisting of cholesterol monohydrate crystals, calcium bilirubinate, and other calcium salts embedded in mucin [51]. Biliary sludge often coexists with gallstones [52], and it is questionable whether the formation of sludge represents an early stage of gallstone formation. Biliary sludge has been reported as causing acute pancreatitis in 3.1% of cases [53], although whether this is due to sludge per se or to associated microlithiasis is difficult to judge.

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Lee et al. assessed 86 patients diagnosed with idiopathic pancreatitis and found evidence of biliary sludge in the majority (67%). Although the presence of biliary sludge did not have a causal relationship with the pancreatitis, its presence was predictive of recurrent episodes of acute pancreatitis [54]. Bile aspiration by ERCP and microscopic observation may be diagnostically useful.

Treatment Strategy

ERCP is used to treat pancreatitis, prevent exacerbations, and improve cholangitis. The latter two uses are controversial. Therefore, the suitability of ERCP for ABP is determined by the presence or absence of cholangitis or biliary obstruction. However, we experienced marked improvement of ABP after ERCP. In such cases, the stone was impacted at the papilla, which required the precut technique to extract or push the impacted stone into the bile duct using a catheter.

In other words, after the diagnosis of acute biliary pancreatitis by the tests described above, if there is no cholangitis or biliary obstruction, a standby ERCP/EST should be performed after usual treatment for acute pancreatitis. If there is cholangitis or obstruction of the biliary duct, perform emergency ERCP/EST and then treat the acute pancreatitis and subsequently perform cholecystectomy.

ERCP

Gallstone pancreatitis is caused by bile duct stones or bile sludge in the common papillary duct, resulting in pancreatic duct obstruction and papillary edema. Pancreatitis severity was more than 80% in cases where pancreatic duct obstruction due to insufficiency persisted for more than 48 hours [55]. Therefore, early ERCP/EST may relieve pancreatic duct obstruction and papillary edema and prevent worsening of pancreatitis and cholangitis by pancreatic duct decompression and bile duct drainage. However, performing ERCP/EST at the extreme stage of acute pancreatitis may cause additional stress to, and thus worsen, the pancreatitis.

Several meta-analyses compare early ERCP with conservative treatment for acute biliary pancreatitis [56–60]. Excluding cases of complications of cholangitis, all reports showed no significant difference in mortality and complication rates between early ERCP and conservative treatment for cholelithiasis, irrespective of the degree of pancreatitis. In 2012, Tse et al. reported [59] that early ERCP significantly reduced the risk of mortality (RR 0.20, 95% CI 0.06~0.68), and local (RR 0.45, 95% CI 0.20~0.99) and systemic complications (RR 0.37, 95% CI 0.18~0.78). However, in RCTs only, excluding patients with cholangitis, early ERCP tended to increase mortality (RR 1.91, 95% CI 0.85~4.30) and the incidence of local (RR 1.15, 95% CI 0.69~1.92) and systemic complications (RR 1.02, 95% CI 0.44~2.36). In 2020, Nicolien et al. reported [61] an RCT of early ERCP vs. conservative treatment in severe cholelithiasis without cholangitis and found no significant difference in the risk of complications or mortality. Based on these results, routine early ERCP is not recommended for all ABP cases. Early ERCP is recommended for patients with or suspected of having acute cholangitis. For patients with uncomplicated acute cholangitis, priority should be given to treatment of acute pancreatitis.

Timing of Cholecystectomy following Acute Biliary Pancreatitis

Recurrent pancreatitis with gallbladder stones may cause ABP as a result of recurrent stone passage from the gallbladder to the duodenum. Cholecystectomy was performed even though CBDS were not detected by various diagnostic modalities.

To prevent its recurrence, cholecystectomy was performed after improvement of ABP. In a study using a Canadian database, the 6- and 12-month cumulative readmission rates for the cholecystectomy and non-extraction groups were 4.9%, 5.6%, 12.4%, and 14.0%. In a study using the Kaiser Permanente database (USA), the incidence of recurrent acute pancreatitis in the ERCP/EST group without cholecystectomy and the no-treatment group was 8.2% and 17.1%, respectively. By contrast, the recurrence rate in the cholecystectomy group was 5.4%. In cases of acute pancreatitis with gallbladder stones, cholecystectomy should be the first choice to prevent recurrence; however, the timing is controversial.

There are claims that early surgery is associated with a risk of perioperative complications [62]. By contrast, there are reports that surgery can be safely performed within 48 hours irrespective of abdominal symptoms and blood test findings, leading to shorter hospital stays [63,64]. The PONCHO trial, an RCT reported in the *Lancet* in 2015, compared a group who underwent cholecystectomy in the same hospital with a group who underwent standby cholecystectomy [65]. The mortality, gallstone-related complication, and rehospitalization due to recurrent pancreatitis rates were lower in the former group than in the latter. However, there was no difference in the rate of transition from laparoscopy to laparotomy. AGA recommend cholecystectomy in the same hospitalization.

There is a report of nine trials comparing early (within 48 hours) and late (after 48 hours) cholecystectomy in mild acute cholecystic pancreatitis [66]. Early surgery reportedly leads to shorter hospital stays without increasing the complication or mortality rate, and early surgical intervention

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is desirable if the condition permits. By contrast, in the 2004 cohort, there were more infectious complications and more postoperative complications in surgeries performed within 5 days of severe acute cholangitis onset or during hospitalization for acute pancreatitis. In AGA, cholecystectomy is recommended in severe pancreatitis with fluid retention around the pancreas after the fluid retention has improved or after 6 weeks if a pseudocyst has formed.

Conclusion

The management of ABP is controversial. There are various disease presentations, and we could not fully classify the clinical features of each to establish treatment strategies. Therefore, well-designed large-scale clinical trials are required.

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13

Genetic Factors in Acute Pancreatitis

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Introduction

Approximately 70% of acute pancreatitis (AP) in adults is attributable to alcohol use or pancreatic duct obstruction from choledocholithiasis [1]. However, it is increasingly recognized that these stimuli are modulated by other susceptibility factors such as trypsinogen activity, pancreatic ductal clearance, and endoplasmic reticulum (ER) stress. This observation is supported by the large number of patients with environmental exposures such as heavy alcohol use who never develop clinical AP [2]. Some predisposing factors are anatomic, such as pancreas divisum, while others are related to germline pathogenic variants leading to alterations in the structure or function of proteins integral to normal pancreas functions. Following alcohol and gallstones, the next most common AP etiologic group is unexplained or idiopathic [1]. With the increasing availability of germline genetic test panels, several studies have reported high rates of germline pathogenic variants among patients with idiopathic recurrent AP (IRAP) [3–5]. Pathogenic variants in pancreatitis-related genes are hypothesized to decrease the threshold to develop AP following exposure to an inciting event. In this chapter, germline pathogenic variants that are associated with increased susceptibility or increased severity of AP will be discussed. The pancreas is divided into different anatomic and functional compartments that are predisposed to distinct mechanisms of injury [6]. Certain genetic factors are directly linked to the proper function of either the acinar cell or duct cell compartments, and it is useful to consider them in context of these compartments (Table 13.1).

The clinical syndrome of pancreatic autodigestive injury, an acute inflammatory response, and a range of local and systemic complications defines AP [6]. Autodigestive injury is promoted by premature activation of pancreatic proenzymes within the acinar cells or within the pancreatic duct. This premature activation is mediated by trypsin and can be influenced by genetic variations. Indeed, the 1996 discovery of the gain-of-function mutations in the cationic trypsinogen gene (*PRSS1*) serves as the prototypical example [7]. Since that discovery, a variety of other susceptibility genes have been described that influence trypsin activity and ductal cell function thereby increasing the risk of AP. The most prevalent genes associated with AP are *PRSS1*, cystic fibrosis transmembrane conductance regulator (*CFTR*), pancreatic serine protease inhibitor Kazal-type 1 gene (*SPINK1*), and claudin 2 (*CLDN2*) [8,9]. Multiple genes have been associated with progression to chronic pancreatitis (CP), including variants in chymotrypsin C (*CTRC*) and calcium-sensing receptor (*CASR*), which are introduced here but are more completely discussed in Chapter 45. Lastly, severity modifying genes have been described, including monocyte chemotactic protein-1 (*MCP-1*), which increase the severity of AP [10].

Acinar Cell-Associated Susceptibility Factors

Calcium dysregulation appears to be the primary pathway for triggering AP within acinar cells [11,12]. In health, multiple protective mechanisms limit trypsinogen exposure to calcium, including trypsinogen packaging in zymogen granules, calcium sequestration in the ER, and numerous cytosolic calcium homeostasis processes [13]. When calcium occupies the calcium-binding domains of the trypsinogen molecule it results in both trypsinogen activation and prevention of its degradation [11]. Therefore, alterations in cellular calcium concentration, zymogen granule formation, or alteration to the calcium-dependent regulatory domains of the trypsinogen molecule can potentially increase the risk of

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Table 13.1 Genes and specific pathogenic variants implicated in the pathogenesis of acute pancreatitis.

Susceptibility factors	
Acinar cell-associated	*PRSS1*: R122H, R122C, N29I, A16V
	SPINK1: N34S, R67H, c.194+2T>C
	CTRC: G60G, R254W, P249L, K247_R254del
	CLDN2: rs7057398, rs12688220
ER stress-associated	*CPA1*: *A*208T, T124I, Y318fs
Duct-associated	*CFTR*^{sev}: F508del, G551D
	CFTR$^{m\text{-}v}$: R117H, R334W, G85E, R1162X, c.2789+5G>A
	CASR: A986S, R69H, c.60T>A
Severity modifying factors	
Proinflammatory cytokines	MCP-1: c.–2518G
	TNF-α: c.–1031C, c.–863A
	IL-8: c.–251A

CFTR^{sev}: severe pathogenic variants in CFTR; CFTR$^{m\text{-}v}$: mild or variable pathogenic variants in CFTR.

pancreatic autodigestion. Several pathogenic variants have been identified among subjects with AP that alter calcium and trypsinogen homeostasis, including variants in *PRSS1*, *SPINK1*, and *CLDN2*.

Cationic Trypsinogen: *PRSS1*

Hereditary pancreatitis is characterized by recurrent AP leading to CP, and is attributed to autosomal dominant inheritance of pathogenic variants in *PRSS1* (located on chromosome 7q35), the gene coding for cationic trypsinogen [7]. Cationic trypsinogen is the predominant trypsinogen found in human pancreatic secretions, followed by anionic trypsinogen (*PRSS2* on 7q35) and meso trypsinogen (*PRSS3* on 9p13) [14]. Trypsinogens are serine proteases synthesized in pancreatic acinar cells and are activated on cleavage of a short exposed peptide chain called trypsinogen activation peptide (TAP). Enterokinase or a second trypsin molecule can cleave TAP, allowing for the transformation of trypsinogen to active trypsin [15]. Once activated, trypsin activates other pancreatic proenzymes to initiate digestion of chyme. Trypsin can also inactivate trypsin at the arginine residue (codon 122) in the side-chain. Trypsin has two calcium-binding domains, one at the activation site and one at the autolysis site, and nearly all of the described variants identified among subjects with hereditary pancreatitis involve one of these two calcium-regulated sites [16].

The first *PRSS1* mutation to be identified was the c.365G>A substitution, replacing arginine with histidine at codon 122 (R122H) [7]. Arginine 122 is the initial site of hydrolysis of trypsin by other trypsin molecules. In the case of the *PRSS1* mutation, the arginine to histidine substitution renders trypsin resistant to fail-safe autolysis leading to prolonged activity of trypsin and pancreatic autodigestion. Over 50 variants of *PRSS1* have been reported, including gain-of-function variants with deleterious effects (R122H, N29I, A16V) and loss-of-function variants with beneficial effects (Y37X) [16]. Among kindreds, a wide variation in phenotype suggests that additional modifying environmental and/or genetic factors are involved in the pathogenesis of hereditary pancreatitis [17,18].

Hereditary pancreatitis due to variants in *PRSS1* has a high but variable disease penetrance (80% by age 20 years, 96% by age 50 years) and typically presents in childhood with recurrent AP [19–22]. After repeated episodes of AP, approximately half of patients with pathogenic variants in *PRSS1* progress to CP [20,23]. Additionally, the cumulative risk of pancreatic cancer approaches 40% of affected patients by age 70 [20,22]. There are no specific therapies directed at *PRSS1*, so the mainstay of treatment is avoidance of toxic exposures (smoking, alcohol), monitoring for pancreatic endocrine and exocrine insufficiencies, and screening for pancreatic cancer beginning at age 40 [24]. A pilot clinical trial investigated the use of amlodipine (dihydropyridine calcium channel blocker) in four subjects and showed a modest reduction in symptoms and analgesic use, but this has not been replicated [25]. Total pancreatectomy with islet autotransplant (TPIAT) is often considered for intractable CP-related pain in hereditary pancreatitis [26]. The indications and outcomes of TPIAT are discussed in Chapter 66.

Serine Protease Inhibitor Kazal Type 1: *SPINK1*

Serine protease inhibitor Kazal type 1 (SPINK1), also known as pancreatic secretory trypsin inhibitor (PSTI), is encoded by *SPINK1* on chromosome 5q32 and is packaged in exocrine granules along with trypsinogen. SPINK1 is a 56-amino-acid acute-phase protein that directly blocks the active catalytic site of trypsin, thus preventing trypsin from activating trypsinogen. The proportion of SPINK1 protein to its RNA has been shown to range from less than 1:1000 in the normal pancreas to at least 6:1 in the inflamed pancreas [18]. This indicates that *SPINK1* translation is rapidly increased *after* pancreatic injury, and therefore likely plays a role in limiting the extent and duration of an attack by inhibiting trypsin [27]. These findings also fit with the observation that SPINK1 is an acute-phase reactant [28].

Several loss-of-function pathogenic variants have been identified in *SPINK1* and the N34S haplotype is the most

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prevalent throughout the world, found in 1–3% of the general population [29]. Pathogenic variants in *SPINK1* are identified in 7–10% of subjects with AP and in 25–50% of cases of early-onset idiopathic CP, including tropical fibrocalculous pancreatitis [30–34]. The N34S variant is more prevalent among alcoholics with CP than among alcoholics without CP, suggesting that loss-of-function of SPINK1 increases susceptibility to alcohol-related CP [35]. The risk and severity of pancreatitis appears to be similar between subjects with homozygous, heterozygous, or compound heterozygous genotypes, suggesting that the genetics underlying the disease state is complex and involves other susceptibility factors [31,32].

Among those who develop pancreatic disease associated with pathogenic variants in *SPINK1*, the phenotype is variable but generally presents in young adulthood [36,37]. Pathogenic variants in *SPINK1* increase susceptibility to recurrent AP and CP, but do not appear to be a major risk factor for sentinel AP [5,11,38]. These observations indicate that SPINK1 acts as a disease modifier, so the clinical phenotype of those with pathogenic variants reflects the etiologic agent of AP [27,35]. No specific therapy exists for patients with AP who have pathogenic variants in *SPINK1*, although a case report of a patient with familial hypocalciuric hypercalcemia and R67H variant in *SPINK1* describes abrogation of recurrent AP when treated with cinacalcet (a calcimimetic agent) [39]. This report demonstrates the disease modifier effect of SPINK1: when the underlying cause of AP (hypercalcemia) resolved, no further AP recurrences occurred. Pancreatic cancer screening is not currently recommended in this group [24].

Chymotrypsin C: *CTRC*

Another pancreatic secretory enzyme involved in trypsin regulation is chymotrypsin C, which is able to rapidly degrade trypsin in the absence of calcium through cleavage of the calcium binding loop [15]. Chymotrypsin C is encoded by *CTRC* (1p36.21) and is stored within zymogen granules until it is released into the pancreatic duct. The function of chymotrypsin C was initially described by Rinderknecht et al. in 1988 as the second line of defense against prematurely activated trypsin, following PSTI/SPINK1 [40]. Thus, it follows that loss-of-function variants in *CTRC* may produce a similar clinical phenotype as loss-of-function variants in *SPINK1*.

Several pathogenic variants have been described in *CTRC*, including the association of R254W and K247_R254del with idiopathic CP [41,42]. One group identified the G60G variant at higher rates among patients with AP than among healthy controls, but subsequent study in the North American Pancreatitis Study II cohort identified similar rates of G60G among subjects with recurrent AP and controls [43,44]. Lastly, an additional case series identified similar detection rates for pathogenic variants (V235I, I259V, K247_R254del) in *CTRC* among AP cases (1.8%) and controls (1.2%) [45]. Thus, similar to *SPINK1*, pathogenic variants in *CTRC* are associated with recurrent AP and CP, but do not appear to be risk factors for sentinel AP. Unlike pathogenic variants in *PRSS1* and *SPINK1*, the natural history and management of subjects carrying variants in *CTRC* has not been well described.

Claudin 2: *CLDN2*

Claudins are a family of transmembrane proteins that regulate paracellular permeability of ions and water [46]. Claudin 2 is encoded by *CLDN2* (Xq22.3), and, in health, localizes to the plasma membrane between pancreatic islet and duct cells [47]. Under stress, pancreatic acinar cells can express claudin 2, which may contribute to the development of pancreatic edema that is characteristic of interstitial AP [48]. Germline polymorphisms in the *CLDN2-MORC4* locus, including rs7057398 and rs12688220, have been associated with increased susceptibility to AP [49,50], IRAP (in homozygous females) [51], and CP [47,52]. In particular, homozygous females and hemizygous males are most susceptible to alcohol-related pancreatic injury, suggesting that variants in *CLDN2* act as a disease modifier in the setting of environmental exposure [47,52]. In contrast to PRSS1, SPINK1, and CTRC, claudin 2 does not appear to interact with the trypsin-dependent pathway of AP [47]. There is no specific therapy for subjects with AP and pathogenic variants in *CLDN2*, although strict abstinence from alcohol should be emphasized.

Endoplasmic Reticulum (ER) Stress-Associated Susceptibility Factors

An additional mechanism leading to AP is ER stress. Although this more commonly predisposes to CP, a brief discussion is included here due to the involvement of similar genes discussed above. For example, the *PRSS1* G208A variant leads to misfolding and accumulation within the cell rather than premature activation within the pancreatic duct [53]. Similarly, misfolded CTRC caused by the A73T and G61R variants precipitates within the cell, causing ER stress and altering microtubule function that ultimately leads to the development of CP [54]. In addition to these variants in *PRSS1* and *CTRC*, variants in carboxypeptidase A1 (CPA-1) also cause ER stress and contribute to the development of CP, but have not been associated with AP.

Carboxypeptidase A1: *CPA-1*

Carboxypeptidases are metalloproteases that cleave C-terminal peptide bonds from dietary polypeptides [55]. Among these carboxypeptidases is CPA-1,

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which is secreted as a zymogen, procarboxypeptidase A1, and is activated by trypsin and chymotrypsin C in the duodenum [56]. Procarboxypeptidase A1 is a highly prevalent protein in pancreatic juice, and loss-of-function variants in *CPA-1* (located at 7q32.2) (N256K, R382W, and c.1073-2A>G) have been associated with early onset CP, but not with AP [56]. The mechanism of injury leading to CP is thought to involve ER stress, as reduced CPA-1 does not affect trypsin activity.

Duct-Associated Susceptibility Factors

Pancreatic ductal blockage is another factor that may contribute to premature zymogen activation within the pancreatic parenchyma. This is most clearly illustrated by gallstone pancreatitis; however, there are additional important duct-associated factors and susceptibility genes that can contribute to the development of AP.

The pancreatic duct cell differs from many other types of epithelial cells in its expression of a combination of ion channels and transporters. The primary apical (luminal) ion channel of the duct cell is CFTR [57], which is permeable to chloride and, to a lesser degree, bicarbonate [58,59]. The continuous entry of bicarbonate into the duct cell is facilitated by a sodium–bicarbonate cotransporter on its basolateral surface [60]. Simultaneously, minimal chloride permeability on the basolateral surface results in bicarbonate being the dominant diffusible anion within the duct cell. In this setting, a concentration gradient across the apical membrane favors bicarbonate secretion [61]. This ion secretion is dependent on CFTR, so any alterations in CFTR function can potentially limit fluid secretion into the pancreatic duct which increases the transit time of protein-rich acinar secretions to the duodenum. Maintenance of a high pancreatic duct pH and presence of trypsin inhibitors reduce the potential for activation of trypsinogen within the pancreatic duct. Failure to flush the pancreatic duct is a susceptibility factor for AP, and *CFTR* loss-of-function mutations represent the prototype genetic defect.

Cystic Fibrosis Transmembrane Conductance Regulator: *CFTR*

The epithelial cells of multiple organs (i.e., lungs, pancreas, intestine, bile ducts) contain the CFTR ion channel, and severe pathogenic variants in *CFTR* (located on 7q31.2) may lead to multiple organ dysfunction resulting in the clinical phenotype of cystic fibrosis (CF) [62]. In health, CFTR-mediated secretion of bicarbonate and chloride into the pancreatic duct dilutes the protein-rich fluid from the acinar cells and maintains a basic pH to prevent premature zymogen activation. Active transport of anions creates a gradient for osmosis, such that CFTR is primarily responsible for creating a fluid current that carries zymogens expediently to the duodenum [63]. The risk of AP among subjects with pathogenic variants in *CFTR* is dependent on the balance of ductal clearance and zymogen production (Fig. 13.1) [64]. Ductal clearance correlates with the activity of mutant CFTR in ductal cells, and zymogen production correlates with acinar cell function, which may be reduced by damage from recurrent AP [65].

The first pathogenic variant in *CFTR* was identified in 1989, and now more than 2000 variants in *CFTR* have been identified [62]. Although the functional role of many of these variants remains unknown, the more commonly identified variants have been categorized according to their effect on the CFTR protein, where classes IV and V are milder mutations ($CFTR^{m\text{-}v}$) and I, II, III, and VI are more severe ($CFTR^{sev}$) [62]. A number of online databases have been created to assist clinicians in interpreting identified variants, including CFTR2.org and

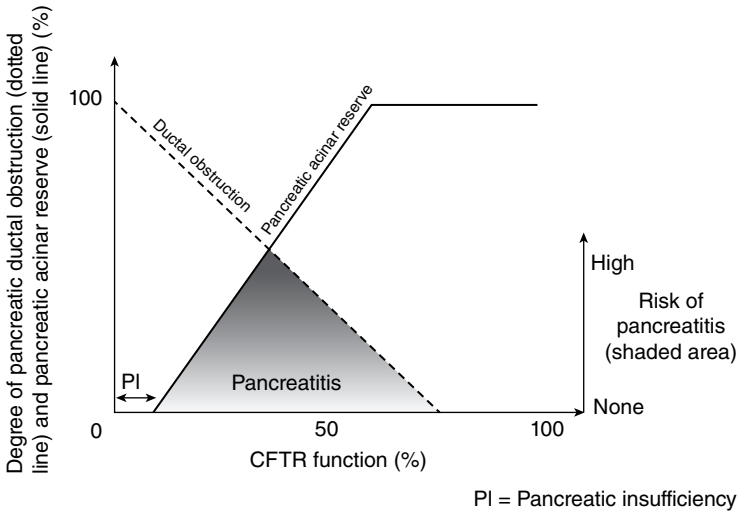


Figure 13.1 Relationship between percent of cystic fibrosis transmembrane conductance regulator (CFTR) function and risk of acute pancreatitis among subjects with cystic fibrosis. *Source:* [104] / With permission of Elsevier.

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umd.be/CFTR, that include genotype and clinical details (i.e., sweat chloride, lung function, and pancreatic sufficiency) [66,67]. The prevalence of the *CFTR* pathogenic variant carrier state is 3–4% in Caucasians [68,69] and 1–2% among those of African descent [68,69]. CF has a prevalence of between 1/2500 to 1/6000 live births [62,70].

Severe pathogenic variants that are found among subjects with pancreas insufficient CF include F508del, the most prevalent variant in Caucasians, I507del, R33X, and G542X [64]. Patients who are homozygous for severe pathogenic variants (i.e., F508del/F508del) or have complex heterozygosity involving severe variants (i.e., F508del/G551D) present with typical CF at a young age, with impaired pulmonary function, exocrine insufficiency, and a low incidence of AP [62]. In contrast, class IV and V mutations reduce CFTR function to 10–49% of normal function and are identified among subjects with pancreas sufficient CF [71]. These pathogenic variants include R117H, R1162X, and c.2789+5G>A, among others [64]. Patients with homozygosity or complex heterozygosity for these milder mutations present with atypical CF, with milder pulmonary symptoms and pancreas sufficiency, and may experience recurrent AP [72,73]. It is increasingly recognized that carriers of *CFTR* mutations are also at heightened risk for CF-related conditions, including AP [74]. This is referred to as CFTR-related disorder (CFTR-RD), and includes subjects who have at least one pathogenic variant in *CFTR* but do not meet diagnostic criteria for typical or atypical CF [75]. In this category are a number of variants including R74Q, R75Q, R117H, R170H, L967S, L997F, D1152H, S1235R, and D1270N that have been associated with recurrent AP and CP without lung disease [76]. In summary, subjects with two milder mutations or a single severe mutation are at increased risk of AP while those with <2% of normal CFTR function have a very low risk of AP [75,77]. Furthermore, it is suggested that some variants of *CFTR* may augment the inflammatory response, predisposing to severe disease [78].

It has been estimated that approximately 20–30% of patients with IRAP or idiopathic CP carry a pathogenic variant of *CFTR*, and only a minority of these will meet criteria for a diagnosis of CF [75]. One of the earliest studies on this topic observed pathogenic *CFTR* variants in 10% of German subjects with alcohol-related CP and 21% of subjects with early-onset, idiopathic CP, but no pathogenic variants were identified in subjects with recurrent AP [79]. Similarly, an Italian cohort identified pathogenic *CFTR* variants in 20% of CP (majority of cases were alcohol-related) but only 6% of AP subjects [80]. These findings have been replicated in a Spanish cohort [81], an Austrian cohort [82], and pediatric and adult American cohorts [3,5,83]. A single cohort in Indian patients found a prevalence of pathogenic variants in *CFTR* of only 2.3% among children with IRAP, but the only CFTR variants used in their study were F508del, G551D, G542X, and A117H, while these other studies generally used *CFTR* panels assessing for over 20 different variants [4]. More recent studies include expanded gene panels and are able to identify *CFTR* pathogenic variants in 10–20% of subjects with alcohol-related recurrent AP and CP, and in nearly half of adult subjects with IRAP or idiopathic CP [84]. Thus, CFTR dysfunction appears to be a major susceptibility factor for alcohol-related or IRAP and idiopathic CP.

The majority of *CFTR* mutations identified among American patients with CF are now targetable by CFTR modulator therapy, including the CFTR potentiator ivacaftor and CFTR correctors elexacaftor, lumacaftor, and tezacaftor. Several observational studies have demonstrated a reduction in AP episodes among patients with CF during treatment with CFTR modulators. In particular, subjects with pancreas sufficient CF appear to have the greatest reduction in AP episodes during treatment [85,86]. The effect of CFTR modulators on AP risk among patients with pancreas insufficient CF is uncertain at this time [86,87]. Subjects with pathogenic variants in *CFTR* are not currently recommended to undergo pancreatic cancer surveillance [24]. Smoking and alcohol use may induce CFTR dysfunction, so abstinence should be emphasized for all subjects with a pathogenic variant in *CFTR* [88].

Calcium-Sensing Receptor: *CASR*

Integral to proper functioning of CFTR is the calcium-sensing receptor (CaSR), located in the apical membrane of ductal cells. CaSR monitors calcium concentration within the pancreatic duct, and may stimulate CFTR and other ion channels to maintain a low calcium concentration within the duct [89]. Gain-of-function and loss-of-function variants in *CASR* (located on 3q13.33) have been inconsistently identified in subjects with AP [5] and CP [90,91] but may contribute to pancreatitis when pathogenic variants in *SPINK1*, *PRSS1*, or *CFTR* are also present [92].

Multiple Genetic Defects and Susceptibility

It has been hypothesized that *SPINK1* could, in fact, act as a disease-modifier gene [93,94]. This is supported by the observation that the *SPINK1* N34S haplotype is relatively common, although there is no specific phenotype associated with this genotype. Furthermore, the severity of disease is similar between patients with homozygous and heterozygous genotypes. A small study of subjects with $CFTR^{sev}/CFTR^{m\text{-}v}$ genotypes with *SPINK1* mutations

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led to the hypothesis that defects in these gene products may act synergistically to increase the risk of pancreatitis [95]. The risk of AP is increased 10-fold in individuals with a *SPINK1* mutation, 40-fold in individuals with *CFTR* compound heterozygosity, and 500-fold in individuals who have both [96]. Finally, pathogenic variants in *CASR* alter pancreatic calcium homeostasis but may require a second hit in pancreatitis-related genes in order to cause pancreatitis [92].

Severity Modifying Factors: Polymorphisms in Cytokines

In addition to modifying the risk of developing AP, genetic factors may also modify the severity of AP by altering the production of proinflammatory cytokines. The interplay of cytokines in the inflammatory response to AP includes TNF-α, IL-1, IL-8, and IL-10, and may involve others as well [97]. Several pathogenic variants have been identified at higher frequency among subjects with severe AP, including variants in the genes coding for MCP-1, IL-1ß, and IL-8.

The earliest pathogenic variant contributing to the development of severe AP was identified in *MCP*-1 [98]. MCP-1 is a key chemokine in the regulation of inflammation, released by mononuclear cells to attract additional monocytes, lymphocytes, mast cells, and eosinophils. A single-nucleotide polymorphism (c.-2518A>G) in the distal regulatory region of *MCP-1* results in a significantly greater MCP-1 response to inflammatory stimuli than the wild-type sequence, which leads to greater severity of AP [10]. The presence of the G allele significantly increased the risk of severe AP from any cause about sevenfold (~40%), whereas subjects with an AA genotype had a low risk of severe AP (~5%) [10].

The acute inflammatory response is a highly regulated process, with proinflammatory and anti-inflammatory factors interacting in sequential and coordinated ways. TNF-α, the earliest cytokine to be released in inflammation, is a principal mediator of immune responses to endotoxin. The c.–308G>A and c.–238G>A polymorphisms in *TNF*-α have not been consistently associated with the incidence or severity of AP [99]. In contrast, the c.–1031C and c.–863A polymorphisms significantly increase the risk of severe AP (odds ratio [OR] 2.7) [100]. IL-8 is produced by macrophages and attracts neutrophils to the site of inflammation. The c.-251T>A polymorphism in *CXCL8* (the gene coding for IL-8) is associated with an increased risk of developing AP (OR 1.4) [101,102]. A number of other candidate cytokines have been investigated, including IL-1ß, IL-6, and IL-18, and pathogenic variants in these genes marginally increase the risk of severe AP (OR 1.23, 1.22, 1.25, respectively) [103].

Future Directions

Since the discovery of pathogenic variants in *PRSS1* among subjects with hereditary pancreatitis, a number of genetic factors have been identified that modify the risk and severity of AP. These are most commonly encountered among subjects with recurrent AP and CP, but may be identified among subjects who have experienced a sentinel AP as well. Among subjects with recurrent AP and an identified genetic predisposition, integrating our understanding of the effect of the mutation with the therapeutic approach is necessary. This may take the form of environmental risk modification, such as cessation of smoking and alcohol use, but may also involve specific drug therapy, such as the case with CFTR modulator drugs in subjects with pancreas sufficient CF. Specific therapies for other predisposing variants are not yet available. Future studies to develop novel therapies to correct high prevalence pathogenic variants is necessary to halt the progression from recurrent AP to CP.

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14

The Role of the Intestine and Mesenteric Lymph in the Development of Organ Dysfunction in Severe Acute Pancreatitis

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Introduction

Acute pancreatitis (AP) is a complex and challenging disease with an unpredictable course [1]. The severity and outcome of AP are primarily determined by local and systemic factors; the presence of infected (peri)pancreatic necrosis (e.g., "acute necrotic collections" and/or "walled off necrosis") and persistent end-organ dysfunction (e.g., cardiovascular, pulmonary and/or renal failure) [2]. Recent improvements in the management and outcomes of infected pancreatic necrosis means that it is less important in driving organ dysfunction/failure and impacting clinical outcome. This is evidenced by the marked diminution of the second (late) peak in the bimodal mortality profile of severe acute pancreatitis [3]. Organ failure is the leading cause of death from AP. The pattern of this organ failure is broadly similar across acute and critical diseases, suggesting common drivers for the "multiple organ dysfunction syndrome" (MODS) [4]. This pattern appears to be no different for severe acute pancreatitis [5,6].

The aim of this chapter is to review the role of the intestine in the development of MODS, the evidence for the gut–lymph concept in promoting MODS in acute pancreatitis and to discuss the potential to translate this to effective clinical treatments.

Role of the Intestine and Mesenteric Lymph in Multiple Organ Dysfunction Syndrome

The concept that the intestine drives critical illness was developed in the 1960s when bacterial endotoxin was demonstrated in the systemic circulation of patients with infective and noninfective severe diseases [7]. This gave rise to the *bacterial translocation hypothesis* where gut organisms were proposed to cross the intestinal barrier to create a "septic-like state" [8]. In the 1980s, the *gut motor hypothesis* expanded this concept to acknowledge the contribution of changes in the intestinal flora and the increased permeability of the gut barrier, postulating that bacterial pathogens and endotoxins enter the systemic circulation via the portal venous system [9]. This was largely discredited when it was not possible to prospectively demonstrate bacteria in the portal vein or systemic circulation in patients with major trauma [10]. A further concept was advanced where neutrophil priming occurred in the mesenteric circulation and that this contributed to both local gut injury and distant organ injury [11–13]. This was the basis of the *second-hit hypothesis*, which implicates the intestine but does not rely on a direct bacterial role.

Using experimental models of hemorrhagic shock and trauma Deitch and colleagues introduced the concept that organ failure might be promoted by gut-derived mesenteric lymph. They suggested that primed neutrophils and other intestine-derived toxic factors were the mediators of MODS, and that this occurred in association with increased gut permeability but independent of bacterial translocation [14]. Deitch went on to demonstrate that these intestine-derived factors were transported by thoracic duct lymph to reach the systemic circulation to promote systemic inflammation and organ dysfunction [14,15]. He termed this the "*gut–lymph hypothesis*" [16]. Demonstrating that lung injury mediated by hemorrhagic shock altered mesenteric lymph was key to validating this concept in the experimental

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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setting. Ligation of the mesenteric lymph duct before hemorrhagic shock prevented lung injury in a rodent model, while done after shock but before resuscitation only partially prevented lung injury [17]. It was found that mesenteric lymph from these rats was cytotoxic to endothelial cells and caused increased permeability to both a monolayer of endothelial cells and lung tissue while portal vein plasma did not [17,18]. The early failure of lung function [4–6] has also been demonstrated in experimental models of burns [19], shock [20], and sepsis [21] and AP [22]. Furthermore, ligation of the mesenteric or thoracic duct ligation in these different models has been shown to prevent neutrophil priming [23], reduce red blood cell deformity [24,25], reduce cardiac dysfunction [26–28], protect against renal injury [29], and increase ATP and ATPase renal activity [30].

The plausibility of the gut–lymph concept is enhanced by considering the anatomy of the mesenteric/thoracic duct lymphatics [31]. Gut and mesenteric lymph drains from the intestine and mesentery to the cisterna chyli and then ascends through the mediastinum in the thoracic duct. Almost 75% of thoracic duct lymph arises from the abdomen and pelvis [32]. The thoracic duct lymph drains into the internal jugular or subclavian veins on the left side of the neck, immediately upstream of the heart, lungs, and kidneys, the organs most often involved in MODS. It is noteworthy that this lymph bypasses the liver and its detoxification processes (Fig. 14.1).

While there has been considerable interest in how intestinal injury contributes to the severity of AP, the gut–lymph concept has only recently been considered of potential clinical relevance [33].

Intestinal Injury and Dysfunction Is Associated with Severe Acute Pancreatitis

There are several mechanisms of intestinal injury during acute pancreatitis. Splanchnic vasoconstriction is a key, but not sole, mechanism (Fig. 14.1), and is the reflex response to redistribute blood from the splanchnic region to vital organs. This splanchnic vasoconstriction can cause ischemic injury to the mucosa and wall of the intestine, as well as the pancreas. In the intestine the microanatomy of the intestinal mucosa makes it particularly prone to ischemic injury. The villus tip is most susceptible to ischemia due to the countercurrent flow of oxygen via the rich capillary network between the parallel artery and vein [34]. This ischemic injury can be compounded by the use of nonselective inotropes in persistently hypotensive patients [35]. Intestinal injury is also increased with fluid resuscitation and reperfusion injury [36]. Intestinal ischemia is related to the severity of AP [37] with a lower gastric intramucosal pH (pHi) in

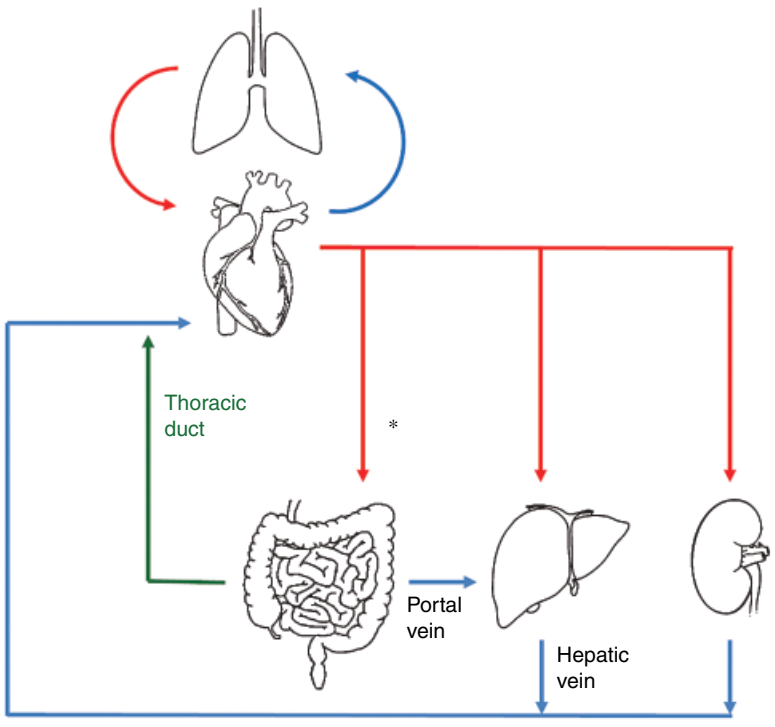


Figure 14.1 Schematic of the gut–lymph concept emphasizing that in acute pancreatitis (and other acute and critical diseases) the vasoconstriction (*) of the intestinal arterial supply to redistribute blood to vital organs results in intestinal ischemia. Drainage of lymph from the intestine via the thoracic duct, bypasses the liver, to enter the circulation proximal to heart, lungs, and kidneys, organs that fail most often.

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patients admitted to intensive care than those that remain on the ward, and a low pHi is correlated with an increased risk of mortality [38,39]. Ischemic injury to the intestine is also known to contribute to the breakdown of protective mucus [40], which is compounded by the action of pancreatic proteases [41,42]. The ischemic environment also induces mucosal atrophy, mitochondrial dysfunction [43], oxidative stress, and cell death. Interestingly the mitochondrial dysfunction found early in AP appears to occur in the pancreas, lung, and jejunum with relative sparing of the liver, heart, and kidneys [43].

There is strong evidence for intestinal dysfunction in AP (Fig. 14.2), and it is estimated to occur in 60% of patients [44]. Clinically this dysfunction can be evident as an ileus (dysmotility) [45], feeding intolerance [46], and at the severe end of the spectrum, nonocclusive intestinal ischemia [47,48]. Although suspected, there is still no clear clinical evidence that increased intestinal permeability, as detected by enterally administered polyethylene glycol, is associated with an increased risk of MODS in AP [49]. Increased urinary intestinal fatty acid binding protein, a marker of intestinal mucosal injury, has been correlated with the severity of AP [37,50]. The depletion of IgG anti-endotoxin antibodies, indicative of exposure to endotoxin and "gut barrier failure," is strongly associated with the development of organ failure and death in severe AP [51]. The administration of enteral nutrition (rather than starvation or parenteral nutrition) has been associated with a reduction in infectious complications and mortality in patients with AP [52], giving rise to the concept of "gut rousing" and "gut protection" to maintain and improve intestine function [53] during AP and other acute and critical diseases.

Altered Gut–Lymph Composition in Acute Pancreatitis

There is a significant body of experimental evidence that mesenteric lymph undergoes significant compositional change during acute and critical diseases, such as hemorrhagic shock, sepsis, trauma, and burns [14]. Comparable experimental evidence is only now emerging for AP. A canine model of AP with thoracic duct cannulation demonstrated that a significant proportion of pancreatic amylase and lipase is transported via thoracic duct lymph compared with peritoneal absorption from pancreatic ascites [54]. A rodent model of acute pancreatitis revealed a profound change in the proteome of mesenteric lymph [55]. Of the eight proteins exhibiting a significant increase in mesenteric lymph seven were pancreatic proteases, and the increase was up to 40-fold. Despite this flooding of mesenteric lymph with pancreatic proteases there was no commensurate increase in the abundance of antiproteases. Lipase is also markedly elevated in

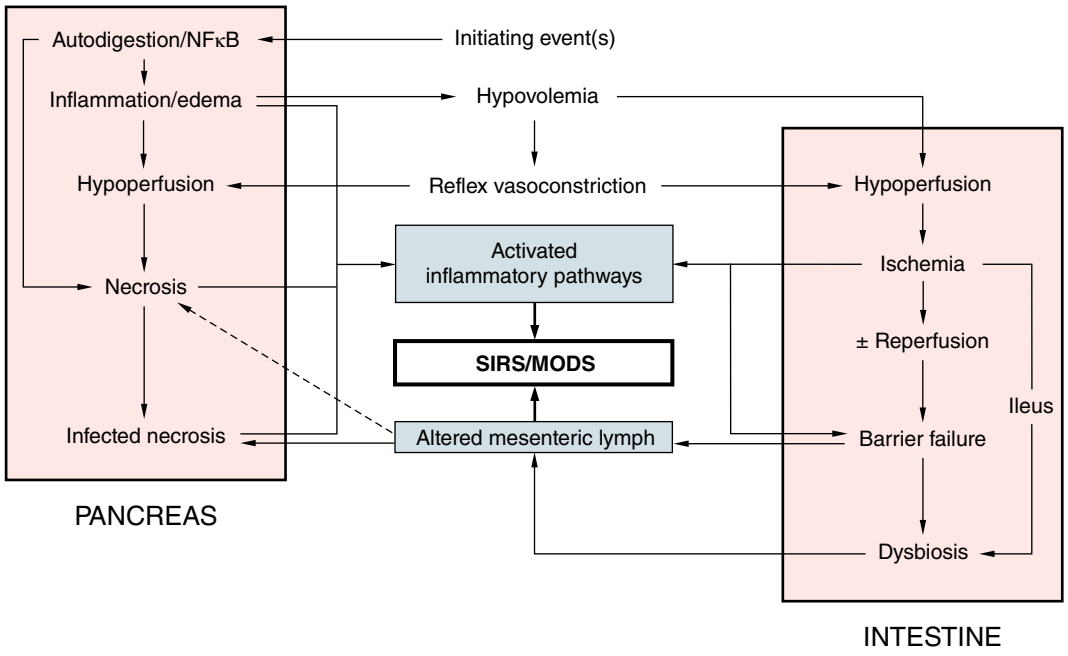


Figure 14.2 A summary of the complex interactions between the pancreas and the intestine in the development of systemic inflammation (SIRS) and multiple organ dysfunction (MODS) in the pathogenesis of severe acute pancreatitis. *Source:* Adams DB (2017)/ John Wiley & Sons.

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mesenteric lymph during AP and generates free and unsaturated fatty acids in mesenteric lymph that are directly toxic to umbilical vein cells [56], exhibit systemic toxicity, and are associated with ARDS and MODS [57]. The gut lymph profile of noncoding microRNA is also altered in AP, in both the experimental and clinical settings [58]. Interestingly, there were seven miRNAs that were increased in intestinal lymph during experimental AP and their log abundance correlated with AP severity [58]. The clinical significance of these microRNA changes has yet to be determined, but these molecules can regulate gene expression, influence cell function in remote organs, and offer potential therapeutic strategies with designer antisense sequences. Other groups have demonstrated changes in mesenteric lymph composition in AP. For example, it has been found that the tryptophan metabolites kynurenine and 3-hydroxykynurenine are elevated in rodent mesenteric lymph and plasma during AP and this elevation correlated with disease severity [59].

One of the challenges in studying the role of mesenteric lymph in patients with severe AP is the difficulty in gaining access to thoracic duct lymph in the clinical setting. A pilot nontherapeutic study was conducted in post-esophagectomy patients which allowed serial sampling of thoracic duct lymph for several days following surgery [60]. While not in AP patients it did allow confirmation of compositional changes in human lymph similar to the rodent studies of AP. The effect of enteral feeding on TD lymph composition, and in particular on the markers of intestinal ischemia and injury, suggested that intestinal injury occurs with enteral feeding in these patients.

Gut–Lymph Toxicity in Acute Pancreatitis

The pathophysiologic and clinical significance of the profound compositional changes in mesenteric lymph in AP is still to be fully elucidated. Some progress has been made by testing the toxicity of the altered mesenteric lymph. In our own studies we have tested toxicity on four levels: organelle (e.g., mitochondrial function), cell (e.g., endothelial, cardiac), organ (e.g., isolated perfused heart and lung), and organism (e.g., rodent AP model). Mesenteric lymph from experimental AP incubated with either endothelial cells or cardiac fibers was toxic, causing increased cell death. In the case of cardiac fibers there was lymph-induced toxicity that induced mitochondrial complex dysfunction [61]. Experimental AP is associated with a reduction in cardiac output, contractility, and impaired relaxation, which can be replicated by infusion of mesenteric lymph collected from an experimental model of AP and then infused into an isolated and paced heart model [28]. Significantly, as further evidence of lymphatic toxicity, experimental work has shown that cardiac dysfunction can be prevented by thoracic duct ligation [28] (Fig. 14.3). In another critical study mesenteric lymph from a rodent model of ischemia-reperfusion injury was intravenously infused into other rats with AP [62] causing an increase in AP severity, augmented microcirculatory collapse and produced evidence of lung injury [62]. Other studies have shown that thoracic duct ligation [22] and lymph diversion [63] have been shown to ameliorate lung injury in AP.

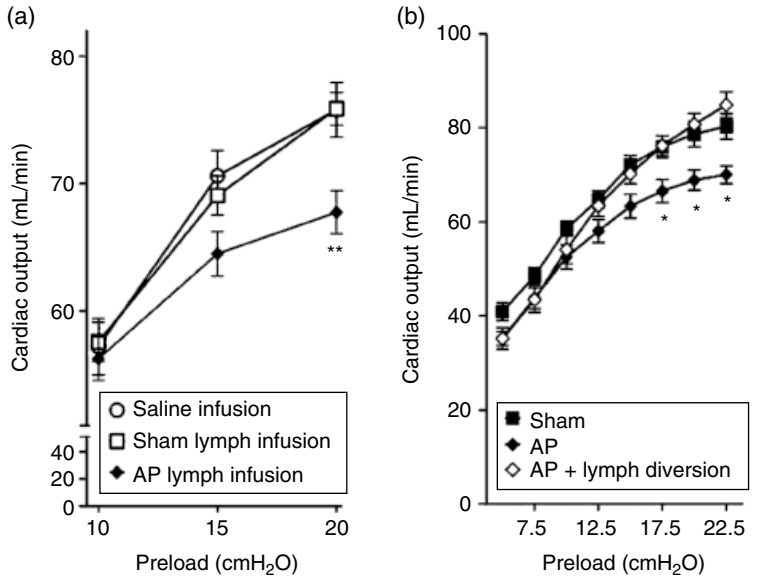


Figure 14.3 (a) Cardiac output is reduced in *ex vivo* working hearts by acute pancreatitis-conditioned gut–lymph when compared to saline or sham lymph. (b) Cardiac output is maintained in rats with acute pancreatitis when compared to sham rats or rats with acute pancreatitis in which the thoracic duct is ligated. $^{*}P < 0.05$, $^{**}P < 0.02$.

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Translating the Gut–Lymph Concept to Clinical Treatments for Acute Pancreatitis

Open surgical drainage of thoracic duct lymph has previously been explored as a treatment for a number of diseases. There have been over 70 publications [64] in the English literature, but none since 2004. There is an even more extensive non-English literature from Eastern European countries [65]. The reasons for the discontinuation of this treatment is likely a combination of the invasive nature of the thoracic duct cannulation and the lack of compelling evidence due to the predominance of underpowered, nonrandomized and uncontrolled study designs. Within this seemingly forgotten literature there were four studies [66–69] in which external lymph drainage was used for the treatment of acute pancreatitis. One uncontrolled study of 10 patients reported an improvement in abdominal pain, peritonism, and shock in a "dose-dependent" manner related to the volume of lymph drained [66]. Three of these studies investigated the effect of thoracic duct lymph drainage on pulmonary function in the setting of AP-associated acute respiratory distress syndrome. One study noted that arterial oxygenation improved once drainage was instituted [67]. Another case series demonstrated elevated levels of pancreatic enzymes and cytokines in lymph and plasma but no clinical improvement [69].

With the evidence that proteases contribute to lung injury in acute pancreatitis [70] and the evidence that thoracic duct lymph is flooded by pancreatic proteases in AP [55] suggests that external drainage is a treatment strategy warranting more careful evaluation. A canine model of thoracic duct external drainage has shown that this is effective in reducing plasma amylase and lipase in AP [54].

One of the major barriers to advancement in this area has been the lack of a reliable, safe, and minimally invasive technique for sampling, monitoring, and draining thoracic duct lymph in patients with severe AP. The advent of innovative retrograde percutaneous radiological techniques for cannulating and externally draining the thoracic duct [71] is stimulating the conduct of more studies to evaluate external drainage of thoracic duct lymph to mitigate an important driver of MODS [72].

Another potential treatment strategy based on the gut–lymph concept is the design and delivery of treatments that target known toxic factors in mesenteric lymph [73]. In an experimental rodent model it was demonstrated that inhibition of tryptophan metabolites kynurenine and 3-hydroxykynurenine, which are elevated in mesenteric lymph of rats with AP, is protective against MODS [74].

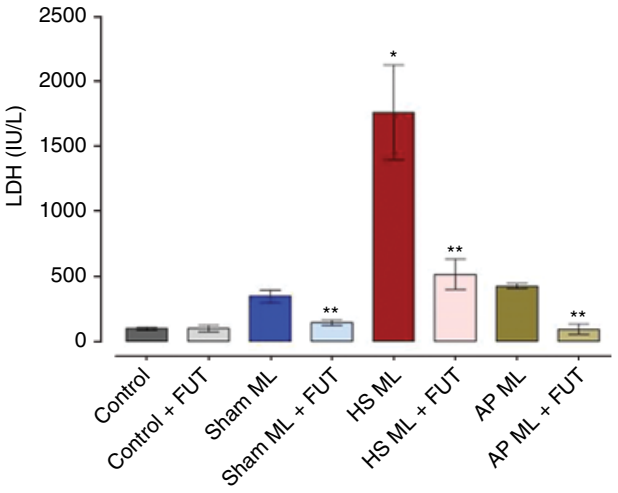


Figure 14.4 Cell death (LDH level) of endothelial cells (HMEC) was increased on treatment with hemorrhagic shock (HS) or AP-conditioned gut–lymph (ML) when compared to control media or mesenteric lymph (ML) from sham-treated rats (*$P < 0.05$). Cotreatment with the antiprotease nafamostat (FUT) reduced cell death (**$P < 0.05$) (unpublished).

In another experiment it was found that antiprotease treatment with nafamostat significantly reduced endothelial cell death when combined with mesenteric lymph from experimental hemorrhagic shock and AP (Fig. 14.4). This raises the possibility of delivering antiprotease treatment to mesenteric lymph by supplementing enteral nutrition with lipophilic transporters. In a similar manner it is possible to deliver anti-lipase treatment (i.e., orlistat) to mesenteric lymph to reduce the generation of toxic fatty acids, which are known to exacerbate organ dysfunction [75]. Enhanced delivery of oral orlistat to mesenteric lymph has been achieved in rodent models [76].

In order to translate the gut–lymph concept into effective clinical treatments, a more complete understanding the role of mesenteric lymph in the pathogenesis of the systemic inflammatory response and organ dysfunction will be required. These experimental studies are examples of potential new treatment strategies.

Conclusion

There is now compelling experimental evidence that altered mesenteric lymph contributes to the systemic inflammation and MODS that characterizes severe AP. The "gut–lymph" concept provides a new disease paradigm, a new field of research, and a long-awaited opportunity to develop new and specific treatments for MODS in severe AP.

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The Role of Neurogenic Inflammation in Pancreatitis

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Introduction

Pancreatitis is a clinical condition in which the main pathology is inflammation of the pancreatic tissue. It has multiple etiologies that include both genetic and environmental components. It also can be classified as acute or chronic pancreatitis. Acute pancreatitis typically resolves, but it is associated with acinar cell death and activation of subsequent inflammatory cascades [1,2]. Chronic pancreatitis, conversely, is a progressive destruction of the pancreas by repetitive insults. This leads to replacement of viable tissue by fibrotic tissue and subsequently alters pancreatic nerves around the area of inflammation [3–5]. Pathological activation of sensory neurons and the inflammatory sequelae are known as neurogenic inflammation. Neurogenic inflammation is the process by which substances released from sensory nerve terminals promote inflammation in their target tissue. The inciting factors that lead to pancreatic inflammation can be varied; however, the resulting pathology has a common histologic presentation, including edema, vasodilation, invasion of immune cells, and varying degrees of breakdown in the barriers between different tissue compartments within the pancreas.

The central and peripheral nervous systems (CNS and PNS, respectively) can adapt to an ongoing disease process in the gastrointestinal tract. A major role has been recognized for the PNS as a driver of inflammatory pancreatic responses, such that it is being investigated as both a prognostic biomarker as well as a therapeutic target. Experiments in animal models indicate that manipulation of the PNS can alter the course of the disease. Specifically, these manipulations have targeted sensory innervation of the pancreas in studies that go back to the early twentieth century, which found that activation of the primary sensory neurons produced vasodilation [6]. The studies by Bayliss [6] were the beginning of the recognition that sensory neurons have an "efferent" function through the peripheral release of small molecules that can act on blood vessels and immune cells to establish "neurogenic inflammation." Here we review the current state of our understanding of the role of neurogenic inflammation in pancreatitis and how this information might be translated into new treatments for human disease.

Innervation of Pancreas

The pancreas is innervated by two distinct neural pathways, vagal and spinal. Historically, they have been further divided into two distinct types of nerve fibers: afferent fibers conducting sensory information from the pancreas to CNS and efferent autonomic fibers (parasympathetic and sympathetic) conveying motor commands from the CNS to the pancreas (Fig. 15.1). The vagus nerve comprises both parasympathetic and sensory fibers. Pancreatic sensory afferents originate from the nodose ganglia (NG) [7]. They transmit information to the nucleus tractus solitarii (NTS) in the brainstem. Preganglionic parasympathetic neurons originate from the dorsal motor nucleus of the vagus (DMV) located in the brainstem and medulla [8]. These fibers activate parasympathetic postganglionic neurons located in the intrapancreatic ganglia [8,9]. The sympathetic efferent fibers of the pancreas consist of preganglionic and postganglionic neurons. Preganglionic

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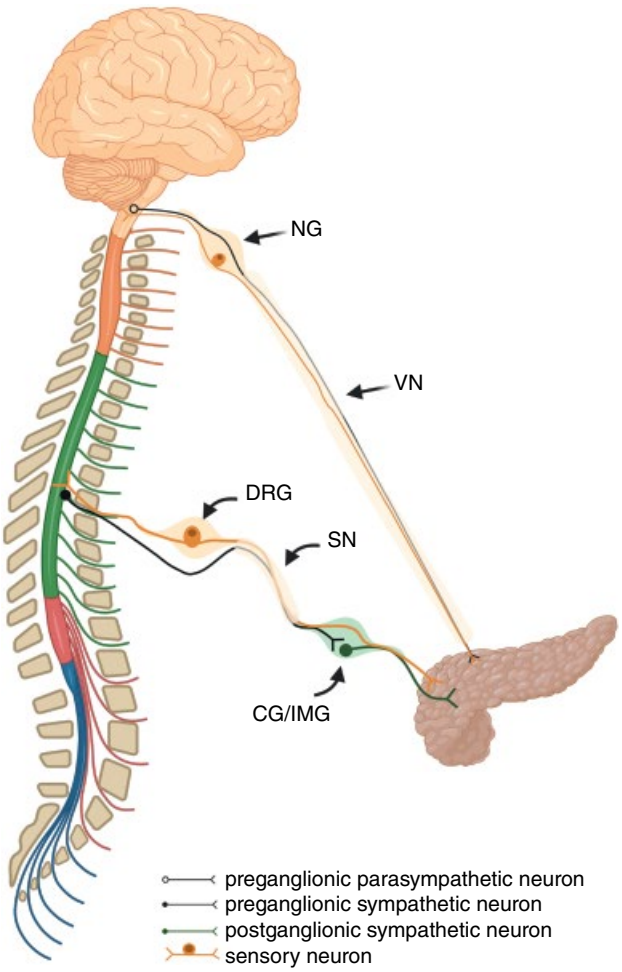


Figure 15.1 The pancreas receives sensory input from primary afferents whose cell bodies are located in the nodose ganglion (NG) and run in the vagus nerve (VN). Sensory innervation from dorsal root ganglia (DRG; also known as spinal ganglia) to the pancreas travels with sympathetic preganglionic axons in the greater splanchnic nerve (SN) and passes through the celiac ganglia (CG), which together with the IMG form the celiac plexus. The VN also contains axons from parasympathetic preganglionic neurons whose cell bodies are located in the brainstem (in the dorsal motor nucleus of the vagus, not shown). These axons synapse on parasympathetic postganglionic neurons (not shown) that are in the organ. Sympathetic innervation arises from sympathetic preganglionic neurons whose cell bodies are located in the spinal cord intermediolateral cell column (not shown) at T5–9 vertebral levels. Axons from these neurons innervate sympathetic postganglionic neurons in prevertebral ganglia found near the organ. The prevertebral ganglia include the CG, whose neurons innervate pancreas. Anatomy shown for human, but rodents are organized in a similar fashion, varying only in the details. Figure created with BioRender.com.

efferent sympathetic fibers project from cell bodies in the lateral horn of the spinal cord called the intermediolateral cell column (C8-L3). Information is transmitted to paravertebral and prevertebral sympathetic ganglia in the celiac plexus (celiac and superior mesenteric ganglia; CG and SMG, respectively). Preganglionic sympathetic neurons synapse on postganglionic sympathetic neurons in the CG and SMG [8,11]. The postganglionic sympathetic fibers subsequently project to intrapancreatic ganglia, islets, ducts, and blood vessels, and release neurotransmitters [12]. Parasympathetic and sympathetic efferent fibers release various neurotransmitters that directly affect blood pressure, pH, temperature, and metabolism of pancreatic tissues [9,12]. Spinal sensory afferent fibers originate from dorsal root ganglia (DRG) at (T6-L2) segments of the spinal cord. These afferent fibers, located in the splanchnic nerves pass through the celiac plexus and transmit information from the pancreas to the spinal cord [8,10].

Neuroimmune Signaling

Under healthy conditions, neurohormonal signaling pathways involving both autonomic (parasympathetic, sympathetic) and sensory nerves regulate the exocrine and endocrine functions of the pancreas [9]. However, given that the primary function of the exocrine pancreas is production of digestive enzymes (proteases), the pancreas is always on the edge of activating inflammatory cascades. Sensory fibers transduce chemical and mechanical stimuli to the CNS, but they also release neurotransmitters and neuropeptides into the parenchyma, which can recruit and activate immune cells, thereby promoting inflammation.

Twenty years ago, patients with AP were reported to have increased levels of circulating inflammatory cytokines [13]. Studies of models of AP established that in response to the initial insult, acinar cells produce and release a variety of inflammatory mediators that initiate the inflammatory response. More specifically, a feedback loop begins when damaged acinar cells release TNF-α, IL-6, IL-8, IL-10, and chemokines into the circulatory system. These mediators subsequently recruit neutrophils, and then macrophages, monocytes, and lymphocytes, to the pancreas. The recruited white cells cause the release of more proinflammatory cytokines, which leads to more edema and local inflammation suggesting that the initial inflammatory responses and signals that recruit leukocytes originate in injured pancreatic acinar cells [14]. It is not exactly clear how acinar cell injury leads to the induction of inflammatory mediators, but the process involves activation of specific transcription factors. NF-κB, in particular, is activated in experimental and human AP, and genetic and pharmacologic approaches have shown its important role in the cytokine storm [15].

In addition, interleukins and TNF-alpha cytokines released by innate immune cells during inflammation are directly sensed by nociceptors, which lead to increased membrane excitability. Nerve growth

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factor (NGF) and prostaglandin E (2) are also major inflammatory mediators released from immune cells that act directly on peripheral sensory neurons to cause sensitization. An important effect of nociceptor sensitization by immune factors is an increased release of neuropeptides at peripheral terminals that further activate immune cells, thereby inducing a positive feedback loop that drives and facilitates inflammation [16]. Under pathophysiological conditions, this bidirectional communication promotes an autoamplification loop that underlies neurogenic inflammation and suggests that the nervous system plays a key role in inflammation and may be a potential therapeutic target.

Role of Neurotransmitters

Neuropeptides

The idea that the sensory nervous system, via neurogenic inflammation (Fig. 15.2), plays a role in pancreatitis has led a number of investigators to test this hypothesis by inducing pancreatic inflammation and manipulating pancreatic sensory input, either surgically or chemically in an effort to identify key neuronal proteins involved in pancreatitis pathology. Nathan et al. [17] hypothesized that sensory neurons were a "final common pathway" for neurogenic inflammation associated with pancreatitis. Using two experimental models of pancreatitis (repeated caerulein injections and common pancreaticobiliary duct ligation), they were able to show that sensory denervation (via neonatal capsaicin treatment) dramatically reduced multiple measures of pancreatic inflammation. Subsequent studies expanded on this concept by using pharmacologic approaches to block pancreatic afferent activity. Sensory nerve fibers innervating the pancreas contain a wide array of neuropeptides; however, substance P (SP) and calcitonin-gene related peptide (CGRP) are the most studies in relation to pain and inflammatory mediators. They not only signal the perception of pain to CNS via primary afferent synapses on spinal cord neurons, but also recruit leukocytes and activate surrounding cells' inflammatory signaling pathways [18]. The origin of SP is thought to be from extrinsic sources of sensory afferent neurons mainly in bilateral DRG [19] (Fig. 15.1).

However, recently, Shen et al. illustrated that pancreas is rich in SP-containing neurons inside intrapancreatic

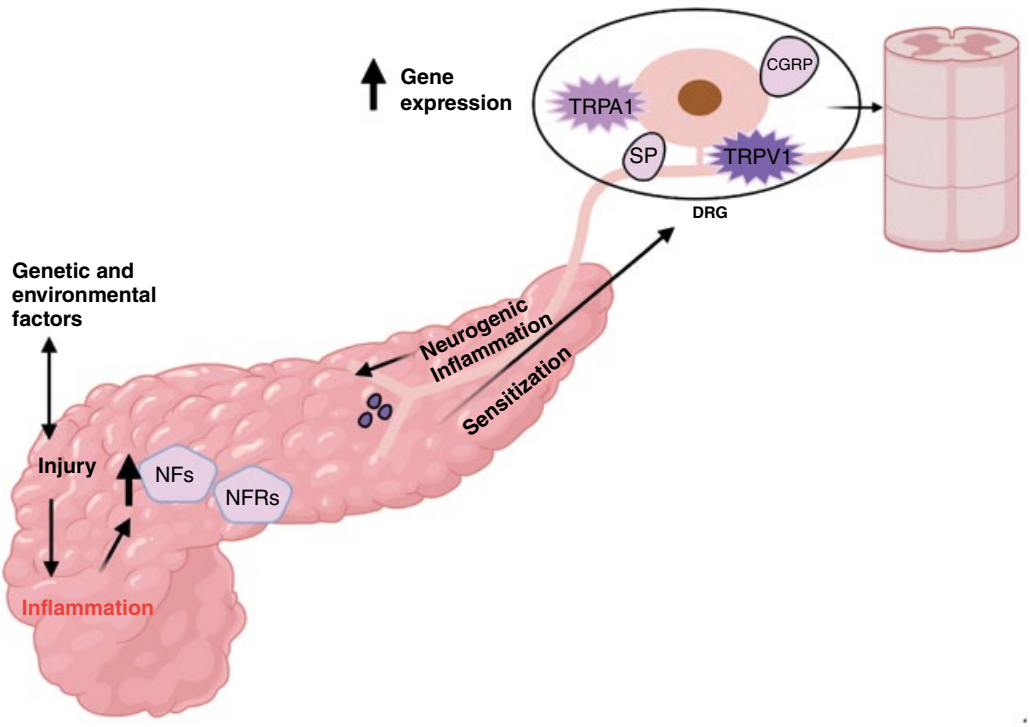


Figure 15.2 Pancreatic injury, exacerbated or induced by environmental and genetic factors, leads to pancreatic injury and inflammation. This inflammation is accompanied by an increase in neurotrophic factors (NFs, e.g., nerve growth factor and artemin) as well as neurotrophic factor receptors (NFRs, e.g., TrkA). The NFs produce sensitization of sensory fibers innervating the pancreas and this leads to an increase in sensory neuron gene expression for receptors/channels that detect noxious stimuli (e.g., TRPA1 and TRPV1) as well increased production and release of small molecules that produce neurogenic inflammation in the pancreas (e.g., substance P [SP], calcitonin gene-related peptide [CGRP]). This feed-forward loop, if not blocked, can lead to fibrosis and permanent damage associated with chronic pancreatitis, as well as setting the stage for cancer development. Figure created with BioRender.com

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ganglia in rats. In their experiment, they surgically denervated posterior branches of bilateral T5 –L2 DRG, SP expression remained >60% in the pancreas. Moreover, after high doses of capsaicin were injected to destroy primary sensory afferents, the remainder of SP protein levels was still >50% in the pancreas. This suggested that half of SP origin were from intrapancreatic ganglia [20]. In the case of pancreatitis, intrinsic SP secretion could be a clue to an autoamplification loop that contributes to acinar cell death. SP executes its function by binding to neurokinin receptors (NK1). Among several inflammatory disease models, the association of SP/NK1R signaling and its contribution to AP through neurogenic inflammation has been well demonstrated. In a recent study, Tskuamato et al. also demonstrated anti-inflammatory action of the NK1R antagonist in a mouse model of AP. Their study results showed NK1R antagonist completely inhibited blood IL-6 levels and subsequently NK kappa B pathway in mast cells [21]. Reduction in IL-6 and a blockade of a potent inflammatory pathway could be promising in decreasing edema, microcirculatory dysfunction, and ultimately pancreatic tissue injury in patients with acute pancreatitis. Han et al. also confirmed a well-established idea that pancreatic SP-NK1R signaling pathways were markedly upregulated in patients with acute pancreatitis. In their experiment, the use of an herbal medicine (containing baicalin, emodin, maglol-immunomodulators, and analgesics) that is commonly used for the management of acute pancreatitis was shown to reduce both pain and the severity of AP via blocking neuron activation-mediated pancreatic SP-NK1R signaling pathways [22]. Reduced activation of SP-NK1R signaling reduces the downstream inflammatory pathway, which subsequently reduces acinar cell necrosis. Their study also emphasized the idea that inflammation and pain positively reinforce each other, therefore, minimizing pain is considered a potential strategy to mitigate inflammation [23]. Interestingly, Green et al. recently challenged our current understanding of the NK-1 receptor as the primary facilitator of SP-generated peripheral neurogenic inflammation and pain. Their study illustrated similar patterns of innate immune cell recruitment in *NK-1R*-deleted mice as that of WT mice, whereby injections of SP caused a significant influx of inflammatory cells. More specifically, the activation of the mast cell receptor Mrgprb2/X2 by SP lead to cytokine release and recruitment of immune cells contributing to inflammatory pain. The finding that SP promoted immune cell recruitment via Mrgprb2 rather than NK-1 receptor provides a novel target in treating inflammation and pain [24].

Many studies have also sought to understand the pathological role of CGRP in patients with pancreatitis. CGRP has been explored as a neuromodulating peptide in diverse painful conditions, due to its localization in unmyelinated sensory nerves that are activated by nociceptive and painful chemical stimuli [10]. Numerous studies have also indicated that CGRP induces vasodilation by the release of nitric oxide and subsequently mediates an inflammatory response by increasing of IL-1β and IL-6 expression [25]. Hu et al. illustrated that patients with acute pancreatitis had elevated trypsin and CGRP in their serum. They have hypothesized that serum CGRP could act as a new detection index of acute pancreatitis and serve as evidence of ongoing pancreatic inflammation [26].

TRP Channels and Protease Receptors

Transient receptor potential (TRP) cation channels, key regulators of nociception, have been implicated in both acute [27] and chronic [28] pancreatitis. Schwartz and colleagues used cerulein-treated mice to demonstrate that antagonists for the TRP vanilloid type 1 and ankyrin type 1 (TRPV1 and TRPA1, respectively) channels effectively block both pain and inflammatory markers, including upregulation of myeloperoxidase and neutrophil infiltration (acute pancreatitis), as well as fibrosis and nerve sprouting (chronic pancreatitis). The question then becomes what are the signals released by the damaged pancreas that produce abnormal activation of pancreatic afferents?

The majority of pancreatic afferents express receptors on their pancreatic terminals that can induce activation and calcium influx into the presynaptic terminal, which can contribute to the release of inflammatory molecules (Fig. 15.2). The receptors in sensory endings that have received the most attention in recent years are the transient receptor potential cation channel subfamily vanilloid type 1 and 4 (TRPV1, TRPV4), a related family member TRP ankyrin 1 (TRPA1) and protease-activated receptor 2 (PAR2). They can be stimulated by numerous endogenous molecules including anandamide (an endogenous cannabinoid), protons, leukotriene B4, hydrogen peroxide, and products of lipid peroxidation such as 4-hydroxynonenal [28–31]. Their activation triggers the release of proinflammatory neuropeptides like SP and CGRP, thereby initiating neurogenic inflammation both at the spinal cord and peripheral sites, thus causing pancreatic inflammation via neurogenic inflammation [32].

Numerous studies have demonstrated that TRPV1 is involved in peripheral inflammation, in the modulation of nociceptive inputs to spinal cord and brain stem centers, as well as the integration of diverse painful stimuli [32]. The role of TRPV1 phosphorylation by protein kinase A/C in the development of inflammatory hyperalgesia is well established [33]. During inflammation, protein kinases phosphorylate TRPV1 and thereby enhance its function, with consequent increases in nociceptor sensitization. Interestingly, a calcineurin inhibitor, Tacrolimus (an immunosuppressant drug) enhances TRPV1 function by reducing

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the dephosphorylation of TRPV1. More specifically, calcineurin blockers increase TRPV1-dependent substance P release from cultured DRG neurons and induce a relapse of acute pancreatitis-related pain in a TRPV1-dependent manner in mice [34,35]. Conversely, dephosphorylation of TRPV1 by a phosphatase (calcineurin) decreases its function. This discovery suggests the involvement of calcineurin in the termination of pancreatic pain. In a recent study, Joseph et al. illustrated that by precisely removing a unique protein kinase phosphorylation site (TRPV1 S801) in mice through CRISPR/Cas9 editing can attenuate inflammatory pain and produce fewer side effects than more general TRPV1 inhibition. This unique observation raises the possibility of engineering novel TRPV1 antagonists that selectively interact at the phosphorylated TRPV1 site [36]. A similar study found that Tacrolimus also interacts with TRPA1 channels in primary sensory neurons. In a mouse model, injection of Tacrolimus evoked licking or biting behaviors and these behaviors were almost abolished in TRPA1 knockout mice. This result indicates that Tacrolimus might also cause pain sensations through TRPA1 activation and confirms the importance of calcineurin (a phosphatase) in pain termination [37].

In recent years, a growing body of studies illustrated that TRPV4 acted as a crucial regulator in neural and inflammatory cells, suggesting TRPV4 may be a potential therapeutic vehicle in inflammatory diseases. TRPV4 plays a significant role in disrupting the epithelial and endothelial barrier function, which suggests an important role in edema formation associated with inflammation and tissue injury [38]. A recent discovery unveils TRPV4 channel's unique interaction with Piezo1 (pressure sensing ion channel type 1). Studies have found that Piezo1 stimulation triggered TRPV4 channel opening, which subsequently led to a sustained elevation in intracellular calcium that caused intracellular organelle dysfunction in pancreatic tissues. Moreover, TRPV4 gene knockout mice were protected from Piezo1 agonist and pressure-induced pancreatitis. This study uncovers a calcium signaling pathway in which Piezo1-induced TRPV4 channel opening causes pancreatitis [39,40].

Moreover, the cooperative interaction between PAR2 and TRPV1, TRPV4 and TRPA1 has been established in hyperalgesia, inflammation, and edema [41]. In the pancreas, trypsin released from the injured pancreatic acinar cells directly activates PAR2, which subsequently sensitizes TRPV1. Their interaction causes neurogenic inflammation in pancreatic tissue [42]. PAR2 can also be activated via tryptase, a substance released from an activated mast cell. When mast cells degranulate and release tryptase, this produces nociception by binding to PAR2 on primary afferents [43–45]. In an experimental animal model Kido et al. illustrated that an agonist of PAR2 induced nociceptive pain behavior and a selective PAR2 antagonist reduced incision-induced guarding pain behavior in rats [46].

Studies have concluded that TRP channels are themselves upregulated by growth factors (NGF and ARTN) that are highly expressed in inflamed pancreata [47–50]. Many studies have attempted to explain the mechanism of NGF-induced pancreatitis pain on sensitization via modulation of TRPV1 [51–53]. Another hypothesized mechanism underlying pain in pancreatitis is the activation of the NGF/trkA pathway [51–53]. These studies indicate that for palliative care, a targeted therapy against TRPs could be essential.

Assuming that pancreatic sensory terminals are similar to other visceral nerve endings, they will express a wide range of receptors that allow them to respond in an autocrine/ paracrine fashion. These receptors could respond to molecules released by adjacent sensory fibers as well as to ATP and norepinephrine released from pancreatic sympathetic postganglionic neurons [54,55]. Many of these molecules may act locally on sensory endings to induce release in the absence of action potential generation. However, once an action potential is generated in a sensory fiber, this will trigger release of proinflammatory neuropeptides and excitatory neurotransmitters. Once this activity reaches the spinal cord it can rebound via a process known as a dorsal root reflex. This reflex produces a retrograde action potential that travels back out to the periphery and initiates release of inflammatory molecules [56–58]. The efficacy of this reflex is exaggerated by spinal cord inflammation, which has been shown to accompany pancreatitis [59,60].

Nerve-Targeted Interventions

Novel experimental models of vagotomy demonstrate contribution to neurogenic inflammation. Szklarczyk and coworkers have recently demonstrated in rat that bilateral vagotomy significantly reduced the severity of AP, which was manifested by decreased activity of serum lipase and improvement of pancreatic blood flow, as compared to the AP rats with intact vagal nerves. In addition, vagotomy caused the increase of anti-inflammatory IL-10 in the blood. Attenuation of AP was supported by the examination of the pancreatic tissue and the reduction of the morphological signs of inflammation such as edema, leucocyte infiltration, and vacuolization of the acinar cells [61]. Their follow-up study indicated that a unilateral vagotomy could also contribute to pancreatic protection. The strong reduction of inflammatory changes was observed in the rats with left vagus nerve removal compared to right vagus nerve removal. Perhaps due to the prevalence of left vagal nerve in pancreatic innervation and predominance of this vagal branch in the

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stimulation of pancreas exocrine function [62]. Since the vagus nerve contains both parasympathetic and sensory fibers, the specific anti-inflammatory mechanism remains unclear; however, these studies have demonstrated that manipulation of the vagus nerve (e.g., vagal inhibitor) could be a potential treatment for pancreatitis.

Moreover, Michalski and coworkers demonstrated that cannabinoid receptors were expressed in the pancreas (on both nerves and other cell types). In cerulein-induced acute pancreatitis, administration of cannabinoid agonists reduced inflammation and alleviated pain in mice [63]. Their follow-up research demonstrated that the addition of cannabinoids leads to a reduced inflammation and fibrosis [64]. To further expand on this idea, Utomo et al. illustrated a direct immune modulatory effect of THC on peripheral blood cell populations in both healthy volunteers and patients with CP. Their study illustrated an immunosuppressive effect of cannabis via deactivation of signaling through the proinflammatory p38 MAP kinase and mTOR pathways and a concomitant deactivation of the pro-mitogenic ERK pathway19 [65].

Although nerve-targeted interventions effectively reduce pancreatitis symptoms in preclinical models, in most experimental paradigms these interventions are applied either simultaneously with the disease-inciting stimulus (e.g., caerulein) or early in the disease process. Thus, their relevance for treatment of patients is unclear, especially for acute pancreatitis where the primary symptom of pain is treated medically with nonsteroidal anti-inflammatory drugs and opioids. Clinicians are reluctant to use more aggressive procedures that include injections into splanchnic nerves or celiac ganglia due to occasional adverse effects that can be severe and difficult to justify for a disease that in many cases resolves relatively quickly. However, for chronic pancreatitis, nerve injections are an important option. There are three primary techniques that are utilized to manage intractable pancreatic pain: celiac plexus block (CPB), celiac plexus neurolysis (CPN), and thoracoscopic splanchnic denervation (TSD). Importantly, there is little or no evidence that these treatments affect non-pain disease features (which would be difficult to assess in the absence of large controlled trials). TSD can effectively reduce adreno-medullary function, pain scores, and opioid use in patients with chronic pancreatitis [66,67]. A meta-analysis of 16 studies reveals that TSD significantly reduces pain and improves quality of life. However, the pain returns in half of those initially achieving relief after just 1.5 years [68,69]. There are many possible explanations for why TSD may not provide complete and lasting pain relief. During the surgical procedure, damage to nearby intercostal nerves or incomplete denervation of the thoracic splanchnic nerves (greater, lesser, least) may contribute to residual pain. However, the splanchnic nerves carry not only sensory fibers, but sympathetic fibers as well. Given that sympathetic activity suppresses pancreas function, the loss of this brake following denervation could result in hypersecretion of digestive enzymes that exacerbates inflammation and pain. Furthermore, some patients may have progressed to sensitization of the CNS meaning that they will continue to experience pain and hypersensitivity in the absence of peripheral input. Separately, the pancreas is still innervated by the vagus. While the role of vagal sensory afferents in pancreatic nociception has not been thoroughly investigated, it is possible that these fibers, which remain intact, are also contributing to the recurrence of chronic pain. Further studies will be needed to parse out the underlying cause for some patients to develop persistent pain following TSD.

Conclusion

The efficacy of silencing sensory neurons for patients with pancreatitis will be worth revisiting in the future with the development of new drugs that have been developed for pain and that act by blocking either sensory nerve function or the inflammatory molecules released by sensory fibers. For example, clinical trials are now under way for both anti-NGF and anti-CGRP antibodies and drugs [70–74]. These drugs may make it possible to conduct sufficiently powered clinical trials to determine if these types of therapies are both safe and effective for this difficult disease. Further studies are needed to clarify the interaction of inflammatory cells and nerves in AP as well as in chronic pancreatitis. A better understanding of the complex cellular and molecular mechanisms of neuroimmune interactions should offer possibilities for innovative therapy and long-term disease prevention.

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16

Molecular, Biochemical, and Metabolic Abnormalities of Acute Pancreatitis

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Introduction

Pancreatitis is an inflammatory disorder of the exocrine pancreas caused, in most cases, by immoderate alcohol consumption or the passage of gallstones. Recent studies involving animal and isolated cell models have elucidated many of the pathophysiological, cellular, and molecular processes involved in the disease onset. More than 100 years ago it was proposed that pancreatitis is essentially a disease in which the pancreas falls prey to its own, prematurely activated digestive enzymes. Why and how digestive zymogens undergo activation within the pancreas early in the disease process has been the topic of extensive research efforts and debate. Premature activation of pancreatic zymogens results in biochemical and later metabolic alterations, the mechanisms of which will be reviewed in the following chapter. Regardless of the underlying etiology the natural course of pancreatitis, a primarily sterile inflammatory disorder, proceeds in three steps: (i) a local inflammatory reaction—caused by tissue edema or characterized by extensive necrosis, (ii) a systemic inflammatory response (SIRS), and (iii) eventually microbial superinfection of the pancreatic necrosis, which frequently results in multiorgan failure and is closely associated with a rise in mortality. Mortality in severe acute pancreatitis peaks at two different time points: patients either pass away during the first 7 days after the onset of pain from an overwhelming inflammatory response syndrome resulting in multiorgan failure (~30%) or they die late in the disease course facilitated by a compensatory anti-inflammatory response syndrome, which permits translocation of gut bacteria into pancreatic necrosis, resulting in uncontrollable sepsis. Frequently, however, a mixed picture of a systemic inflammatory response and a compensatory anti-inflammatory reaction, called MARS (mixed anti-inflammatory response syndrome), is observed. The pathogenesis of the inflammatory response in acute pancreatitis is indistinguishable from that of other traumatic or infectious immune reactions, but pancreatitis is often characterized by an overwhelming course. Thirty percent of all patients admitted to hospital suffering from acute pancreatitis display symptoms of a two-organ failure at admission. Outside the pancreas the most frequently affected organs are the lungs, kidneys, and the gut [1].

Molecular and Biochemical Abnormalities

Pathophysiological Significance of Digestive Protease Activation

Trypsinogen and other pancreatic proteases are synthesized by acinar cells as inactive proenzyme precursors and stored in membrane-confined zymogen granules. After activation in the small intestine, trypsin converts other pancreatic zymogens such as trypsinogen (*PRSS1*, *PRSS2*), chymotrypsinogen (*CTRC*), proelastase, pro-carboxypeptidase, or pro-phospholipase A2 to their active forms [2]. Although small amounts of trypsinogen are probably activated within the pancreatic acinar cell under physiological conditions, two protective mechanisms normally prevent cell damage from proteolytic activity: (i) Pancreatic secretory trypsin inhibitor (PSTI), the product of the *SPINK1* gene, is co-secreted with pancreatic zymogens. PSTI can inhibit up to 20 % of potential trypsin activity in humans [2].

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The fact that mutations in the *SPINK1* gene are associated with certain forms of human pancreatitis [3,4] indicates that this protective mechanism may play a role in pancreatic pathophysiology. The implications of SPINK1 overexpression in a disease model of pancreatitis have recently been reported [5]. (ii) Cell biological experiments using living rodent acini provided evidence that trypsin limits its own activity by autodegradation under conditions that mimic pancreatitis [6]. In humans, mesotrypsin has been labeled a candidate for autoactivation of trypsinogen. This minor trypsin isoform constitutes less than 5 % of total secreted trypsinogens. Interestingly, mesotrypsin is poorly inhibited by PSTI, which led to the suggestion that it might participate in degradation of other zymogens and proteases. Recently, the evolutionary signature mutation of human mesotrypsin was introduced into mouse cationic trypsinogen, to recapitulate salient features of human mesotrypsin. In these animals, no change in experimental pancreatitis severity was observed excluding a crucial role of mesotrypsin in the course of pancreatitis [7].

The suggestion that prematurely activated digestive enzymes play a central role in the pathogenesis of pancreatitis is based on the following observations: (i) The activity of both pancreatic trypsin and elastase increases early in the course of experimental pancreatitis. (ii) The activation peptides of trypsinogen and carboxypeptidase A_1 (CPA_1), which are cleaved from the respective proenzyme during the process of activation, are released into either the pancreatic tissue or the serum early in the course of acute pancreatitis [8]. (iii) Pretreatment with gabexate mesilate, a serine protease inhibitor, reduces the incidence of ERCP-induced pancreatitis [9]. (iv) Serine protease inhibitors reduce injury in experimental pancreatitis [9]. (v) Hereditary pancreatitis is often associated with various mutations in the cationic trypsinogen gene that could render trypsinogen either more prone to premature activation or may render active trypsin more resistant to degradation by other proteases. (vi) Triplication of the trypsinogen locus in humans, i.e., an assumed gain in the trypsin activity that is expressed in affected subjects leads to hereditary pancreatitis. (vii) Mutations in the *SPINK1* gene, which might render PSTI less effective, are associated with certain forms of chronic pancreatitis [3].

Certain mutations associated with human hereditary pancreatitis stabilize cationic trypsin against autolysis by blocking CTRC-dependent trypsinogen degradation or by increasing CTRC-mediated processing of the trypsinogen activation peptide [10]. However, it has been shown that decreased autodegradation, opposite to intracellular trypsin activity mediating autoactivation, outweighs in the course of pancreatitis [6]. Recently, *in vivo* studies employing trypsinogen-7 (T7) knockout animals, resembling human PRSS1, revealed a minimal effect on inflammation in acute pancreatitis, moreover a ~50% reduction of intrapancreatic trypsin activity was detected. Knockout of T7 did not exert a significant effect on chronic pancreatitis severity [11]. Recently, a humanized PRSS1 mouse model revealed that mice carrying a humanized PRSS1 p.R122H mutation did not exert spontaneous intracellular autoactivation; however, in conjugation with established risk factors led to more severe pancreatitis [12]. A similar approach of humanized PRSS1 p.K23R knockin showed severe pancreatitis driven by intracellular trypsin autoactivation [13].

In clinical and experimental studies that investigated the time course of pancreatitis it was detected that trypsinogen activation occurs very early in the course of acute pancreatitis, and is dependent on a pathological intracellular calcium signal. One study that employed the caerulein model of acute pancreatitis reported a biphasic pattern of trypsin activity that reached an early peak after one hour and a later second peak after several hours [8]. This observation is interesting because it suggests that more than one mechanism may be involved in the activation of pancreatic zymogens and the second peak may require the infiltration of inflammatory cells into the pancreas. Taken together these observations represent compelling evidence that premature, intracellular zymogen activation plays a critical role in initiating acute pancreatitis.

Clinical Evidence for Digestive Protease Activation

A number of recent studies involving patients have greatly contributed to understanding the role of zymogen activation in pancreatitis. In patients who underwent endoscopic retrograde cholangiopancreatography (ERCP), an interventional medical procedure that requires cannulation of the pancreatic duct and is associated with a significant complication rate for pancreatitis, the prophylactic administration of a small molecular weight protease inhibitor reduced the incidence of pancreatitis [14]. While protease inhibitors have not been found to be effective when used therapeutically in patients with clinically established pancreatitis, the result of the prophylactic study supports the conclusion that activation of pancreatic proteases is an inherent feature of the disease onset. Moreover, since reasonably specific antibodies have become available that detect the trypsinogen activation peptide (TAP) but do not cross-react with either active trypsin or inactive trypsinogen, the presence of TAP in serum and urine of patients with acute pancreatitis provides direct evidence for an activation of trypsinogen during

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pancreatitis. The amount of TAP released also appears to correlate with the disease severity [15].

Cathepsin B in Premature Digestive Protease Activation

Several lines of evidence have suggested a possible role for the lysosomal cysteine protease cathepsin B in the premature and intrapancreatic activation of digestive enzymes [9]. The largely circumstantial evidence for this "cathepsin B hypothesis" is based on the following observations: (i) CTSB has been shown to activate trypsinogen *in vitro*; (ii) during the initial phase of acute pancreatitis in several animal models a redistribution of CTSB into a zymogen granule-containing subcellular compartment was detected by density gradient centrifugation [16]; and (iii) experimental approaches to show an essential role of CTSB in premature zymogen activation by inhibition of this lysosomal enzyme with synthetic inhibitors rendered contradictory results either increasing or decreasing premature zymogen activation, or failing to improve the course of experimental pancreatitis [17]. To test the cathepsin B hypothesis more directly and to overcome the shortcomings of lysosomal enzyme inhibitors, which have only limited specificity for CTSB, a CTSB-deficient mouse strain that was generated by targeted disruption of the *ctsb*-gene was studied in experimental pancreatitis [6]. The results of these studies were unequivocal: 90% of intrapancreatic trypsinogen activation during pancreatitis depends on the presence of cathepsin B [6].

Human genetic studies excluded CTSB as a susceptibility gene for pancreatitis. An association with chronic pancreatitis was detected in the Indian population but the effect size was small and could not be replicated in other cohorts [18]. *In vitro*, the majority of hereditary-pancreatitis-associated cationic trypsinogen mutations that increased autoactivation had no effect or even diminished CTSB-mediated activation. Thus, a knowledge gap remains whether CTSB-mediated trypsinogen activation observed in rodent models is relevant to the human condition.

All the above data suggest that cathepsin B-induced protease activation is a critical component in the onset of pancreatitis and the time has finally arrived for evidence from human studies to emerge in support of this hypothesis. It has been recently shown that cathepsin D (CTSD) is expressed in pancreatic acinar and inflammatory cells, undergoes subcellular redistribution and activation during experimental pancreatitis, and regulates disease severity by potently activating CTSB. Its impact is only minimal and transient in the early, acinar cell-dependent phase of pancreatitis and much greater in the later, inflammatory cell-dependent phase of the disease [19]. However, a number of additional issues regarding the cathepsin-hypothesis of pancreatitis remain to be addressed: (i) the conditions under which two physiologically colocalized classes of enzymes begin to activate or degrade each other remain unknown and may have important therapeutic implications; (ii) the cellular basis of the subcellular redistribution phenomenon of lysosomal enzymes remains poorly understood and could involve either protein sorting or vesicular fusion events; (iii) if either the ratio of lysosomal cathepsins and digestive proteases, or the processing of lysosomal cathepsins itself, were to vary from one class of vesicular compartment to the next, or even within the same compartment, this may change the interpretation of the role of cathepsins in pancreatitis and therefore needs to be explored.

Conclusions

During the course of pancreatitis the extent of acinar cell necrosis is not proportional to intrapancreatic trypsin activity [16]. This lends to the hypothesis whether acinar cell damage beyond a certain threshold is irrelevant for the progression of pancreatitis, or whether only a given degree of trypsin activation is required to elicit activation of other digestive enzymes in a cascade inside the acinar cells to drive pancreatitis severity. To support the first assumption, trypsin must have other effects beside the protease activation cascade or even outside pancreatic acinar cells. One such cellular compartment where trypsin plays a role outside the exocrine pancreas is trypsin activation within macrophages, leading to macrophage activation [20]. Furthermore, extracellular trypsin affects the capacity of inflammatory cells to enter the pancreas and it activates protease-activated receptors (PAR) on pancreatic ductal epithelial cells.

Metabolic and Systemic Abnormalities

In the past, patients with acute pancreatitis have been categorized according to the presence or absence of complications and the definitions of severe disease and the Atlanta classification [21] has codified this concept. Complications include systemic organ failures as well as local disease manifestations. Recently, it has been shown that organ failure during the first week of admission is invariably associated with a high mortality rate of >50% [22]. An investigation of 290 patients with predicted severe acute pancreatitis showed that early organ failure was present in 60% of patients. When organ failure was

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only transient clinical outcome was good (mortality below 1%), whereas persistent organ failure resulted in a mortality rate of 35% [1]. A better understanding of the pathogenesis of early multiorgan failure might therefore be essential for the development of new strategies for the prevention or treatment acute pancreatitis.

Pathogenesis of Pulmonary Failure

ARDS (acute respiratory distress syndrome), later termed ALI (acute lung injury) is a frequently occurring manifestation of organ dysfunction in an intensive care setting and can be the cause of death in critically ill patients. The exact incidence remains unknown but may be as high as 75 per 100,000 population in the USA [23]. Overall acute pancreatitis is a condition in which patients rarely develop ARDS (8%) of total, but severe attacks are frequently associated with acute lung injury (ALI) and respiratory failure (ARDS). The definition set in 1994 for ALI reads as follows: a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiological, physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension [24]. The distinction between ALI and ARDS is the degree of hypoxemia. The incidence of pulmonary complications in acute pancreatitis varies between 15% and 55% and their severity ranges from mild hypoxemia without clinical or radiological signs to severe ARDS. The major cause of hypoxemia is ventilation/perfusion mismatch, which results in right to left pulmonary shunting. In ARDS the injured lung is believed to go through three phases: exudative, proliferative, and fibrotic but the course of each phase and the overall disease progression are variable. The pathophysiological features of the lung in ARDS arise from severe injury to the alveolo-capillary unit. The histological features are dense eosinophilic hyaline membranes and alveolar collapse. The endothelial cells swell, the intercellular junctions widen and pinocytic vesicles increase, causing capillary leak and edema formation. Approximately 10% of patients with acute pancreatitis show alveolar edema on chest radiographs and one third of patients develop progressive hypoxemia during the first week of hospitalization [45]. The cause for the development of alveolar edema is an increase in microvascular permeability in the context of SIRS. This was shown by applying labelled transferrin as an indicator for lung vascular permeability within 48 hours after hospital admission, which was found to be significantly increased in the lung tissue of patients who had later died in the disease process [25]. A similar observation demonstrated an increase in the gallium-transferrin pulmonary leak index strongly correlated with the mortality rate [26].

Lankisch and coworkers determined the incidence of pulmonary infiltrates in 140 consecutive patients with acute pancreatitis with 26% within 24 hours after admission to hospital [27] (see Fig. 16.1). The mortality rate of acute pancreatitis significantly correlated with the presence of pulmonary infiltrates and effusions. Logistic regression analysis showed that radiologic abnormalities were associated with a 15-fold increase in mortality rate. A reduced PaO2 on hospital admission has long been regarded as a prognostic factor for the severity of pancreatitis and is part of the Ranson Score, the Imrie Score, and the newly released UK guidelines, which recommend to hold peripheral oxygen saturation above 95% to prevent organ failure as a treatment goal [28].

With respect to the pathophysiology of ARDS in acute pancreatitis two case series showed that massive cytokine release may have a contributing role in SIRS. Especially IL-8 was reported to be significantly higher in patients at admission who later developed acute severe lung injury [29]. In pleural effusions TNF-α, IL-1, IL-6, and PMN-elastase were significantly higher in serum in ARDS patients, which may point to a direct impact of these cytokines on the development of ARDS but could also occur because of a diminished excretion of cytokines into pleural effusions [30].

Phospholipase A2 (PLA-2) has long been regarded as a major culprit for acute lung injury in acute pancreatitis. Out of numerous phospholipase A2 (PLA-2) subtypes, PLA-2 type I and PLA-2 type II, have been implicated in the pathogenesis of pancreatitis. PLA-2 type I is expressed by pancreatic acini (cytoplasmic PLA-2 type Ib). Data from Creutzfeldt and coworkers dating back to

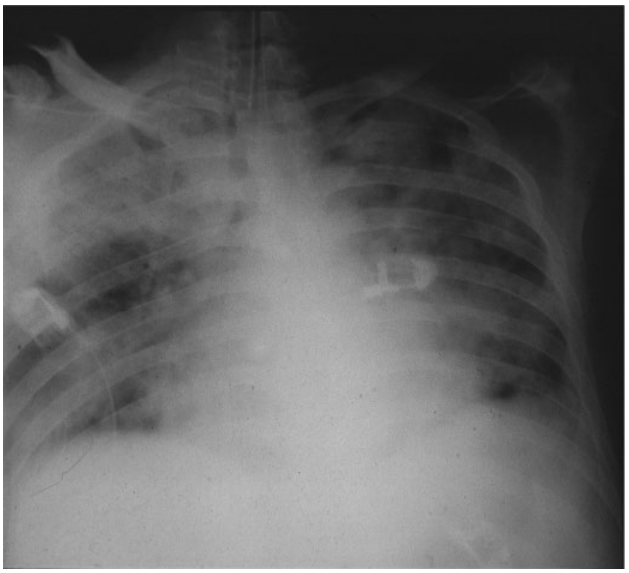


Figure 16.1 Severe adult respiratory distress syndrome in severe acute pancreatitis.

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1969 suggested that PLA-2 type II is responsible for the cell necrosis in acute pancreatitis by converting its endogenous substrate lecithin (part of the lipid bilayer of cell membranes) into the more toxic compound lysolecithin. Thus PLA-2 could break down pulmonary surfactant which consists of phospholipids and could therefore impair oxygenation and increase vascular permeability. This notion was confirmed as elevated circulating plasma levels of PLA-2 correlated with more severe pulmonary changes in patients with gram-negative septic shock [31]. Furthermore, intratracheal application of nonpancreatic PLA-2 induced lung injury with interstitial edema and accumulation of inflammatory cells, but the concept that release of pancreatic PLA-2 from necrotic acinar cells mediates lung injury had to be abandoned. In addition to the hypothesis of a direct impact of PLA-2 other pancreatic zymogens and nitric oxide released from pulmonary macrophages have been implicated in contributing to pulmonary complications in acute pancreatitis. An experimental study testing this concept showed that intravenous application of elastase or trypsin resulted not only in pulmonary damage through NFκB activation and TNF-α release with subsequent transmigration of neutrophils but also in an increase in lung vascular permeability. Neutrophils have been implicated in mediating lung injury in acute pancreatitis and inhibition of neutrophil-derived serine proteases such as PMN-elastase seem to be promising treatment targets [32].

In conclusion, severe attacks of acute pancreatitis are frequently associated with acute lung injury. Arterial hypoxemia, pulmonary infiltrates, pleural effusions as well as ARDS may develop as complications of the disease. Within the first few days following the onset of severe acute pancreatitis lung injury develops because of acute pancreatitis. Sepsis is the predominant cause of lung injury in the later phase of the disease. Besides best supportive care, protective mechanical ventilation, hemodynamic monitoring as well as enteral nutrition and renal replacement therapy have been considered to be of potential benefit to treat pulmonary complications.

Pathogenesis of Renal Failure

Acute renal failure (ARF) occurs in 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock with positive blood cultures [33]. The cytokine-mediated induction of nitric oxide synthesis that occurs in SIRS and sepsis decreases systemic vascular resistance. This arterial vasodilatation predisposes patients with SIRS to ARF [34]. Patients who develop ARF in the setting of critical illness are more likely to die than dialysis-dependent patients admitted to ICU, suggesting that the bad outcome associated with the recent development of renal failure is due to SIRS, rather than merely due to renal dysfunction [35]. The clinical syndrome of ARF in the setting of critical illness, manifested by rising serum creatinine and decreasing urine output, results from injury to the tubular epithelial cells or acute tubular necrosis. In necrotizing pancreatitis renal insufficiency occurs in 21% of patients after a median time period of 8.3 days after the onset of pancreatitis. In analogy to the pathogenesis of ARF in critically ill patients suffering from SIRS a combined pathomechanism of prerenal failure due to extensive fluid loss into the third space together with a prolonged cytokine-mediated organ failure even after fluid resuscitation can be assumed to be operative. Simmons and coworkers showed that increased plasma proinflammatory cytokine levels (TNF-α, IL-1b, IL-6) predict the mortality in patients with ARF [36]. This finding is supported by the fact that in animal models infusion of high concentrations of proinflammatory cytokines can lead directly to the development of multiorgan system failure. Furthermore, patients with SIRS and associated ARF show signs of intense endothelial damage and hypercoagulability as indicated by increased vWF, thrombomodulin, t-PA, PAI-1, and D-dimer activity [37]. In conclusion, ARF is a frequent extrapancreatic complication of acute pancreatitis but studies on the pathogenesis of ARF are urgently needed to treat this potentially fatal complication.

Pathogenesis of Paralytic Ileus and Gut Permeability

Patients with acute pancreatitis often suffer from severe intestinal motility disturbances, which render them prone to bacterial translocation into the pancreatic necrosis due to bacterial overgrowth and increased gut permeability, which is then burdened with an increase in mortality (Fig. 16.2). Studies on CDE-diet fed mice revealed that acute necrotizing pancreatitis inhibits gastric emptying and intestinal transit *in vivo*. The global reduction in jejunal contractility is explained by the disruption of the intestinal motor function at the postreceptor level, which plays an important role for the development of an intestinal ileus during acute pancreatitis [38].

In an animal model of acute pancreatitis Ryan and coworkers reported a significant increase in intestinal permeability to macromolecules that correlated with disease severity. The pathogenesis of gut barrier failure can be attributed to local (intestinal) factors namely: mucosal ischemia, disruption of mucosal epithelial integrity, reperfusion injury, disruption of intestinal bacterial ecology, as well as impaired mucosal immunity. Thoracic epidural analgesia for pain also augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis [39].

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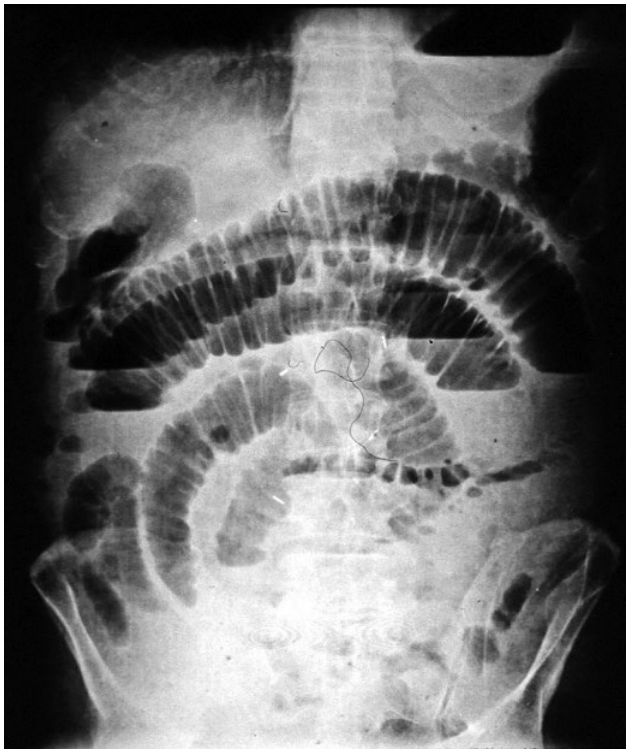


Figure 16.2 Paralytic ileus in severe acute pancreatitis.

Pathogenesis of Coagulopathies

The systemic inflammatory reaction and the development of organ failure in acute pancreatitis share similarities with a complicated course of sepsis, major trauma, or burns [40]. Ranson and coworkers noted abnormalities in coagulation factors during severe acute pancreatitis. They concluded from a prospective analysis of 35 patients in which they correlated amylase levels with respiratory, renal, and hepatic dysfunction that enzyme-related intravascular coagulation is involved in the pathogenesis of these coagulation complications during acute pancreatitis [41]. In systemic inflammation a rapid activation of coagulation may turn into a global or selective exhaustion of physiological anticoagulant systems. The interactions between coagulation and inflammatory pathways are essential for the pathogenesis of disseminated intravascular coagulation. For example, the proinflammatory cytokines TNF-α, IL-1, and IL-6 upregulate thrombin formation and downregulate physiological antithrombotic defence mechanisms, especially the protein C pathway [42]. The protein C pathway is both a major physiological anticoagulant system and a central link between inflammation and coagulation. The zymogen protein C is converted to activated protein C (APC) by thrombin bound to thrombomodulin on the endothelial surface. While the underlying mechanism is incompletely understood, recombinant APC decreased the levels of IL-6 and D-dimer and reduced mortality in severe sepsis patients. Investigating levels of APC, PC, and D-dimer in 31 patients with severe acute pancreatitis showed that PC deficiency and decreased APC generation contributed to a compromised anticoagulant- and anti-inflammatory defence, which subsequently aggravated multiorgan failure. Clinical trials evaluating treatment with PC are warranted in severe acute pancreatitis. In addition to the therapeutic impact of restoring coagulation in severe acute pancreatitis a recent clinical study has shown that signs of disseminated intravascular coagulation are also of high prognostic value. The aggravated coagulation parameters predict a fatal outcome in patients with acute pancreatitis. An AT-III level <69% was the most accurate marker for poor outcome of acute pancreatitis at admission [43].

Electrocardiographic Abnormalities in Acute Pancreatitis

Acute pancreatitis has been reported to be associated with electrocardiographic abnormalities including arrhythmias, bradycardia, T-wave changes, intraventricular conduction disturbances, and ST-segment elevation termed "pseudoinfarction" (Fig. 16.3). The clinical relevance and causes of such electric abnormalities are poorly understood. However, experimental studies performed on a murine model of acute pancreatitis have reported ultrastructural disturbances including interstitial edema and cardiomyocyte hypoxia, myofiber overcontractility, intracellular edema between cardiomyocytes, and cardiomyocyte hypertrophy with collagenization of myocardial stroma [44]. Albrecht and Laws proposed a direct cardiotoxic effect of proteolytic pancreatic enzymes as a cause of ST-segment elevation and myocardium specific enzyme increase (particularly phosphokinase MB fraction). Other mechanisms that have been proposed to explain electrocardiographic abnormalities appearing during AP are those associated to metabolic disturbances, hemodynamic instability, vasopressor drug use, pericarditis, myocarditis, exacerbation of underlying cardiac disease, coagulopathy, and coronary artery spasm [45]. Patients with acute pancreatitis have a high risk to develop metabolic abnormalities. The consequences of low or high serum electrolyte levels on cardiac electric activity include changes in the T-wave morphology, bundle branch blocks arrhythmias, QT-internal shortening or prolongation, asystole, prominent U-wave, ST-segment depression or elevation, ventricular fibrillation [46]. Recently two prospective studies have reported abnormalities on ECG and correlated these changes to the severity of acute pancreatitis.

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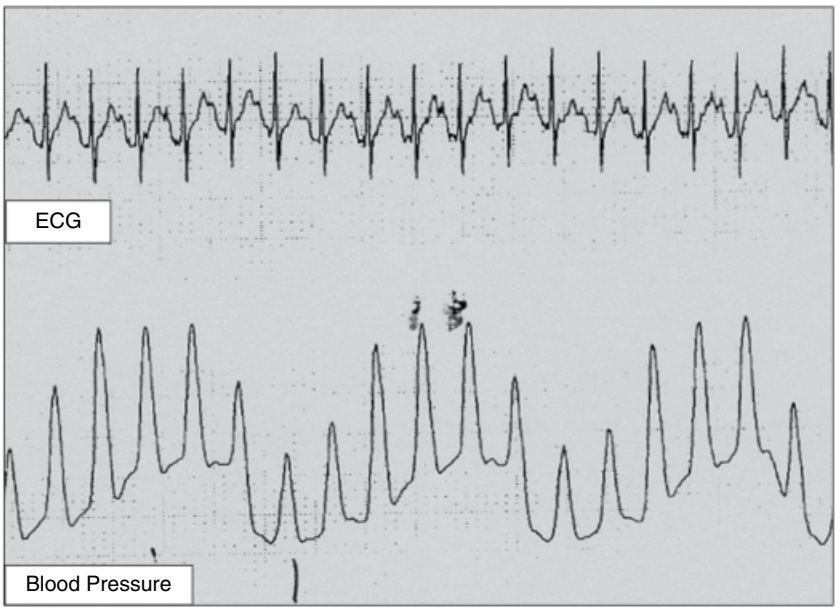


Figure 16.3 ECG changes in severe hypovolemia and hypopotassemia.

The Role of Hypocalcemia and Hypomagnesemia

Hypocalcemia is a frequent finding in patients with severe acute pancreatitis and has been implicated to be of prognostic value by the Ranson scoring system [47]. It has been demonstrated that hypocalcemia is more frequent in severe attacks as compared to mild attacks of pancreatitis (86% vs. 39%) [48]. Prevalence of hypocalcemia ranges between 15% and 88% in critically ill patients. Several pathogenetic mechanisms contribute to the development of hypocalcemia and need to be considered in evaluating hypocalcemia: (i) Serum calcium levels reflect only part of the physiologically active ionized calcium. More than half of the circulating calcium is bound to albumin and serum calcium levels need to be corrected for serum albumin levels as albumin is lost to the third space. When calcium levels are corrected for albumin, the majority of patients display normocalcemia, which explains the absent symptoms of hypocalcemia like arrhythmias and tetany. (ii) In response to decreased serum calcium levels circulating parathyroid hormone levels (PTH) are increased. This subsequently leads to calcium mobilization from bone and calcium reabsorption in the kidneys is increased. In a prospective study by McKay PTH levels were determined to be invariably elevated in response to hypocalcemia in acute pancreatitis but significantly increased concentrations were found in patients with a complicated course of the disease [49]. Inadequate mobilization of calcium from bone indicating end-organ failure could offer an alternative explanation for hypocalcemia. However, patients suffering from acute pancreatitis were shown to react with an adequate rise in serum calcium levels and urinary cyclic adenosine monophosphate upon infusion of exogenous PTH. These findings had been previously substantiated by data from animal experiments [25]. Hypomagnesemia together with hypocalcemia can inhibit PTH secretion as well as peripheral action of PTH. Intracellular magnesium levels in patients with acute pancreatitis are thus believed to be decreased [50]. Patients with acute pancreatitis and hypocalcemia commonly also show intracellular magnesium deficiency despite normal serum magnesium concentrations. Magnesium deficiency could therefore play a significant role in the pathogenesis of hypocalcemia in acute pancreatitis. It has been reported that bivalent cation Mg^{2+} counteracts the intracellular calcium signaling and thereby ameliorates the deleterious effect of intracellular premature zymogen activation. Moreover, in preliminary experiments we were able to show that Mg^{2+}-therapy readily administered as a food supplement in an animal model of acute pancreatitis has a beneficial effect on the course of the disease. Currently we are conducting a multicenter, multinational, randomized, placebo-controlled phase II trial to investigate the efficacy of oral magnesium for the prevention of painful acute episodes of hereditary and idiopathic pancreatitis (EUROPAC-2) [3]. The role of increased free fatty acids (FAA) in the pathogenesis of hypocalcemia in acute pancreatitis has not been clearly elucidated and different pathophysiological mechanisms have been proposed. Circulating lipase and phospholipase released from necrotic pancreatic acinar cells may cleave triglycerides and hereby lead to elevated serum FAA. Warshaw determined the effect of FFA on

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serum calcium levels in an animal model. His findings suggested that (i) changes in the concentration of FFA occur spontaneously but may have an impact on calcium levels; (ii) the observed depression of calcium may be due to intravascular sequestration of calcium by FFA-albumin, but increased flux of circulating calcium-FFA complexes into extravascular and intravascular sites may also be important; and (iii) the markedly increased FFA concentration in some patients with acute pancreatitis may contribute significantly to hypocalcemia and calcium flux [51]. In conclusion, hypocalcemia is a frequent finding in severe acute pancreatitis.

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17

Histopathology of Acute Pancreatitis

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Introduction

In this chapter, the histopathology of acute pancreatitis is reviewed and the various patterns of tissue damage that have been described so far are related to the known etiologic factors and the discussed pathogenetic mechanisms. Finally, an attempt is made to correlate the histopathologic findings with the clinical and radiologic criteria of the 2012 Atlanta Classification of Acute Pancreatitis [1] that revised the 1992 Atlanta classification [2].

Definition

Acute pancreatitis is in most cases a necroinflammatory autodigestive damage that initially involves the intrapancreatic and extrapancreatic fatty tissue and is caused by noninfectious factors. Rarely acute pancreatitis has an infectious cause and shows initially an acinar cell necrosis [3]. Clinically and histologically, it can be classified into a mild form called acute interstitial edematous pancreatitis affecting 90–95% of patients, and a severe form called acute necrotizing pancreatitis affecting only 5–10% of patients. The mild form of acute pancreatitis is often associated with gallstone disease, while the severe form is usually linked to alcoholism.

Histopathologic Patterns of Tissue Necrosis

Fatty tissue necrosis within and outside the pancreas is the most frequent histologic lesion that can be seen during the initial phase of most cases of acute pancreatitis based on an autodigestive process (type 1 necrosis pattern) (Fig. 17.1). The necrotic process that emanates from fat cells in the interlobular spaces of the pancreas and in the peripancreatic area, and the later inflammatory reaction, are very variable in degree and extent. Another, but rare, pattern of tissue damage is characterized by necrosis of the duct epithelium which becomes the starting point of a ductal and periductal inflammation. In the third pattern, which is also rare, the acinar cell necrosis is the key lesion that is followed by a perifocal intralobular inflammation [4].

Acute Pancreatitis with Fatty Tissue Necrosis Pattern

Most cases of mild and severe acute pancreatitis are characterized by the fatty tissue necrosis pattern. The degree and extent of this necrosis pattern determines the severity and the course of acute pancreatitis and its classification into mild/interstitial edematous or severe/necrotizing pancreatitis [1] (Table 17.1).

Initial Phase

Interstitial pancreatitis leads commonly to an edematous swelling of the pancreas, but the pancreas may also be normal in size. In addition the pancreas displays tiny white disseminated spots of fatty tissue necrosis on its surface and also in the interlobular fatty tissue [5] (Fig. 17.2). Because this form of pancreatitis has a mild nonlethal course, the study of the described histologic changes is nowadays largely limited to rare resected pancreatic tissue specimens, in which an interstitial pancreatitis developed, either in association with long-term operations or in conjunction with preoperative investigations.

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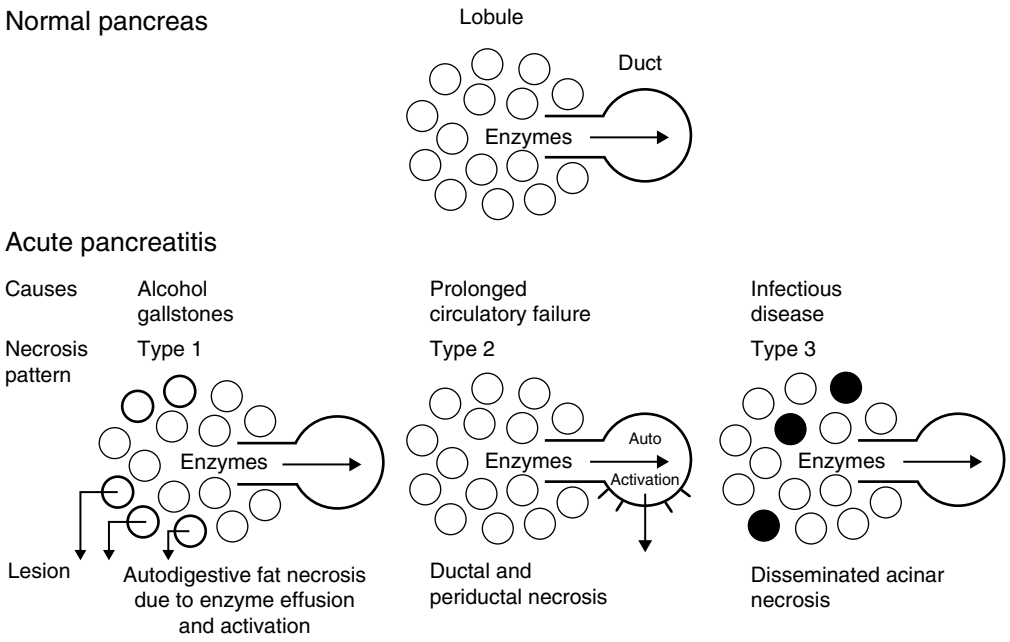


Figure 17.1 Schematic presentation of three necrosis patterns observed in human acute pancreatitis related to potential causative factors.

Table 17.1 Atlanta classification 2012 of acute pancreatitis: type and severity correlated with complications, imaging findings and histopathologic features.

Type and severity	Complications and imaging findings	Histopathologic features
Interstitial edematous pancreatitis		
Mild	None	Parenchymal edema with tiny fat necroses Peripancreatic fat necrosis
Moderately severe	Transient organ failure and/or acute peripancreatic fluid collection (APFC)	
	Pseudocyst (deriving from unresolved APFC)	Pseudocyst (without debris)
Necrotizing pancreatitis		
Severe	Acute necrotic collection (ANC) with persistent organ failure and systemic complications	Large peripancreatic fat necrosis with or without parenchymal necrosis and hemorrhage
	Walled-off necrosis (deriving from ANC)	Well-demarcated pseudocyst emerged from peripancreatic and pancreatic necrosis

Necrotizing pancreatitis is characterized by numerous large and confluent areas of fat necroses extending into the peripancreatic tissue (Fig. 17.3). In addition, the pancreas shows parenchymal necrosis, although it is usually much less extensive than the peripancreatic necrosis. The extent of fat necrosis correlates roughly with the amount of interlobular fatty tissue present in the individual pancreas. This means that the pancreas of obese subjects may show more extensive necrosis than the pancreas of normal weight individuals. Where large fat necrosis involves blood vessels, especially veins, the necrosis becomes hemorrhagic, because of vessel wall damage followed by thrombosis or rupture. Arteries, because of their thick walls, are more resistant to necrosis, but if also affected, can develop thrombosis, resulting in panlobular ischemic necrosis. Another important complication of large fat necrosis that involves the surrounding tissues, is the destruction and thus opening of interlobular ducts that lead to duct leakage of secretions. Surprisingly, acinar cells adjacent to fat necrosis seem to be well preserved for a long time. The only change may be a widening of acinar lumina, which have PAS-positive secretions. The islets are not affected, unless they are lying in lobules that are largely or entirely necrotic. In the course of the disease, the necrotic foci are

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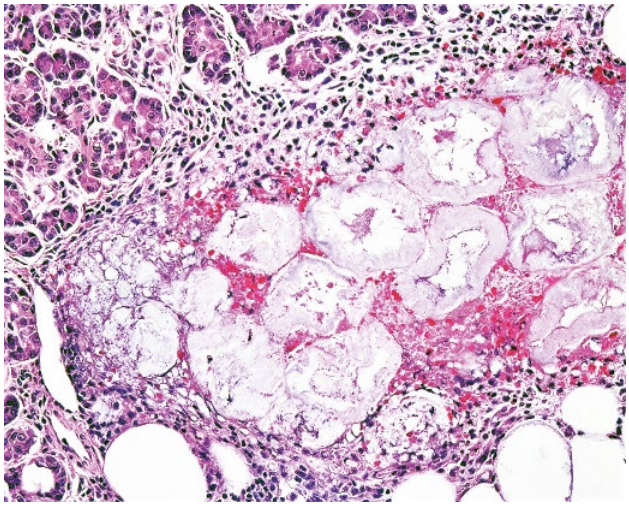


Figure 17.2 Acute interstitial pancreatitis: tiny fatty tissue necrosis within the pancreas. Note the preservation of the adjacent acinar cells.

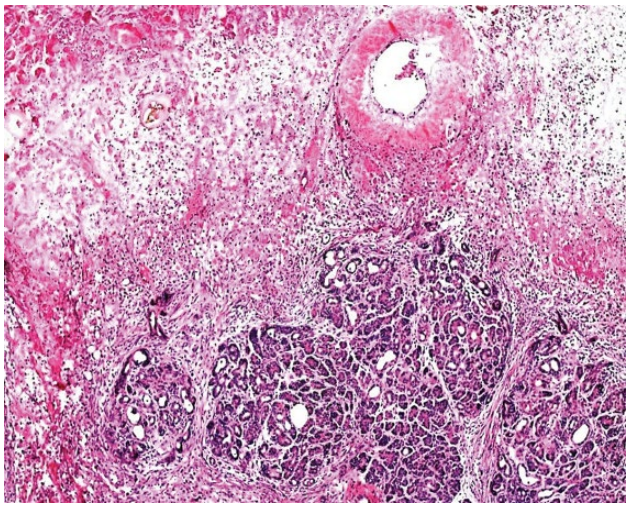


Figure 17.3 Acute necrotizing pancreatitis: extensive peripancreatic fat necrosis with hemorrhage involving the wall of a duct (top) and extending into the interlobular spaces of the pancreatic tissue below.

delimited by a collar of foamy macrophages intermingled with granulocytes that later are increasingly replaced by myofibroblasts to build up a wall of granulation tissue separating the necrosis from intact tissue.

Outcome

In *interstitial pancreatitis*, the edema, which is probably rich in pancreatic enzymes, is usually resolved by macrophages within a few days and leaves no changes behind. The same happens to the tiny foci of fat necrosis. Since the diameter of these fat necroses are usually smaller than 10 mm, they are barely detectable by imaging. Larger liquefied foci of peripancreatic fat necrosis, which probably correspond to the radiologic lesion called "acute peripancreatic fluid collection," are rare. If such a rare lesion does not resolve and gets encapsulated by granulation tissue (see later), it may become a pseudocyst.

In *necrotizing pancreatitis*, the large fat necroses liquefy. Follow-up studies by imaging have shown that necroses not exceeding 2–5 cm in diameter, can be slowly reabsorbed by macrophages. Larger necrotic areas (usually >5 cm), especially when they also involve pancreatic parenchyma, may not resolve spontaneously and their liquefied and hemorrhagic content is then lined by macrophages that, together with some granulocytes and lymphocytes, form a thin layer of granulation tissue within 10–20 days of the onset of the disease. This change may correspond with an "acute necrotic collection" as described by the radiologist (Table 17.1) [6]. Often the macrophages in the granulation tissue contain hemosiderin as a sign of the phagocytosis of hemorrhagic tissue. After 20–30 days, the granulation tissue starts to be replaced by fibrosis with collagen type 1 and 3. If the fibrotic demarcation is fully developed the change is radiologically called "walled-off necrosis" that corresponds to the old term "pseudocyst associated with necrosis" (Table 17.1). Most of these advanced lesions are found outside the pancreas, particularly around the head of the pancreas [7,8]. The fact that walled-off necroses/pseudocysts contain amylase suggests communications with the pancreatic duct system. This may be particularly the case in those pseudocysts which, in time, increase in size and by growing compress or erode such structures as the bile duct, duodenum, stomach, vessels, or peritoneum. The involvement of vessels may also lead to sudden hemorrhage.

Another severe complication is a colonization of the necrotic areas with (mostly gut-derived) bacteria or fungi. This usually takes place during the period (days 4–20) when the demarcation of the liquefied necrotic area still consists of only a small rim of granulation tissue.

The resolution of necrotic tissue within the interstitial spaces of the pancreas is usually followed by the development of interlobular fibrosis replacing the necrotic tissue (Fig. 17.4) [9,10]. If this necrosis-fibrosis process [11] takes place repeatedly because of recurrent attacks of necrotizing acute pancreatitis, and also involves the large interlobular ducts and the main duct, relapsing acute pancreatitis may evolve into chronic pancreatitis [12,13].

Acute Pancreatitis with Duct Epithelium Necrosis Pattern

Initial Phase

Disseminated duct cell necrosis of small to medium-sized interlobular ducts as initial key lesion is accompanied by intraductal aggregates of granulocytes mixed

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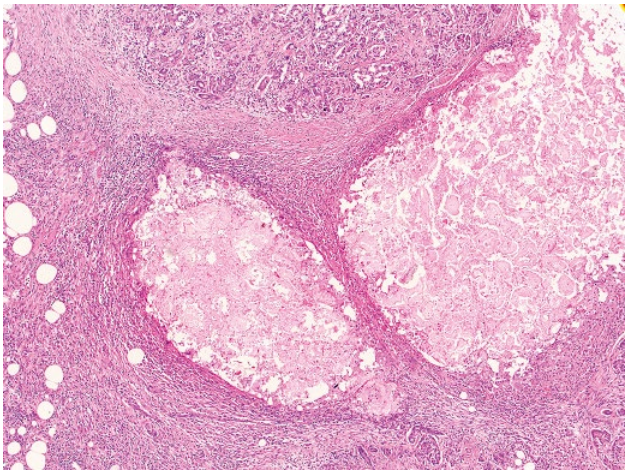


Figure 17.4 Acute necrotizing pancreatitis 6 weeks after onset. Development of cell-rich interlobular fibrosis induced by the resorption of a fat necrosis (center). H&E, ×125.

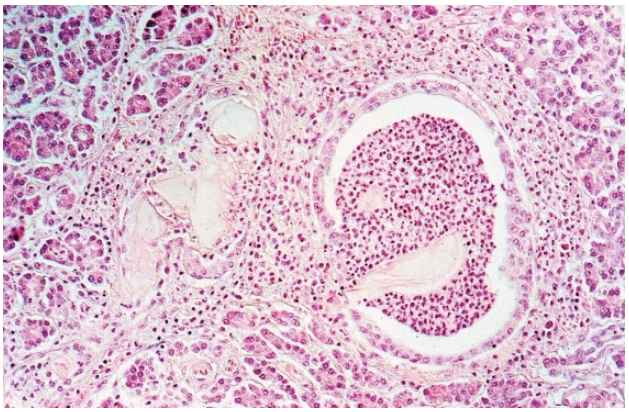


Figure 17.5 Acute pancreatitis with duct epithelium necrosis pattern. Interlobular duct filled with aggregated neutrophilic granulocytes and secretions. Rupture of the duct epithelium with granulocytes infiltrating the periductal interstitial space. H&E, ×120.

with precipitations of eosinophilic secretions. There is also duct rupture and extension of the necrotic process and the granulocytic process into the periductal area (Fig. 17.5). This may be a solitary change, but is also observed in association with foci of fat necrosis elsewhere [14–16]. The ensuing acute pancreatitis seems to be usually mild.

Outcome

The outcome of acute pancreatitis with duct epithelium necrosis is largely unknown because the patients in whom this necrosis pattern has been observed and described all died from prolonged circulatory failure that was usually not caused by acute pancreatitis, but by various extrapancreatic diseases such as hepatic failure. Our only observation of type 2 necrosis so far, made in a pancreatic resection specimen from a patient with hereditary pancreatitis [16], could suggest that in this setting the initial necrosis of the duct-lining cells, followed by an inflammatory involvement of the surrounding interstitial tissue, may result in structural changes such as irregular dilatations and periductal scarring of the affected pancreatic ducts.

Acute Pancreatitis with Acinar Type Necrosis Pattern

Initial Phase

Scattered intralobular foci of acinar cell necrosis are the key lesions of this type of necrosis in acute pancreatitis (Fig. 17.6). It is accompanied by a perifocal inflammatory infiltrate consisting of single neutrophil granulocytes and macrophages. Fat and ductal necrosis are absent. These changes are indicative of a pancreatitis caused by an infection.

Outcome

In acute pancreatitis with acinar necrosis the outcome seems to be favorable in most cases, since the cases that have been reported so far showed a mild pancreatitis [17].

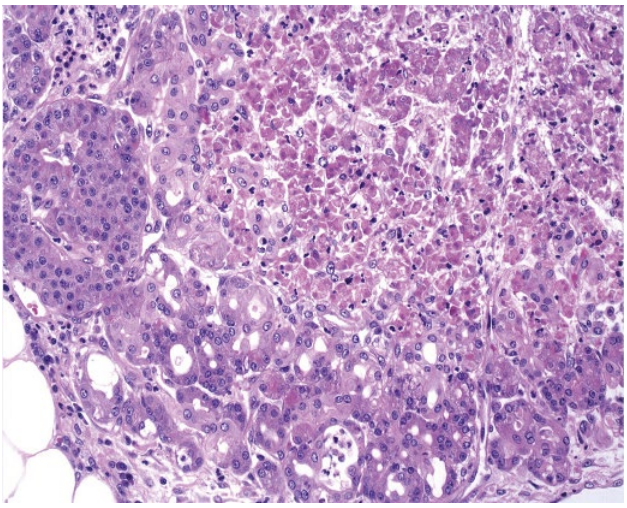


Figure 17.6 Acute pancreatitis with acinar cell necrosis pattern. Intralobular focus of acinar necrosis surrounded by few granulocytes and macrophages.

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Histopathology Related to Etiologic Factors and Pathophysiologic Mechanisms

Acute pancreatitis with *a fat necrosis pattern* is most often associated with alcohol abuse and gallstone disease. The only difference between the two etiologic factors on the resulting morphologic changes seems to be the disease severity, since biliary pancreatitis usually follows a mild course as compatible with interstitial pancreatitis, while alcoholic pancreatitis is a severe necrotizing disease. Rare causative factors are metabolic or drug-associated processes, and familial-hereditary or circulatory failure-related conditions.

The pathophysiologic mechanisms that lead to sudden autodigestive fat necrosis in the human pancreas are still unidentified or hypothetical. Based on findings in experimental pancreatitis it has been suggested that disruption of intracellular compartmentalization leads to an intracellular enzyme activation by lysosomal hydrolases with subsequent acinar cell damage [18,19]. However, acinar cell necrosis has not yet been convincingly proven as the initial histologic lesion in acute human pancreatitis caused by the most common etiologic factors [20]. It must therefore be assumed that etiologic factors such as alcohol abuse and gallstone disease lead to a functional rather than a structural acinar cell damage, which results in a sudden and uncontrolled release of digestive enzymes from the acinar cells into the adjacent interstitial tissue [20]. It is possible that among the released proenzymes lipase plays an important role, because it is one of the few pancreatic enzymes that does not require activation [21,22] and may therefore directly cause the liquefaction necrosis of interstitial fat cells. Whether fat necrosis depends on the action of lipase alone or the combined action of lipase plus other enzymes, such as phospholipase A_2, is not known, but it is likely that several proenzymes as well as cytokines become activated by fat-cell necrosis and may then help to destroy adjacent tissues and trigger the inflammatory process that determines the severity of the clinical course.

Another pathophysiologic theory related to the fat necrosis pattern, which rests on the frequent association of gallstone disease with pancreatitis, is the duct obstruction–bile reflux theory (based on Opie's common channel theory) [23]. It postulates that temporary obstruction of the common bile duct and the main pancreatic duct by a gallstone (or tumor tissue or inspissated secretions as in cystic fibrosis) [24] causes increased intraductal pressure and/or ampullary incontinence, with duodenopancreatic and bile reflux. This in turn activates pancreatic proenzymes, which leak from small ducts into the interstitial space. However, despite the obvious clinical association between gallstone migration and pancreatitis, definite functional and histologic proof of the ductal-obstruction pathogenesis is, thus far, lacking in human acute pancreatitis.

Acute pancreatitis with necrosis of the duct epithelium is associated with prolonged circulatory failure. In this case the tissue hypoxia in the pancreas seems to injure especially the medium-sized interlobular ducts and cause its necrosis. In addition, there could be an autoactivation of trypsinogen within the duct lumen, as the ducts are found to be filled with dense pancreatic secretions and neutrophil granulocytes [14]. This could be due to a stasis of pancreatic juice, which became viscous and sluggish because of a general slowdown of secretory processes in the exocrine pancreas, because of a severe circulatory failure. Since we saw a comparable picture in a case of familial pancreatitis, it may be speculated that a similar duct damage as in prolonged circulatory failure may occur due to mutation-related changes of the trypsinogen molecule (e.g., by *PRSS1* mutations) allowing its uncontrolled premature activation [25].

In acute pancreatitis with acinar cell necrosis and without any significant autodigestive interstitial necrosis, there seems to be a direct cytotoxic damage to the acinar cells by microorganism such as mumps virus or bacterial agents.

Unsolved Questions

There are several unsolved questions in acute pancreatitis, but the most important one concerns its pathogenesis and pathophysiology. It is not known how etiologic factors such as alcohol abuse, gallstone disease, hypercalcemia, or circulatory failure lead to premature digestion in the pancreas. Moreover, the pathophysiologic concepts currently discussed usually refer to experimental pancreatitis models [18,26,27]. Although these models have markedly improved our knowledge on pathogenetic mechanisms in acute pancreatitis, it must be emphasized that none of these models is fully comparable to what is seen in humans.

Another question that is still to be solved relates to the severity of acute pancreatitis. It is not yet known which factors govern the mechanisms that decide the extent of autodigestion and thus lead either to a mild or severe course of the disease.

A final question is how the criteria that define the Atlanta 2012 classification [1] and are solely based on radiologic [6] and clinical features relate to the morphologic findings in acute pancreatitis? Table 17.1 therefore tries to summarize and correlate the most important criteria of the Atlanta 2012 classification with the histopathologic changes that can be seen in conventional acute pancreatitis.

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18

Severity Classification of Acute Pancreatitis

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Introduction

The accurate classification of acute pancreatitis severity is important because it will "improve communication and advance our understanding of the disease and its management" [1]. When specific treatments become available for clinical trials in acute pancreatitis "an inclusive clinical classification system will assume increasing importance" [2]. Systems for classifying severity will continue to evolve with new scientific knowledge and for this reason they are best considered "working" classifications. The aim of this chapter is to outline the reasons for classifying severity, review the systems currently available, and identify aspects for further improvement.

Reasons for Classifying the Severity of Acute Pancreatitis

Classification systems are valuable in clinical and research settings, to assist communication between clinicians, patient monitoring and allocation to clinical studies, auditing of clinical outcomes, and comparison between centres (Table 18.1). Some of these reasons are best met by predicting severity, rather than by classifying severity, although these are sometimes confused [3–5]. When the ultimate disease severity needs to be anticipated ahead of time, prediction of severity is required. When the severity needs to be defined at a particular time point, classification of severity is required. In this way prediction is about the future and classification is about the present and the past. Prediction is usually required early in the disease course, whereas classification can be useful at any time during the disease course.

Severity Classification Systems

The first severity classification system for acute pancreatitis was published in 1983 [6], followed by the widely used original Atlanta classification in 1993 [7], which was a clinically based classification system that defined a binary approach: mild and severe disease. While there has never been difficulty in identifying patients with mild and uncomplicated acute pancreatitis, this is not so for severe disease. Nor is it so for patients with non-mild acute pancreatitis who represent a heterogenous group with varying severity and outcomes that were not captured by the original Atlanta classification.

Two systems for classifying the severity of acute pancreatitis were introduced about a decade ago and have replaced the original Atlanta classification (Table 18.2): the "determinant-based classification" (DBC) in 2012 with four categories of severity [8] and the "revised Atlanta classification" (RAC) in 2013 with three grades of severity [9]. It has been suggested that DBC and RAC are "equivalent" and "comparable and complementary" [3,4], but there a "few differences" [10] worth noting (Table 18.3). There have also been questions about which is the more valid, which has higher utility, and which should be used [11]. A number of studies have compared the validity of the DBC and RAC classification systems (Table 18.4). Most of the studies have been from single tertiary centers and subject to selection bias.

The DBC defines severe AP on the basis of either persistent organ failure (without infected pancreatic necrosis) or infected pancreatic necrosis (without persistent organ failure). The RAC defines severe AP on the basis of persistent organ failure alone, with infected pancreatic necrosis a diagnostic criterion for the moderately severe grade [9]. The explanation given for this was that "infected necrosis without persistent organ failure . . . has a lesser

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Table 18.1 The reasons for classifying the severity of acute pancreatitis.

Related to clinical decision-making	Triage of patients regarding initial treatment intensity[a]
	Transfer of patients to specialist unit or intensive care[a]
	Tracking trajectory of patient's clinical course
	Treatment (e.g., ERCP, enteral nutrition)[a]
Related to research decision-making	Audit of outcome
	Allocation of patients to trial arm[a]
	Analysis of interventions

[a] Denotes reason that is more appropriate for prediction than classification systems.

Table 18.2 Classifications for the severity of acute pancreatitis.

Determinant-based classification [8]	
Mild	No (peri)pancreatic necrosis and no organ failure
Moderate	Sterile (peri)pancreatic necrosis and/or transient organ failure
Severe	Infected (peri)pancreatic necrosis or persistent organ failure
Critical	Infected (peri)pancreatic necrosis and persistent organ failure
Revised Atlanta classification [9]	
Mild	No organ failure and no local or systemic complications
Moderately	Severe transient organ failure and/or local or systemic complications or exacerbations of preexisting comorbidities
Severe	Persistent organ failure (single or multiple)

Table 18.3 Key differences between the DBC and RAC classification systems.

	Severity classification systems	
Criteria	**DBC category**	**RAC grade**
Exacerbation of comorbid disease	Not included	Moderately severe
Infected (peri)pancreatic necrosis without persistent organ failure	Severe	Moderately severe
Infected (peri)pancreatic necrosis with persistent organ failure	Critical	Severe

DBC: determinant-based classification; RAC: revised Atlanta classification.

mortality rate than infected necrosis with persistent organ failure." Thus, the principle difference between the DBC and RAC is the importance attributed to infected pancreatic necrosis. In some studies patients with infected pancreatic necrosis without persistent organ failure have been shown to have a similar outcome to those with severe acute pancreatitis [12,13]. These findings are consistent with the meta-analysis of 14 studies which was the basis for the DBC [14]. This demonstrated that infected (peri)pancreatic necrosis and persistent organ failure were independent and virtually equivalent determinants of mortality. It was for this reason that the DBC included infection of pancreatic necrosis in the severe category.

Given the significant advances in the management of infected pancreatic necrosis, fueled by technology developments and the seminal randomized trials from the Dutch Acute Pancreatitis group [22], it is reasonable to ask how important infected necrosis still is as a determinant of mortality. Open necrosectomy, which is responsible for new-onset organ failure and increased mortality, has been superseded by the "step-up approach." The original meta-analysis [14] has recently been repeated using data from the modern era and it has confirmed that infected pancreatic necrosis has become less important as a determinant of mortality (publication pending). This change has virtually abolished the second peak of the bimodal mortality curve, which was previously attributed to infected pancreatic necrosis [23]. In the nationwide prospective cohort study from 26 hospitals in Spain it was found that infected pancreatic necrosis correlated with high morbidity and had a mortality comparable to sterile necrotizing pancreatitis [24].

Approach to Severity Classification Depends on the Setting

In a peripheral hospital the incidence of severe and critical acute pancreatitis is low and the fundamental clinical decision is whether the patient is going to develop sufficiently severe acute pancreatitis to warrant transfer to a tertiary center. In this setting a binary classification system (non-severe vs. severe) might well suffice. In a tertiary center the requirements are different and the incidence of severe and critical acute pancreatitis higher. In this setting there is value in having more than two categories of severity. With different

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Table 18.4 Studies that compared the determinant-based classification (DBC) and revised Atlanta classification (RAC) systems from the same dataset.

	Ref	Setting	Study design	Key findings
Nawaz (2013)	3	Tertiary (SC) Pittsburgh	Retrospective (prospective database)	DBC and RAC comparable for predicting ICU admission, ICU length of stay, and mortality. The RAC was better at predicting hospital stay and DBC better for predicting the need for intervention
Acevedo-Piedra (2014)	12	Tertiary (SC) Spain	Retrospective (prospective database)	No significant differences in the distribution and outcomes between the two classifications, but very low incidence of severe and critical categories
Chen (2015)	15	Tertiary (SC) Nanjing	Retrospective (prospective database)	RAC and DBC comparable in relation to long-term clinical prognosis, major complications, and clinical interventions. Critical category very high risk and distinct from severe category in DBC
Mircea (2015)	16	Tertiary (SC) Bucharest	Retrospective	Similar for clinical outcomes, although RAC has slight advantage for hospital length of stay and DBC for ICU admission and length of stay. DBC easier to use
Xu (2015)	17	Tertiary (SC) Lanzhou	Retrospective	Similar distribution and outcomes. Recommended combining RAC and DBC
Guo (2105)	18	Tertiary (SC) Chengdu	Prospective	No significant difference between RAC and DBC. Mortality similar and distribution of severity marginally different
Kadiyala (2016)	4	Tertiary (SC) Boston	Retrospective (prospective database)	The RAC and DBC were essentially equivalent in predicting mortality, need for admission to the ICU, ICU length of stay, and hospital length of stay. Paucity of critical category, limited utility. Neither classification accounts for multisystem persistent organ failure, the strongest predictor of mortality
Bansal (2016)	19	Tertiary (SC) Birmingham	Retrospective (prospective database)	The RAC and DBC perform equally well. DBC critical category associated with doubled mortality risk, ICU stay and need for drainage or surgery greater than RAC, with definite implications for prognosis
Fernandes (2016)	20	Tertiary (SC) Portugal	Retrospective	RAC and DBC were similar for outcomes
Zubia-Olaskoaga (2016)	21	Tertiary (MC) Spain etc.	Prospective observational	Proposed a modified DBC for only ICU patients. Superior to DBC and RAC for mortality. Similar to DBC for morbidity and superior to RAC. Severe DBC category separated into two groups: transient organ failure with infected local complications and persistent organ failure and no infected local complications

ICU: intensive care unit.

treatment options available there is the need to accurately allocate patients to research arms and to tailor treatments to individual patients, it is desirable to have distinct and homogeneous patient subgroups to study and treat. For instance, if there were a new treatment for organ failure to be tested it would confound interpretation of outcomes if all patients were included with organ failure, even if this contained those who would respond promptly (e.g., transient organ failure), those who might not respond (e.g., persistent organ failure), and those who cannot respond (e.g., no organ failure). Further, if the purpose of a treatment were to reverse established organ failure it would be necessary to exclude patients with transient organ failure. If the purpose were to prevent the development of persistent organ failure it would be necessary to include patients with transient organ failure. These examples indicate that while a binary classification is probably sufficient for those in primary and secondary care settings, more categories are required in the tertiary setting. Tailoring the severity classification needs to be tested, particularly in the secondary setting.

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Table 18.5 Modified determinant-based classification (DBC) system for patients admitted to intensive care with organ failure [21]. Note that patients with mild acute pancreatitis are not included. *Source:* Adapted from [21].

	Parameters				
Group	**Organ failure**	**Infected necrosis**	**Mortality**	**Intensive care LOS**	**Interventions**
1	TOF	No	2%	Short	–
2	TOF	Yes	6.6%	Long	+
3	POF	No	41%	Short	–
4	POF	Yes	59%	Long	+

TOF: transient organ failure; POF: persistent organ failure; LOS: length of stay.

The use of severity classification has also been studied in the intensive care unit setting. In 2016 a modified DBC was recommended following a large prospective study involving 46 intensive care units [21] and subsequently validated [25,26]. Four groups were defined (Table 18.5), with mild acute pancreatitis excluded as these patients are not admitted to ICU. These studies provide compelling evidence that the severe category of AP, as defined by the DBC, represents two distinct subgroups. Patients with local complications (infected pancreatic necrosis, abdominal hemorrhage, and intestinal perforation), but without persistent organ failure ("group 2") have a high morbidity but low mortality. In contrast, patients with persistent organ failure but without local complications ("group 3") have a high mortality but relatively low morbidity.

These studies also confirmed that patients with critical acute pancreatitis ("group 4") had a clinically and statistically different clinical course in regard to morbidity and mortality. Others have questioned the utility of this category because of its relatively infrequency [4], while in other series it is associated with a significantly higher mortality and is endorsed [13,19,26]. The critical category has more clinical relevance in the ICU setting [27] (31% of patients with 54% mortality) [25] than in the tertiary hospital setting (1% of patients with 61% mortality) [26]. In the Spanish study [21] only 2.2% (37/1655) had critical AP but a mortality of 54%, compared with 39% with a mortality of 5.8% (97/1655) for severe AP. The time to oral feeding (median 24.2 vs. 9.4 days), need for invasive treatment (100 vs. 39.2%), admission to intensive care unit (97.3 vs. 53.6%), and hospital stay (median 88 vs. 34.2 days) were all significantly increased in patients with critical acute pancreatitis.

While the setting is important in regard to the approach to severity classification, there are other factors that might be considered including the quality of the evidence base, method used for development, the validity and ease of use.

Future Developments

The differences between classification systems represent an opportunity for further improvement, and some research priorities have been published [29]. In the editorial accompanying the DBC publication it was pointed out that there are severity determinants other than infected pancreatic necrosis and organ failure, including obesity, diabetes, and genetic predisposition, and if incorporated might have improved the DBC [2]. All three classifications (DBC, RAC, and modified DBC) fail to account for patients with "early severe" acute pancreatitis and organ failure on admission, which is a particularly challenging subgroup with a high mortality risk [30–33]. This suggests that the timing of the onset of organ failure might be factored into an improved classification system [34]. Incorporating different aspects of organ dysfunction/failure may also help, including the duration, number, combination, and sequence of the organs affected [35]. Data on these dimensions may allow more accurate classification of patients with severe and critical acute pancreatitis. Increased stratification, beyond the four categories of the modified DBC, has been suggested because of the multiple therapeutic goals (in addition to reducing mortality) and the desire to personalize treatment [36]. A "two-step approach" that distinguishes single and multiple persistent organ failure and includes 13 severity categories has been reported and requires prospective validation. Further improvements in severity classification might go beyond these clinically defined determinants to incorporate biomarkers that more accurately define severity.

Conclusions

Classifying the severity of acute pancreatitis is important for the clinical care of patients and for research purposes. The RAC and DBC have been in use for over a decade, we know they perform reasonably well. We

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also know that predicting (and not classifying) the severity of acute pancreatitis is required in the community and secondary care settings because the key decision is whether a patient needs to be transferred or not. In the tertiary setting, especially in the ICU setting, the modified DBC should become the preferred approach, noting that it would be helpful to move away from numbered groups to clinical descriptors (e.g., 0 = mild, 1 = moderate, 2 = moderately severe, 3 = severe, and 4 = critical) [21]. These are clinically distinct subgroups of patients which when classified accurately will improve the delivery of care to these patients and the study design for testing new treatments. Advances in the care of patients with acute pancreatitis will require improvements on current methods for classifying severity. Ultimately, these improvements will come from the discovery of early biomarkers of severity that accurately reflect the key real-time changes in the pancreas and distant organs. For now, we are reliant on clinical indicators related to the presence of organ failure and infected local complications for the RAC, DBC, and modified DBC. The differences between the classifications provide opportunities for further research to improve the accuracy and utility of severity classification. This includes determining how best to tailor severity classification to setting (e.g., secondary or tertiary hospital) and purpose (e.g., clinical management or research).

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Clinical Assessment and Biochemical Markers to Objectify Severity and Prognosis

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Introduction

Among the inflammatory digestive disorders acute pancreatitis continues to challenge physicians as the least and most difficult one to predict in terms of clinical course and outcome. Ever since the first classification system of acute pancreatitis was established in Marseille in 1965 [1] the definition of "severe" disease has been linked to disease-specific complications with an increased risk of mortality [2–5]. Stratification of severity is required for targeting individual patients for interventions against evolving complications or for referral to specialist centers on the one hand and for comparing patients for scientific purposes or recruitment into clinical trials, on the other. The type and clinical relevance of a complication rendering the course of acute pancreatitis as "severe" has been the subject of continuous development and changes. New insights into pathomechanism and natural course of acute pancreatitis, development of laboratory variables and diagnostic imaging procedures as well as novel therapeutic approaches have strongly influenced definitions and classification systems and continue to do so.

Historical Perspectives: Approaches to Severity Assessment

Attempts to stratify severity and prognosis date back to the second half of the last century and have been driven by major advances in new imaging procedures and laboratory tests. The development of serum amylase measurement in 1929 [6] was the first step toward a noninvasive diagnosis of acute pancreatitis and subsequently showed that in the majority of patients a mild course with uneventful recovery was the rule rather than the exception. Supported by the development of intensive care treatment and more restrictive indications for surgical treatment in patients with clinically severe disease, interest in prognostic assessment has gained considerable headway since the 1960s. Attempts to define objective criteria for assessing disease severity and prognosis were pioneered by John Ranson in New York [7] and Clement Imrie in Glasgow [8] in the 1970s, which found widespread application in the pancreatic community.

During the early 1980s intraoperative findings revealed local-morphological features such as presence and extent of necrosis [9,10] and infection of necrosis [11) showing an excellent correlation with systemic severity and outcome. Flanked by the introduction of contrast-enhanced computed tomography (CE-CT) and percutaneous guided fine-needle-aspiration (FNA) nonoperative assessment of these complications became possible and assigned morphology-based severity stratification a predominant role. Hence, imaging procedures have become indispensable for assessment of severity in acute pancreatitis and an integral part of new classification systems [2–4] and treatment algorithms [5,12–16] alike.

After almost two decades of mainly morphology-based severity stratification the role of systemic aspects in terms of onset, severity, and persistence of pancreatitis-related organ failure was recognized as a central determinant of severity [17–29]. Moreover, early and persisting multiorgan dysfunction syndrome (MODS) has been found to outweigh morphological factors such as necrosis and even infection of necrosis as far as nonsurvival is concerned [20,29].

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Dynamics of Organ Failure

The prognostic role of early pancreatitis-associated organ failure was already recognized during the early 1970s. Objective measurement of pulmonary failure by arterial oxygen pressure or renal failure by serum creatinine had become available and had been integrated into prognostic multiparameter scoring systems according to Ranson [7] and Imrie [8]. However, it took another three decades until pancreatologists realized that the occurrence of a temporary single organ failure does not necessarily indicate a life-threatening disease. Specific aspects such as onset, severity, and persistence of organ failure have gained special attention in the past two decades.

Early Organ Failure

The role of "early" organ failure, defined as failure of one or more organ systems within the first 3 days after onset of acute pancreatitis/hospital admission was first described by Isenmann et al. in 2001 [17]. The presence of "early" single or multiple organ failure leads to a significant increase in mortality up to 56% irrespective of whether necrosis is sterile or infected [17–19,21,22]. Early multiple organ failure represents an important risk factor for death and even seems to outweigh local morphological complications such as extent or infection of necrosis [20,29].

Persistent Organ Failure

The dynamics of organ failure in terms of response/resolution or nonresponse/persistence despite intensive care treatment has been identified as another major determinant of complications and death. In many pro- and retrospective studies resolution of organ failure within the first week of the disease resulted in mortality rates close to zero, whereas mortality rates rose to 55% if organ failure persisted beyond the first week [22–25,27]. Moreover, organ failure nonresponding to intensive care treatment closely correlates with the development of pancreatic infections and death [26,28,29].

There is little doubt that organ failure is one of the most important determinants of prognosis and mortality in acute pancreatitis. The revised Atlanta classification of 2012 [3] and the international multidisciplinary "Determinant-based classification" of 2012 [4]) therefore defined organ failure as a central criterion to differentiate up to four severity groups of acute pancreatitis (Table 19.1).

Table 19.1 (a) Definition of three grades of severity in acute pancreatitis according to the revised Atlanta classification 2012. *Source:* [3]/BMJ Publishing Group Ltd.

* **Mild acute pancreatitis:**	• no organ failure • no local or systemic complications
* **Moderately severe acute pancreatitis:**	• organ failure that resolves within 48 h (transient organ failure) *and/or* • local or systemic complications without persistent organ failure
* **Severe acute pancreatitis:**	persistent organ failure >48 h • single organ failure • multiple organ failure

(b) Definition of four grades of severity in acute pancreatitis according to the "Determinant-based classification" 2012. *Source:* Adapted from [4].

* **Mild acute pancreatitis:**	• no organ failure • no peri-/intrapancreatic necrosis
* **Moderate acute pancreatitis:**	• organ failure that resolves within 48 h (transient organ failure) *and/or* • sterile peri-/intrapancreatic necrosis
* **Severe acute pancreatitis:**	• persistent organ failure >48 h *or* • infected peri-/intrapancreatic necrosis
* **Critical acute pancreatitis:**	• persistent organ failure >48 h *and* • infected peri-/intrapancreatic necrosis

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Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS), defined as intra-abdominal pressure >20 mmHg and newly developed organ failure [30], was re-recognized as a determinant of prognosis more than a decade ago. Abdominal hypertension (intra-abdominal pressure >15 mmHg) is observed in up to 75% of patients with severe acute pancreatitis [31–33] and ACS in about 25–38% [33–35]. Several studies revealed a strong association between intra-abdominal hypertension and the development of multiple organ dysfunction, which occurred in more than 90% of patients [18,31]. Multiple organ dysfunction in turn carries excessively high mortality rates. Clinical evidence suggests that "early" multiple organ failure may be the result of undiagnosed ACS arising from the extensive inflammatory process in the retroperitoneum and an aggressive fluid resuscitation. Beyond its prognostic role, the diagnosis of abdominal compartment syndrome has therapeutic implications that have been shown well in a few studies [36,37].

Multiparameter Scoring Systems

Analysis of numerous objective clinical and biochemical variables associated with complications and death led to the development of the very first multiple parameter scores by John Ranson [7] and Clement Imrie [8]. Both systems still offer a good level of accuracy, but have the disadvantage that valid calculation is restricted to primary admissions within the first 48 hours of treatment, whereas recalculation beyond 48 hours is impossible. Since their original description, the requirements of researchers and clinicians have changed and are driven by the need for speed and simplicity more than ever. Supported by the recognition of organ failure as a major determinant of outcome, scoring systems such as the Marshall [38] and sequential organ failure assessment (SOFA) [39] score, which have all been developed and validated in the intensive care setting, have led to more flexible and practicable assessments of severity and prognosis in acute pancreatitis.

The APACHE II Score

Dissatisfaction with the temporal applicability of the Ranson and Imrie systems led pancreatologists to search for more flexible scoring systems. One of the first multiple parameter scores applied in acute pancreatitis was the acute physiology and chronic health evaluation (APACHE) score in the early 1980s. A modification of the initial system [40] by the Intensive Care Research Group from Washington, DC, USA reduced the number of physiological variables from 35 to 11 and was termed APACHE II score [41], which, despite further modifications, remains the most commonly used version. Larvin et al. from Leeds, UK published the first evaluation in 290 attacks of acute pancreatitis [42]. Initial APACHE II scores of 10 or more revealed a sensitivity of 63% and a specificity of 81% (PPV 46%, NPV 90%) in predicting "severe" disease. By 24 hours APACHE II scores >10 provided a sensitivity of 71% and a specificity of 91% (PPV 67%, NPV 93%), which further rose to a sensitivity of 75% and a specificity of 92% (PPV 71%, NPV 93%) at values >9 after 48 hours. The APACHE II scores at 24 hours outperformed both the Ranson and Imrie scores at 48 hours. The results of the Leeds study have been confirmed exhaustively in subsequent years [43–48].

The advantage of the APACHE II system is clearly its flexibility and greater speed with possible recalculation at any time throughout the course of the disease for monitoring purposes. Conversely, calculation of this score is complex and time-consuming and carries the risk of miscalculations.

Organ Failure-Related Scoring Systems

Organ failure-related intensive care scores such as the Marshall [38] and the SOFA [39] scores have been applied in AP by a number of studies to assess organ failure or outcome [23,26,28,46,49,50–53]. The two scores belong to the newer generation of organ failure-related systems, which can describe the evolution of individual and multiple organ dysfunction over time. Both scoring systems rely on six major organ systems: pulmonary, cardiocirculatory, renal, hepatic, and neurologic function, as well as coagulation. Failure of each organ system is scored as absent or up to 4 points with escalating severity. The SOFA score is a further development of the Marshall score, because specific treatment such as ventilation and vasopressors are included, thus reflecting clinically relevant severity of organ failure [39].

Marshall Score

The first detailed validation study of the Marshall score was published by Halonen et al. in a large series of Finnish patients with severe acute pancreatitis. This scoring system provided a sensitivity of 59% and a specificity of 91% in predicting mortality within 72 hours of hospital admission, comparable results were obtained using the APACHE II system (sensitivity 65%, specificity 91%) [52]. In another retrospective study of the same group in 113 patients with severe acute pancreatitis admitted to the intensive care unit both admission and peak Marshall scores were as accurate as SOFA scores in assessing the risk of hospital mortality. Unfortunately no information about optimum cutoff levels, sensitivity, and specificity

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was provided [51]. A modification of the Marshall score excluding hepatic and neurologic function has been applied in two prospective studies [23,24] and the original score in a retrospective study [25] from the UK to quantify organ failure. The components for pulmonary, cardiocirculatory, and renal function match well with the definitions of the original Atlanta classification, but hepatic (bilirubin), neurologic (Glasgow coma scale), and coagulation parameters (platelet function) may further increase total scores, even if true organ failure is absent. The revised Atlanta classification of 2012 has adopted the Marshall components for pulmonary, cardiocirculatory, and renal function to define and quantify early pancreatitis-associated organ failure [3].

SOFA Score

Two detailed evaluation studies in acute pancreatitis are available for the SOFA score. In a prospective international multicenter study, SOFA scores >4 were predictive of death with a sensitivity of 86% and a specificity of 79% (PPV 27%, NPV 98%) 48 hours after onset of symptoms [53]. Corresponding results have been reported by a Finnish study for admission scores in an ICU population-based cohort at a cutoff level >8 [51]. Among the critical care scoring systems the SOFA system offers obvious advantages since it includes therapeutic requirements such as mechanical ventilation and inotropic substances. The SOFA score is an integral means for severity stratification of sepsis and septic shock in the critical care community worldwide and is therefore a valid tool in severely ill patients with acute pancreatitis requiring intensive care treatment [54].

The advantage of organ failure scores clearly lies in their widespread implementation in critical care medicine, which allows a good comparison with other critically ill patients (e.g., patients with sepsis). The introduction of the modified Marshall score in the revised Atlanta classification has overcome the problem of erroneously high scoring points by omitting the hepatic and neurologic components. The latter are truly problematic in acute pancreatitis, because high bilirubin values or delirium tremens are frequent features of biliary or alcoholic pancreatitis, albeit not representing organ failure.

Bedside Index of Severity in Acute Pancreatitis (BISAP)

Considering both the cumbersome calculation of multiparameter scoring systems and the 48-hour delay of pancreatitis-specific scoring systems, the BISAP score was dedicated to estimate pancreatitis-related mortality within 24 hours of hospital admission. It includes five easy to obtain parameters: blood urea nitrogen (BUN), mental status, SIRS, age, and presence of pleural effusions reaching scores from 0 to 5 points [48,55]. The score was initially developed and validated in two multicenter patient cohorts of around 18,000 cases with acute pancreatitis [55]. In the validation cohort the BISAP score reached an area under the curve (AUC) of 0.82 in the receiver operating characteristic (ROC) analysis, which was equal to the APACHE II score with an AUC of 0.83. Mortality rates ranged from 0.1% in patients with 0 up to 9.5% in patients with 5 points [55]. A systematic review confirmed the BISAP score as a reliable tool to identify patients at high risk for unfavorable outcomes. Compared with the Ranson criteria and APACHE II score, the BISAP score outperformed in specificity, but showed a suboptimal overall sensitivity for prediction of mortality and of a severe course of acute pancreatitis [56].

Laboratory Variables

In the mid-1960s, the first evidence arose that acute pancreatitis is reflected by abnormalities of many serum/plasma variables [57]. Hence, a multitude of laboratory markers have been identified that allow early stratification of patients at risk to develop complications such as necrosis, infection of necrosis, organ failure, and death. Beyond the potential to predict disease severity, many of these parameters were found to be determinants of disease progression and subsequent complications in the pathomechanism of acute pancreatitis such as proteases, cytokines, chemokines, adhesion molecules, and acute phase proteins. An ideal laboratory test to assess severity of acute pancreatitis should be simple in test performance, readily available under routine and emergency conditions, accurate, and cost-effective. However, despite a large array of potentially useful parameters, their large-scale clinical use is frequently limited by moderated accuracy, and time-consuming and expensive assay procedures. Consequently, only a few tests have passed the threshold to routine clinical application.

Routine Laboratory Variables

Since the introduction of Ranson and Imrie scores, single routine laboratory components such as hematocrit, creatinine or blood urea nitrogen, and blood glucose have been extensively investigated, either alone or in combination, to predict complications and thus "severe" disease.

Hematocrit

Admission hematocrit and its subsequent changes during fluid resuscitation still represent a simple and good prognostic estimate. An admission hematocrit >44% was found to be closely associated with complications in terms of necrosis and organ failure [58] or pancreatic infection [59]. An overall high negative predictive value of around

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90% excluding "severe" acute pancreatitis at admission hematocrit <44% [58] and <40% [60] was reported by some authors. However, admission hematocrit of >41% to >44% failed to predict severity, organ failure or death in other large studies [43,60]. In a recent international multicenter analysis in 1,612 patients with acute pancreatitis admission hematocrit ≥44% and increasing BUN levels at 24 hours were able to predict persistent organ failure and pancreatic necrosis in 54% and 60% of patients, respectively [61]. Hematocrit is one of three variables of the "harmless acute pancreatitis score [HAPS]," which allows a fast and accurate identification of patients with nonsevere acute pancreatitis [62]. Taken together, hematocrit serves as a widely available and good estimate to exclude severe attacks, but is not a reliable means to predict severity or any other specific complications accurately.

Serum Creatinine and Blood Urea Nitrogen (BUN)

Creatinine and blood urea nitrogen (BUN) are surrogate laboratory tests that indicate and define renal failure. Renal failure, defined as creatinine >2 mg/dl (177 µmol/l) by the Atlanta classification belongs to the most serious of organ complications in AP and has been shown to be an independent risk factor for fatal outcome [51,52,63]. However, the widely used cutoff level >2.0 mg/dl is frequently not reached on the day of hospital admission, which limits the use of this variable for "early" risk estimation. As far as disease severity in terms of local or systemic complications is concerned, admission BUN achieved no satisfactory test performance [48,64,65] reaching a maximum sensitivity of 79% and a specificity of 67% (PPV 43%, NPV 91%) only [64]. In the largest patient cohort ever published, rising BUN within 24 hours after admission achieved a sensitivity of <60% in predicting persistent organ failure or pancreatic necrosis [61], but revealed increasing diagnostic accuracy rates beyond 48 hours after admission [66].

Acute-Phase Proteins

Acute-phase proteins constitute a family of inflammatory proteins, which are mainly synthesized in the liver in response to infectious and noninfectious stimuli. The most famous member is C-reactive protein (CRP), which has become the most widely established single laboratory marker for biochemical severity stratification of acute pancreatitis. The availability of fully automated immunoassays for CRP is an essential feature for its large-scale routine application.

C-Reactive Protein

Severity stratification of acute pancreatitis by CRP has a long tradition and still represents the "gold standard" for both early severity stratification and monitoring the course of the disease [65,67,68,69,70,71]. CRP is the laboratory variable of choice to differentiate necrotizing from interstitial edematous acute pancreatitis. However, the majority of the studies focused on the discrimination between mild and severe acute pancreatitis according to the original Atlanta classification of 1993. Therein, CRP achieves diagnostic accuracy rates of between 70% and 80% at a cutoff level >150 mg/l within 48 hours after disease onset [71]. As has been well documented for all acute phase proteins CRP is not useful for prediction of infected necrosis, organ failure or death within the first week after disease onset [65,72]. Another shortcoming of CRP is the relatively long delay of its induction with systemic peak values at 72 to 96 hours after disease onset thus making very early severity assessment impossible.

In contrast to CRP, SAA failed to show any relevant benefit over CRP in estimating severity or prognosis of acute pancreatitis [67,69].

Cytokines and Chemokines

A wealth of experimental and clinical studies during the 1990s have convincingly outlined that cytokines and chemokines play a key role in the pathophysiology of acute pancreatitis by promoting local tissue destruction and mediating distant organ complications [73,74]. Therefore, cyto- and chemokine measurement was thought to offer an excellent approach to biochemical severity assessment. Despite the development of fast and fully automated assay techniques, the vast majority of the cytokine and chemokine family members play no role as biochemical markers for acute pancreatitis in the clinical setting. So far, only the cytokine interleukin-6 (IL-6) has passed the threshold from pathophysiological importance to clinical application.

Interleukin-6

Systemic concentrations of IL-6 have been found to be early and excellent predictors of severity. A large number of clinical studies have uniformly shown that IL-6 is dramatically increased in complicated attacks [65,70,71,75–77]. IL-6 concentrations generally rise 24–36 hours earlier than CRP levels and remain significantly elevated as long as complications persist. One of the first series in 24 patients from Glasgow found a sensitivity of 100% and a specificity of 71% (PPV 71%, NPV 100%) at a cutoff level >130 IU/ml for IL-6 in predicting a severe attack within 36 hours of symptom onset [75]. Beyond discriminating mild from severe attacks, IL-6 closely correlates with evolving organ failure [65,70,76]. A recent systematic review indicated superiority of IL-6 for the early prediction of moderate to severe acute pancreatitis compared with 29 other biochemical markers [71]. IL-6 has been introduced as routine parameter in some

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laboratories and represents an easy and rapid means to select patients at risk to develop severe disease. However, a large-scale use of IL-6 measurements in acute pancreatitis has never been reached.

Procalcitonin

Ever since its first description in 1993 [78] procalcitonin (PCT) has become an established marker for predicting bacterial/fungal infections, sepsis, and septic shock in the intensive care and emergency surgery settings [13,54,79,70]. A close correlation between elevated PCT concentrations and the development of infected necrosis was first described in a cohort study comprising 51 patients with acute pancreatitis by our group in 1997. At a cutoff level of >1.8 ng/ml PCT was able to predict this complication with a sensitivity and specificity of more than 90% within the first days after onset of symptoms [72]. An international multicenter trial in 104 patients with severe acute pancreatitis has shown that PCT is able to predict serious complications such as pancreatic infections or death with a sensitivity of 79% and a specificity of 93% (PPV 65%, NPV 97%) at a cutoff level >3.8 ng/ml within 48–96 hours after onset of symptoms [80]. This observation was confirmed by a number of subsequent studies which have been subjected to a meta-analysis and a systematic review. Herein, PCT reached a cumulative sensitivity of 80% and a specificity of 90% for predicting infected necrosis in acute pancreatitis [66,81]. Notably, PCT is of little or no value for simple stratification of patients as "mild" or "severe" according to the original Atlanta classification of 1993. The international guidelines for the management of sepsis and septic shock and the World Society of Emergency Surgery guidelines recommend the use of PCT as the most sensitive laboratory test to detect sepsis/pancreatic infections [13,54].

PCT measurements are available as fully automated assay for routine use, a semiquantitative strip test is an alternative for a fast and easy quantification. On the basis of the data available, PCT is a valuable tool for an early stratification and consecutive monitoring of patients at risk to develop the most serious complications in acute pancreatitis.

Table 19.2 provides an overview of relevant multiparameter scoring systems and laboratory markers for severity stratification and prediction of specific complications in acute pancreatitis.

Table 19.2 Relevant multiparameter scoring systems and laboratory markers for severity stratification and prediction of specific complications in acute pancreatitis.

Variable	Severity	Pancreatic infection	Overall prognosis
Ranson-/Imrie Score	++ (48 h)	–––	++ (48 h)
APACHE II Score	++	–––	+++ (>7 d)
SOFA-/Marshall Score	++	–––	+++ (>7 d)
BISAP Score	++ (24 h)	–––	++ (24 h)
Hematocrit	++ (48 h)	–––	–––
Creatinine/blood urea nitrogen	+	–––	++ (>7 d)
IL-6	+++ (<48 h)	–––	–––
CRP	+++ (72–96 h)	–––	–––
PCT	–––	+++ (72–96 h)	+++ (72–96 h, > 7 d)

Optimum accuracy after symptom onset of acute pancreatitis:
<48 h: within less than 48 h after symptom onset
48 h: within 48 h after symptom onset
72–96 h: within 72 to 96 h after symptom onset
>7 d: beyond the first week after disease onset.
APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; IL-6: interleukin-6; CRP: C-reactive protein; PCT: procalcitonin.

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Acute Pancreatitis Associated with Congenital Anomalies

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Introduction

Acute pancreatitis secondary to congenital anomalies remains an uncommon cause of childhood abdominal pain, representing about 5% of cases of pediatric pancreatitis [1–3]. A higher incidence of structural anomalies, up to 33%, is reported in children with recurrent and chronic pancreatitis, though a majority of those patients have multiple risk factors [4]. The most commonly encountered congenital causes are developmental abnormalities of the pancreaticobiliary system, such as pancreas divisum, annular pancreas, ectopic pancreatic tissue sources, enteric duplication cysts, and choledochal cysts [5]. Congenital structural variants of the pancreas occur up to 10% in the Western population [6], but the majority are silent as the incidence of pancreatitis is two orders of magnitude less [7]. Biliopancreatic ductal system variants encountered during diagnostic evaluation of idiopathic acute pancreatitis plague the clinician with a significant question of relevance regarding consequence and management.

Pancreas Divisum

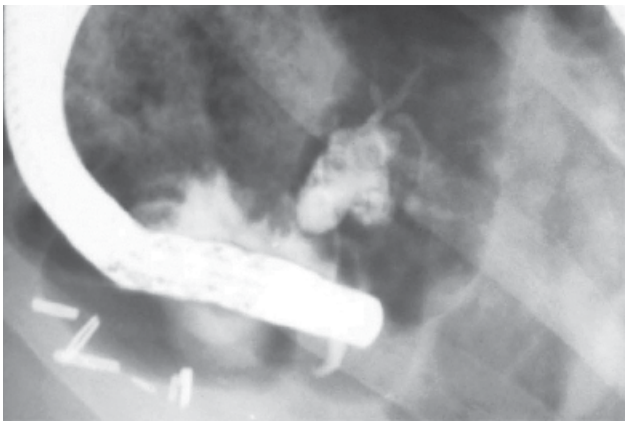
The cause, incidence, clinical relevance, and treatment of pancreatitis in patients with pancreas divisum (PD) has been hotly debated. In complete PD, the ventral and dorsal pancreatic ducts do not communicate, and usually the dorsal pancreatic duct is larger than the ventral (Fig. 20.1a) [8]. Acute pancreatitis may result from obstruction, either at the minor papilla or a junction in the ductal system, or from localized ductal ectasia in the uncinate process [9,10]. Pancreatitis is experienced by 0.1% of the population while PD is present in 4–5%, calling into question if PD is the inciting source [11–14].

Treatment is directed at relief of the obstruction, whether by sphincteroplasty for acute pancreatitis or longitudinal pancreaticojejunostomy for more distal chronic obstruction, or endoscopic approaches. Accessory papilla sphincteroplasty improves symptoms in adult patients with documented stenosis, best predicted by presentation with pancreatitis and a positive ultrasound-secretin test [15]. A pediatric study found that success was best predicted by presence of pancreatic ductal stones [10].

Surgical dual sphincteroplasties result in good to excellent outcomes in patients with PD and pancreaticobiliary sphincter dysfunction established via manometry [16]. Smaller studies have reported various success rates with endoscopic sphincterotomy and longitudinal pancreaticoduodenectomy; however, morbidity rates range from 15% to 40%, and many patients require multiple procedures [9,16,17]. Successful duodenum-preserving pancreatic head resection in patients with chronic pancreatitis and PD has been described in both children and adults [18,19]. For patients with PD and chronic pancreatitis with significantly dilated pancreatic ducts a longitudinal pancreaticojejunostomy can be therapeutic, and total pancreatectomy with islet cell transplantation can be performed in patients with significant ductal fibrosis. However, both procedures can have significant morbidity and are often reserved for patients who fail other therapies [20,21].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Companion website: www.wiley.com/go/beger/thepancreas4e

(a)



(b)

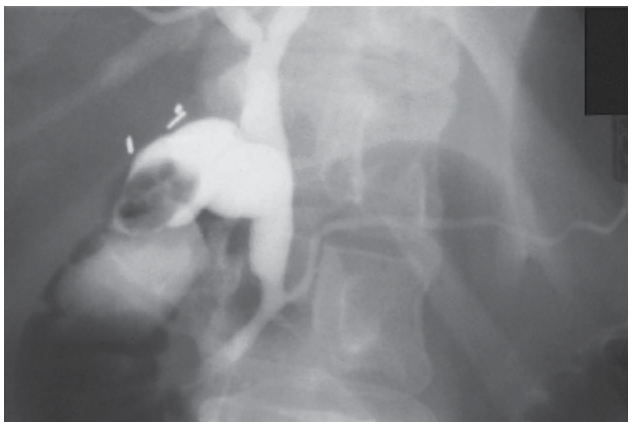


Figure 20.1 (a) A 15-year-old girl presented with recurrent attacks of pancreatitis. Endoscopic retrograde pancreatography showed pancreas divisum with cystic dilation of the ventral pancreatic duct containing stones. She was treated by pancreaticoduodenectomy. (b) Cholangiopancreatogram in a 12-year-old boy with a choledochal cyst and anomalous pancreatico–biliary junction. The pancreatic duct inserts into the common bile duct more than 2 cm proximal to the ampullary orifice. Such patients are prone to acute and chronic pancreatitis.

Anomalous Pancreaticobiliary Ductal Union

Anomalous pancreaticobiliary ductal union (APBDU) results from the pancreatic and common bile ducts joining proximally to the ampulla of Vater with a hypothesized resulting admixture of refluxed pancreatic and biliary secretions into the biliary tree or pancreas [22,23] and has been associated with a higher incidence of congenital choledochal dilation (Fig. 20.1b) [22–25]. APBDU is defined as a common channel greater than 15 mm in length or a contractile segment totally distal to the biliary and pancreatic ductal union [26,27]. APBDU is further delineated into subtypes according to the order of insertion of the pancreatic and biliary ducts [27,28]. In B-P, the bile duct enters the main pancreatic duct and in P-B (or in some series, P-C for choledochal) the pancreatic duct enters the common bile duct [27].

APBDU has been considered a factor in the development of pancreatitis, choledochal cysts, and hepatobiliary cancers [27,29]. APBDU was identified by ERCP in 8.7% of patients with an incidence of 13.2% for biliary pancreatitis and 2.2% for nonbiliary pancreatitis. B-P subtype was associated with choledochal cyst formation whereas P-B subtype was associated with biliary pancreatitis, gallbladder cancer, and adenomyomatosis. A proposed mechanism for this relatively high rate of pancreatitis and the observation of recurrent pancreatitis in patients with APBDU is sphincter of Oddi dysfunction [30]. In rare cases, APBDU and PD can coexist [31].

Surgical treatment of APBDU relies on disruption of the contiguous anatomical relationships. Roux-en-Y hepaticojejunostomy is offered [32], but cholecystectomy and alternate biliary tract reconstruction [33] or endoscopic sphincterotomy alone can be beneficial [30]. APBDU with choledochal cysts are often managed by cyst excision, although duodenopancreatectomy may be required [34].

Choledochal Cyst/Choledochocele

Choledochal cysts are noted in 0.1% of adult ERCPs and in 1 in 150,000 North Americans [35,36]. Rates are higher in East Asia and in females, with a male to female ratio of 1 : 3–4, and associated pancreatitis more common in younger patients aged 2–16 years (36%) [37]. The classic triad of abdominal pain, jaundice, and a palpable right upper quadrant abdominal mass occurred 6.7 times more frequently in children [38] with adults more likely to present with abdominal pain diagnosed as pancreatitis or biliary tract pathology prior to cyst identification [39,40]. Cyst rupture is rare and most commonly presents in children and infants with biliary peritonitis [41]. Children with pancreatitis and choledochal cysts are more likely to have fusiform dilation of the cysts or a dilated common channel [42]. Pancreatitis and cancer were more common in patients with both choledochal cyst and APBDU [43]. The possible role of APBDU in causing choledochal cysts is discussed above.

Choledochal cysts were first classified according to the 1977 Todani system [44,45]. Except in the case of type III disease, in which endoscopic approaches or marsupialization may be indicated, complete excision of the extrahepatic choledochal cyst with hepaticojejunostomy is the goal [46,47]. Malignancy is identified increasingly

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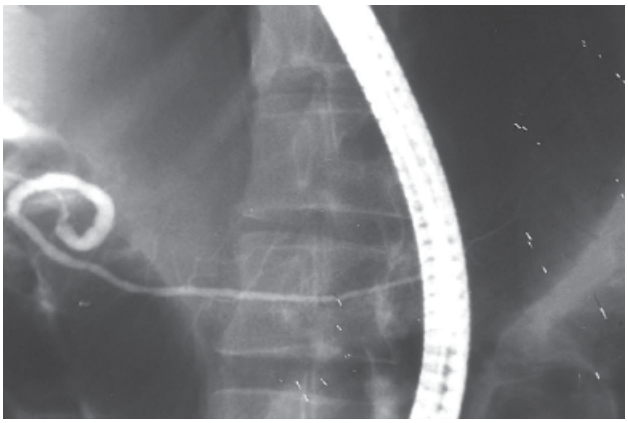
with choledochal cyst retention; therefore internal drainage or bypass procedures should be accompanied by a near-complete resection [37]. Interposition of the jejunum or appendix are unsuitable due to high rates of graft dysfunction and cholangitis [48,49].

Annular Pancreas

Annular pancreas, potentially arising from dorsal and ventral anlage hypertrophy or abnormal adherence of the ventral duct to the duodenum during rotation, envelops the duodenum (Fig. 20.2a, b) [50]. Obstruction or pancreatic inflammation secondary to annular pancreas occurs in the third decade of life or later with a prevalence of roughly 25% [51,52]. Pancreatitis secondary to annular pancreas is rare in the newborn and presents with duodenal blockage, with bilious emesis and "double bubble" on abdominal films [51,53]. Differentiation between upper obstruction etiologies, such as duodenal atresia, malrotation without volvulus, and annular pancreas, must not delay emergent operative care in the case of volvulus. Annular pancreas is associated with a high rate of congenital anomalies. Seventy percent of infants with annular pancreas will have another anomaly, such as duodenal stenosis or atresia (40%), Down syndrome (16%), tracheoesophageal fistula (9%), or congenital heart defects (7%) [51].

Surgical correction of annular pancreas in childhood is usually undertaken by performing diamond duodenoduodenostomy and leads to faster feeding and discharge when compared to side-to-side anastomosis or duodenojejunostomy [54]. Gastrojejunostomy should be avoided in children as the most anatomic reconstructions are linked to the best growth outcomes [55]. Surgical correction in adults follows suit, with less concern about growth retardation with gastrojejunostomy [56]. There is an increased incidence of malignancy in adults presenting with symptomatic annular pancreas [56,57]. In any case of duodenal obstruction, volvulus must be first excluded as a life-threatening surgical emergency.

(a)



(b)

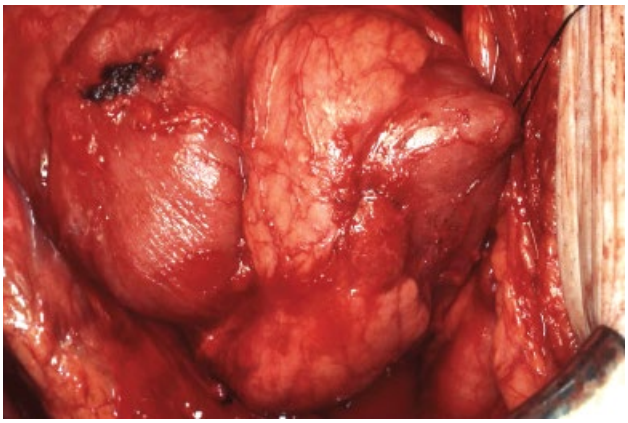


Figure 20.2 (a) Pancreatogram in a young boy with annular pancreas. The proximal pancreatic duct encircles the duodenum within the annular segment. (b) Annular process.

Ectopic Pancreatic Tissue

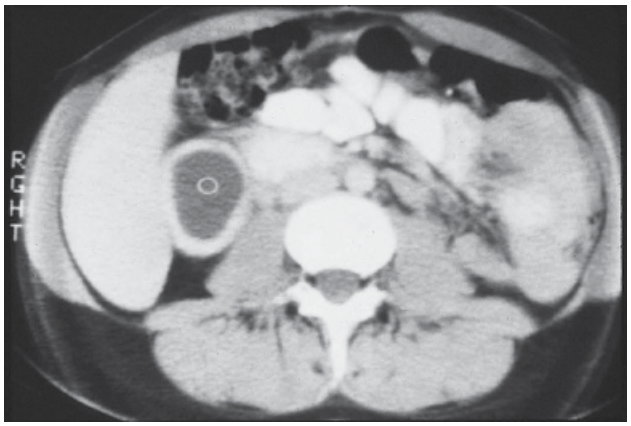
Ectopic pancreatic tissue is a relatively common anomaly with an incidence of up to 13% at autopsy [55,58]. A normally organized aberrant rest of pancreatic tissue is discontinuous with the entopic pancreas. A majority are identified in the submucosa of the stomach, duodenum, and jejunum [50] and although uncommon, come to clinical attention from intussusception, obstruction, inflammation or degeneration [59,60]. Inflammation of an ectopic pancreas without pseudocyst with both elevated serum amylase and lipase and ectopic tissue inflammation has been reported [58,61]. In a total of 32 histologically documented cases of ectopic pancreas, half were identified incidentally [62]. The remaining cases were clinically significant for hemorrhage, obstruction, or ulceration. The majority of cases are asymptomatic, but nearly all pathologies of the pancreas can arise in ectopic tissue, including pancreatitis and malignancy [63]. A tentative link between ectopic pancreatitis in the duodenal wall and duodenal stenosis has been established in six pancreaticoduodenectomy specimens [64].

Enteric Duplication Cysts

Gastrointestinal duplication cysts are congenital foregut anomalies with gastrointestinal mucosa of any type or pancreatic tissue and are named for their anatomic

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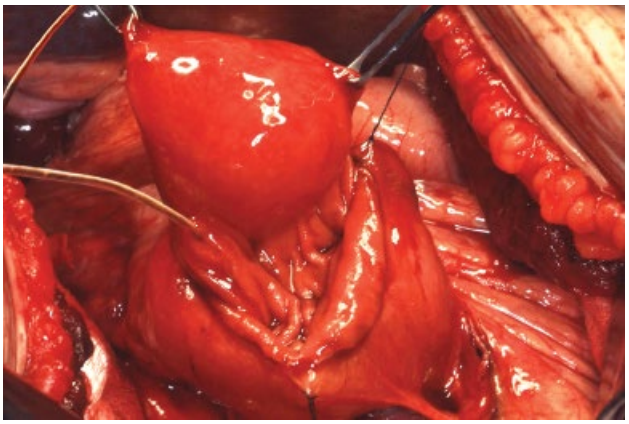


Figure 20.3 (a) CT scan in a 21-year-old woman with a history of several years of recurrent acute pancreatitis. The circle indicates an abnormal thick-walled cystic structure adjacent to the head of the pancreas. (b) Operative photograph of a pancreatic duplication cyst bulging into the duodenal lumen, as previously identified on abdominal CT. The catheter has been introduced through the ampulla into the pancreatic duct. Excision of the cyst with suture ligation of its narrow neck was curative of her recurrent pancreatitis.

proximity rather than mucosal content [51]. Duplication cysts within the pancreas have been reported and are generally termed as duodenal or gastric duplications since they lack a contiguous structure (Fig. 20.3a, b) [59]. Although most enteric duplications do not present with pancreatitis, multiple cases have been identified [65,66]. Duodenal duplication occurs in 10% or fewer cases and may cause "obstructive pancreatitis" from compression between the duodenal wall and the biliopancreatic duct [67,68]. Juxta-pancreatic duplications with pancreatic ductal communication may shed blood or mucous into the main pancreatic duct resulting in obstruction [69–71]. Pancreatitis may occur within the duplication itself, as is found in esophageal duplications containing gastric mucosa and pancreatic tissue (43%) [72]. Local resection is preferred; however, marsupialization of cysts with removal of mucosa, either surgical or endoscopic, may be employed if local resection is not possible [73,74].

Conclusions

Infrequently, congenital anomalies may be the cause of idiopathic acute pancreatitis. Nonanatomic congenital causes must be assessed by diligent investigation. Regarding anatomic congenital anomalies, strict definition of the anatomic relationships and associated anomalies is necessary to direct appropriate therapy. Because congenital anomalies are often unique, unusual anatomic relationships may be discovered in each case. Previous case series in the literature provide useful longitudinal data to help in predicting outcomes and avoiding known pitfalls.

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21

Acute Pancreatitis in Children

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Introduction

The Second International Symposium in Marseilles in 1984 defined acute pancreatitis (AP) as acute abdominal pain accompanied by the finding of increased pancreatic enzymes in blood or urine [1]. However, the pathophysiology of acute pancreatic inflammation has remained difficult to describe, partly due to the relative inaccessibility of the pancreas on physical examination, and to the frequently nonspecific nature of symptoms resulting from diseases of the pancreas. Despite these difficulties, understanding of *adult* pancreatitis has increased in an exponential manner in recent decades. Unfortunately, the understanding of the *pediatric* counterpart has lagged, although much progress has been made in recent years.

Pediatric AP poses a challenge to clinicians. Depending on the age and developmental level of a child, it can be extremely difficult to assess the nonspecific symptoms of abdominal pain and nausea or vomiting. Defining the location and nature of the pain and identifying factors that aggravate or alleviate the pain can be particularly challenging in a pediatric patient. Compounding this challenge is that many healthcare professionals still do not consider pancreatitis in the differential diagnosis of pediatric abdominal pathology. Hence, children may experience symptoms from pancreatic inflammation and be diagnosed with "viral gastroenteritis." For all these reasons, unraveling the complexities of pediatric AP remains an ongoing process.

The challenges in pediatric AP lie in three major areas:

- potential etiologies, many of which are more particular to children;
- diagnosis, including serum biochemistry and imaging techniques;
- assessing and following for disease severity and complications.

This chapter will strive to cover these areas as they pertain to pediatric AP.

Incidence

The prevailing impression amongst pediatric specialists is that the incidence of pediatric acute AP is increasing. A number of population-based series have attempted to quantify the incidence of AP [2–13]. These studies suggest that the incidence of AP in children has truly increased over the past several decades. Since the initial study by Lopez showing a steady increase in the absolute number of cases of AP per year in a single institution, a number of other centers throughout the world have reported similar observations [2] (Table 21.1). An estimate of incidence ranged from 1 to 3 cases per 10,000 children. Proposed explanations for the increasing diagnosis of AP in children include increased awareness that AP occurs in children, a true rise in new cases of pediatric AP, increased referral of children to tertiary care centers, and an increase of AP in children with other systemic diseases [2,12,13]. Likely, a combination of these events explains the increased incidence.

Etiology

An adult presenting with a first episode of AP is questioned and investigated to identify the presence of one of two major etiologies for adult AP: biliary disease and

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Table 21.1 Series looking at the incidence of AP. Studies reporting increase in number of cases of AP diagnosed in children over time.

Location	Years	Author	Incidence in last year	Further study details
United States: Children's Medical Center of Dallas	1993–1998	Lopez [2]	Not reported	Total cases/yr: 5, 19, 20, 38, 79, 113 (1993–98)
United States: Children's Hospital of Pittsburgh of	1993–2004	Morinville [13]	1.3 per 10,000 children	Number of cases increased from 28 to 141 per year
Australia: Royal Children's Hospital, Melbourne	1993–2002	Nydegger [3]	0.35 per 10,000 children	Consistent, progressive increase in cases of AP per year over the study period
United States: Children's Hospital of Wisconsin	1996–2011	Werlin [5]	Not reported	Noted a consistent increase in number of AP cases over study period with the exception of 2001
Mexico: Hospital of Pediatrics, Guadalajara	1990–2005	Sanchez-Ramirez [4]	53 per 10,000 hospitalizations	Reported a nonlinear increase in new cases over the study years
United States: Yale-New Haven Hospital	1994–2007	Park [12]	8.9 per 10,000 ED visits	Increase in number of patients admitted for AP over time. Normalization to number of ED visits showed same rate per 10,000 visits
United States: Healthcare Cost and Utilization Project Kids' Inpatient Database	2000–2009	Pant [6]	35 per 10,000 hospitalizations	Relied on ICD9 codes to identify 55,012 patients
United States: Nationwide Emergency Department Sample	2006–2011	Pant [7]	1.6 per 10,000 ED visits	Relied on ICD9 codes to identify 78,787 patients with ED visits for AP
United Kingdom: Liverpool	1999–2009	Wilkinson [8]	0.3 per 10,000 children	Identified patients by ICD10 codes from Hospital Episode Statistics database
India: Sanjay Gandhi Postgraduate Institute of Medical Science	2003–2014	Poddar [9]	Not reported	5-fold increase in AP cases
United States: Cincinnati Children's Hospital Medical Center	2006, 2009, 2012	Abu-El-Haija [10]	Not reported	Kids' Inpatient Database Significant increase in diagnosis of AP over the study period
Taiwan: Taiwan National Health Insurance Research Database	2000–2013	Cheng [11]	0.3 per 10,000 children	Incidence increased steadily from age 13 to 18 years

AP: acute pancreatitis; ED: Emergency Department.

alcohol ingestion. These, in fact, appear to account for most cases of AP in adults. In children, by contrast, the etiologies of AP are more broadly divided (Table 21.2). Figure 21.1 summarizes the breakdown of presumed etiologies based on previously published series from multiple countries. In general, the largest categories are divided up amongst idiopathic (24%), trauma (17%), systemic (15%), structural (14%), and medications (10%). A recent single-center study suggested that drug-induced pancreatitis is the leading known cause of AP [14]. The same center also reported that first attack of pancreatitis was associated with genetic risk factors in 18% of patients [14]. Since genetic testing is not often done with the initial episode of AP, many studies may underestimate the role of genetic variants. The various risk factors may act alone or jointly to lead to a clinical episode of AP [15].

Pathophysiology

The pathophysiology of pediatric AP is believed to be identical to that of adult AP.

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Table 21.2 Potential etiologies of acute pancreatitis. The differential list is extensive. A clinician must consider the particular patient's history of present illness, past medical history, and family history in considering the potential trigger of an attack of AP.

Category	Examples
Anatomic abnormalities	Annular pancreas
	Anomalous choledochopancreaticoductal junction
	Choledochal cyst, choledochocoele
	Intestinal duplication or cyst
	Pancreas divisum
Biochemical abnormalities	Diabetic ketoacidosis
	Hypercalcemia (hyperparathyroidism, familial hypocalciuric hypercalcemia)
	Hypertriglyceridemia
	Uremia
Gallstone disease	Biliary sludge
	Choledocholithiasis
	Microlithiasis
Genetic	Hereditary pancreatitis: *PRSS1*
	SPINK1
	CFTR
	CTRC
	Others
Iatrogenic	Following ERCP
	Following liver transplant (postsurgery anatomy + medications)
	Following nongastrointestinal surgery (Fontan heart operation, spinal fusion surgery)
Idiopathic	Unidentified infections, toxins, drugs or trauma, genetic risks
Inborn errors of metabolism	Acute intermittent porphyria
	Branched-chain ketoaciduria (maple syrup urine disease)
	Cationic aminoacidurias
	Cystinuria
	Glycogen storage disorders
	Homocystinuria
	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
	Pyruvate kinase deficiency
Infectious agents	**Bacteria** (*Campylobacter fetus, Escherichia coli, legionella, Mycoplasma pneumoniae, Salmonella typhii, Yersinia*)
	Viruses (coxsackievirus, cytomegalovirus, enterovirus, echovirus, Epstein–Barr, hepatitis A, influenza A,influenza B, measles, mumps, rubella, rubeola, varicella
	Other (*Ascaris lumbricoides* (obstruction), *clonorchis ninensis* (obstruction), leptospirosis, malaria)
	Immunocompromised host (*mycobacterium avium intracellulare, pneumocystis carinii, cryptosporidium parvum*)
Medications	**Analgesics** (acetaminophen overdose, aminosalicylic acid, sulindac, indomethacin, propoxyphene)
	Anti-acid (cimetidine, ranitidine)
	Anticonvulsants (fosphenytoin, phenytoin, valproic acid)
	Antimicrobials (erythromycin, sulfonamides, trimethoprim-sulfamethoxazole, tetracycline, isoniazid, metronidazole, nitrofurantoin, pentamidine)

(Continued)

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Table 21.2 (Continued)

Category	Examples
	Chemotherapeutics (L-asparaginase, cytarabine)
	Diuretics (furosemide, ethacrynic acid, ACE-I, thiazides, chlorthalidone)
	Illicit drugs (amphetamines, cocaine, heroin)
	Immunomodulators and anti-inflammatories (sulfasalazine, 5-ASA products, 6-mercaptopurine, azathioprine, gold)
	Sex hormone-related (estrogen, tamoxifen, danazol, corticosteroids)
	Others: cholestyramine, cyproheptadine, diazoxide, diphenoxylate, histamine, interleukin, methyldopa, phenformin, procainamide
Obstruction, acquired	Neoplasm-associated
	Periampullary obstruction (celiac disease, Crohn disease, mucosal inflammation)
	Sphincter of Oddi problem (stenosis; dysfunction?)
Systemic illness	Crohn disease
	Hemolytic uremic syndrome
	Henoch–Schonlein purpura
	Kawasaki syndrome
	Polyarteritis nodosum
	Sarcoidosis
	Systemic lupus erythematosus
	Sickle cell disease
Toxins	Boric acid
	Ethanol and methanol
	Methylene chloride
	Organophosphates/insecticides
	Scorpion bite
Trauma	Accidental (bicycle handle bar injury, MVA) Child abuse

ACE-I: angiotensin-converting enzyme inhibitors; 5-ASA: 5-aminosalicylic acid; MVA: motor vehicle accident.

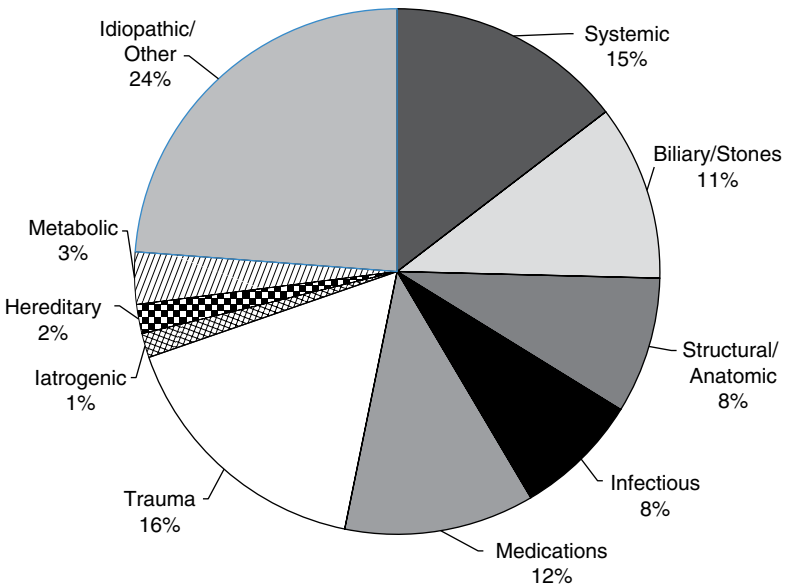


Figure 21.1 Etiology of acute pancreatitis (AP) in children. Contrary to adults where biliary tree pathology and alcohol account for more than two-thirds of cases, children have a greater spread among the etiologic categories of AP. The following reflects distribution of etiologies of AP in 1961 children from different countries. Please refer to Table 21.2 for examples of subcategories in each of the included series.

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Investigations

A great diversity of potential etiologies of AP is demonstrated in Table 21.2. Clinical finesse is involved in determining which causes should be considered for each child presenting with a first episode of AP. Unlike many pediatric diseases, the etiology of AP does not vary significantly among individual age groups [16–18]. A stepwise consideration of probable, possible, and rare etiologies in conjunction with elicited history of present illness, past medical history, family history, and findings on physical examination will direct investigations and limit invasive and sometimes painful procedures for the pediatric patient, as well as minimize unnecessary costs. Since genetic risk factors are common in children, a thorough family history for documented pancreatitis, pancreatic cancer, pancreatic insufficiency including insulin-dependent diabetes, and/or family members exhibiting symptoms that could be consistent with acute recurrent pancreatitis is particularly important.

Diagnosis

In 2012, an international group of pediatric gastroenterologists published a consensus statement defining AP in childhood [19]. The clinical diagnosis of AP requires the presence of at least two out of three criteria:

- A combination of abdominal pain that is consistent with pancreatic origin;
- The presence of elevated amylase or lipase or both to at least three times the upper limit of normal;
- Radiological imaging with findings consistent with AP.

Even with these criteria, the diagnosis of AP can present challenges for the clinician. History and physical examination findings are variable: there may be epigastric to right upper quadrant pain, left upper quadrant pain, back pain, nausea, vomiting, jaundice, tachycardia, guarding, or even signs of shock. In children under the age of three, pain may present as increased irritability, and abdominal distension and fever were more common than in older children [16]. Clinicians must maintain a high degree of suspicion, especially in younger children in whom verbal communicative skills may be limited.

A particular pediatric consideration is that newborn levels of pancreatic type isoamylase are very low to nondemonstrable, and total amylase levels reach normal adult values by only approximately 8–16 months of age [20,21]. Pancreatic isoamylase activity might not even reach adult values until the age of 10 to 15 years [22]. In a similar fashion, lipase values at birth are significantly lower than those observed for adults and appear to have the greatest increase within the first year of life [23,24]. Hence, in a young patient, amylase and lipase levels may not always reflect potential pancreatic inflammation particularly if adult ranges of normal enzyme levels are used as references [25].

Clinical scales are utilized to classify adults as having mild or severe disease. Several different scales for children have been proposed over the years. None have been widely applied. Two recent reports suggested that BUN levels or the lipase level and the presence of a pediatric systemic inflammatory response syndrome on admission were prognostic indicators for severe AP in children [14,26]. There was considerable overlap between mild and severe AP for both. It remains to be seen if either gains widespread acceptance and utilization, and thus pediatric severity indices represent an area of necessary research [25].

Imaging

Imaging methods may be helpful in (a) diagnosis, (b) determining severity and complications, and (c) visualizing any anatomic factors leading to AP [27].

Transabdominal ultrasonography (TUS) is widely available, relatively inexpensive, and does not expose a child to radiation or contrast agent. Historically, TUS has often been the initial diagnostic modality in suspected AP. It can repeatedly be performed in almost any setting to follow the course of illness and does not require procedural sedation. Ultrasonography may demonstrate enlargement of the pancreas, altered echogenicity, duct diameter abnormalities, and fluid collections (intra- or extrapancreatic) [28], abnormalities of the pancreaticobiliary drainage system, including the presence of a choledochal cyst, or common bile duct stones [27]. Limitations include air within the stomach interfering with image acquisition from the body and tail of the pancreas, and differentiation of normal from abnormal pancreas in cases of pancreatitis where echogenic changes may or may not be present. A recent study showed that TUS is only moderately sensitive for diagnosing AP and that cross-sectional imaging such as computed tomography (CT) provided higher sensitivity [29]. In addition, CT with contrast may be more useful in more severe cases of AP to assess for local complications. The main drawback to more widespread CT scan utilization is its radiation exposure.

The capability of magnetic resonance cholangiopancreatography (MRCP, with or without secretin) to diagnose most cases of pancreas divisum, choledochal cyst, cholelithiasis, pancreaticobiliary junction anomalies and obstructive abnormalities has decreased the use of endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes even though MRCP might not be as sensitive

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as ERCP in detecting pancreatobiliary abnormalities [30,31]. Although MRCP offers imaging without radiation, there are still pediatric factors to take into consideration. Due to the relatively long duration of the procedure (15 to 45 minutes), younger children will require sedation, ranging from oral sedatives to intravenous general anesthesia and intubation. Additionally, the quality of MRCP images depend on the protocol utilized for image acquisition as well as the radiologist's interpretation of these [32].

When indicated, pediatric ERCP in experienced hands is safe and effective at all ages, although infants and young toddlers may require slimmer pediatric duodenoscopes [33,34]. Pediatric uses include stone removal, assessment of pancreatic duct anatomy and injuries, drainage of nonresolving pancreatic pseudocysts, sphincterotomy, and stent placement. ERCP at the time of cholecystectomy is safe and effective in pediatric patients [35]. The obvious difficulties with ERCP include the need for sedation (typically general anesthesia), and the use of ionizing radiation during fluoroscopy.

Experience with pediatric EUS has increasingly been reported in recent years [36]. EUS provides detailed imaging of pancreatic parenchyma and ducts without the use of radiation, but with the need for sedation. Its benefits include not only its role in imaging, but also in interventions, with the capacity to sample tissue and fluid collections through fine needle aspiration and biopsy, as well as accomplish drainage of fluid collections such as pseudocysts. As endoscopists increasingly become comfortable with pediatric use of EUS, its role in diagnosis and management of AP will become better defined.

All radiological and endoscopic tests may offer complementary information regarding the cause or complications associated with pediatric AP. Clinicians must weigh the potential benefits offered by an imaging technology against the drawbacks particular to each technique and decide on an algorithm for a particular patient. Typically, pediatric patients are first assessed by TUS. Subsequently, with a prolonged AP course, there may be a need for either MRCP or CT to better delineate anatomy and to visualize potential complications. With the need for a therapeutic maneuver, both ERCP and EUS are becoming increasingly child-friendly and experience to date shows they are safe and effective.

Management

The general measures undertaken in children with AP are similar to those in adults. In most pediatric AP cases, clinical improvement occurs within a few days and discharge is possible in less than a week. Several changes in management of patients with AP have occurred in recent years. In 2018, the Pancreas Committee of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition Studies published a position paper on the management of pediatric AP [37]. The role of i.v. fluids in the treatment of AP has been the subject of several studies in adults and children. However, details of i.v. therapy such as volume, rate, timing, and composition of the fluid are not firmly established. In one pediatric study, fluid rates 1.5 to 2 times maintenance in the first 24 h shortened length of stay and severity of disease [38]. A second study showed that patients given lactated Ringers solution had a shorter length of stay compared to patients given normal saline [39]. Another major change in management is the recognition that early enteral feeding whether by mouth or feeding tube is safe and may improve outcome [38,40–42]. Early feeds did not increase pain or length of stay and may shorten length of stay. Additionally, patients with higher fat intake did not have higher pain scores.

Outcomes

Overall, children generally have a mild clinical course and only a small fraction have severe complications. Pseudocysts represent the most frequent complication occurring in 10–30% of cases [4,5,43]. They typically present as a persistent abdominal discomfort, abdominal mass on physical examination, continued elevation of pancreatic enzymes, or identified on follow-up imaging. Pseudocysts usually resolve spontaneously and rarely require intervention. When indicated, potential therapeutic options include percutaneous catheter drainage (radiological placement or surgical), cyst-gastrostomy stent placement via EUS guidance, pancreatic duct stenting via ERCP, open surgical cyst-enteric anastomosis drainage and, perhaps, antibiotic therapy [44,45].

Despite a generally positive outcome for pediatric AP, up to 6% of children develop multiorgan failure or pancreatic necrosis [46]. Some studies have found an association between particular triggers of AP and serious complications. As might be predicted, it appears that children who have complex medical histories, including those experiencing AP post liver transplantation, or in the context of a systemic disease, are more susceptible to severe and potentially fatal courses [46]. Mortality data has rarely been reported in children. A database study from 2000 to 2009 of 55,012 children hospitalized with AP reported a mortality rate of about 1.0% [6].

Acute Recurrent Pancreatitis

Acute recurrent pancreatitis (ARP) is defined as at least two distinct episodes of AP separated by a return to normal baseline status [19]. It has been estimated that

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10–35% of children have recurrent episodes of AP [46]. Most often the second episode occurs within 5 months of the first one [47]. Upon the first presentation, etiologies that are amenable to therapy should be sought and if identified, managed appropriately (including hypercalcemia, hypertriglyceridemia, biliary factors, and structural abnormalities). Any reversible cause should be eliminated whenever possible (including culprit medications). With additional attacks other investigations should be considered. Secretin-stimulated MRCP may unveil anatomic abnormalities predisposing to ARP. After a second episode of AP, genetic testing for known risk variants should be done [48]. In a large multi-center study, almost half of patients with ARP had mutations in *PRSS1, SPINK1, CFTR,* or *CTRC* [49]. Since not all patients in this cohort had genetic testing or were screened for fewer than four genes, the percentage of patients harboring gene mutations is likely higher. In the same study, 75% of patients with chronic pancreatitis (CP) had genetic mutations. Mutational analysis is now commercially available for these genetic loci. It is anticipated that a high proportion of children with ARP and CP will have genetic predispositions eventually identified. Along with mutational analysis, a comprehensive search for rare causes of AP is typically indicated [50]. As it is believed that recurrent attacks of AP may eventually lead to morphological changes of CP, prevention of further pancreatic injury is a key interventional goal, and identification of etiologic factors represents the first step.

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22

Acute Pancreatitis Associated with Metabolic, Infections and Drug-Related Diseases

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Introduction

Immoderate alcohol consumption and gallstones are by far the most frequent etiologic factors for acute pancreatitis, accounting for up to 70% of all cases. The remaining 30% are patients where no triggering event can be identified (idiopathic pancreatitis, approximately 15%) and in 15%, rare causes are identified in association with acute pancreatitis. These include anatomical variants, metabolic disorders, drugs, tumors, genetic abnormalities, and infectious diseases. In this chapter we review some of the rarer causes of acute pancreatitis.

Metabolic Diseases

Hyperlipidemia and hypercalcemia are the best-known metabolic causes for acute pancreatitis. To a lesser extent, diabetic ketoacidosis (DKA), a severe complication of diabetes mellitus can cause pancreatitis.

Hypercalcemia

Hypercalcemia often results from primary hyperparathyroidism (pHPT), a disorder of the parathyroid glands that is defined by an inappropriate secretion of parathyroid hormone (PTH) [1]. Elevated calcium levels affect other organs, including the gastrointestinal tract. However, determination of the incidence of *hyperparathyroidism-related* pancreatitis is difficult because patients often harbor comorbidities such as concomitant alcohol abuse, cholecystolithiasis, or hypertriglyceridemia. In many cases a definite assignment of the etiology of acute pancreatitis is not possible because patients have additional risk factors for acute pancreatitis. A coincidence of pancreatitis has been observed in 1.5–6.8% of patients with primary hyperparathyroidism, for example. The highest incidences were reported from India where a higher predisposition for (tropical) calcific pancreatitis was also observed [2–4]. Mean serum calcium levels are higher in patients with primary hyperparathyroidism and coexisting acute pancreatitis (12.8–13.3 mg/dL) compared to individuals with hyperparathyroidism who do not develop pancreatitis (11.6–12.1 g/dL) [2,5,6]. After parathyroidectomy, the causative therapy for pHPT, risk of pancreatitis dramatically reduced [4].

Hypercalcemia resulting in acute pancreatitis may also be attributed to unrelated diseases of the parathyroid glands but these cases are extremely rare. Reports of secondary hypercalcemia due to either solid or hematologic malignant tumor disorders, including multiple myeloma [7] and iatrogenic causes of hypercalcemia such as calcium-containing infusions during cardiac surgery [8] or for parenteral nutrition [9] underline that high circulating calcium levels predispose to pancreatitis.

The molecular mechanisms of hypercalcemia-induced pancreatitis are gradually being resolved. Ca^{2+} is important for intracellular signaling and homeostasis. Disturbances in intracellular calcium levels impair its signaling function and high cytosolic levels within the exocrine acinar cell trigger premature protease activation [10]. Blocking the uptake of calcium into the cells or chelation of intracellular ionized Ca^{2+} largely prevents digestive zymogen activation and pancreatic damage [11]. Mutations in the calcium-sensing receptor gene (CASR), encoding a G protein-coupled receptor regulating calcium homeostasis, were associated with chronic pancreatitis but are not directly related to acute pancreatitis

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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in pHPT patients [12]. Several clinical trials have been set up to investigate the possibility of reducing the incidence and severity of pancreatitis by interfering with the intracellular effects of calcium.

Hypertriglyceridemia

It is known that elevated lipid levels are associated with cardiovascular diseases. However, hyperlipidemia is a rare but well-established cause of acute pancreatitis as well. This is mostly related to hypertriglyceridemia, because hypercholesterolemia by itself does not cause acute pancreatitis. Hypertriglyceridemia and hyperlipidemia in general are becoming more common in industrialized countries and it has been reported that over 1.5% of the US population has severe hypertriglyceridemia (defined as a serum concentration of 500–2000 mg/dL) [13]. Normal triglyceride levels for adults should be less than 150 mg/dL [14].

Acute pancreatitis secondary to hypertriglyceridemia is seen in between 1.3% and 3.8% of patients [15–17]. Typically, triglyceride levels above 1000 mg/dL (or 11.4 mmol/L) precipitate acute pancreatitis with a risk of around 5%. Triglyceride levels exceeding 2000 mg/dL more than double that risk to 10–20%. In addition, data from a large Danish registry-based study indicate that even nonfasting mild to moderate triglyceride levels ≥177 mg/dL (2 mmol/L) increase the risk of pancreatitis so that dyslipidemia needs to be considered as a potential cause of acute pancreatitis more often than previously assumed [18].

Plasma triglycerides can be of exogenous or endogenous origin. Normally, dietary triglycerides are the main source and form the main lipid component in very-low density lipoproteins (VLDL). Once hydrolyzed in the small intestine they are absorbed and incorporated into chylomicrons and transported via lymphatic vessels to peripheral tissues for further utilization. Cells of all parenchymal tissues secrete lipoprotein lipases that hydrolyze triglycerides and surface components of chylomicrons and VLDL to release free fatty acids for energy supply. Fatty acids are converted to fatty acid ethyl esters (FAEE) by carboxylester lipase (CEL), an enzyme also expressed in pancreatic acinar cells. FAEE themselves exert toxic direct effects on cells and also raise intracellular Ca^{2+} concentrations that further promote cellular damage [19].

Patients with hypertriglyceridemia often have a concomitant history of diabetes mellitus (72%), hyperlipidemia (I, IV, and V according to Fredrickson's classification, 77%), alcohol abuse (23%), or gallstones (7%). Triglyceride levels are also elevated in the setting of DKA [16,20]. Typically, a lipid abnormality presents as a secondary factor (obesity, diabetes mellitus) whereas isolated hyperlipidemia (usually type I or V) is much less common [21]. Moreover, mild to moderate hypertriglyceridemia is not infrequently seen in alcoholic pancreatitis patients as a secondary effect of excessive alcohol consumption and this is much more common than hyperlipidemia-induced pancreatitis in association with primary or inherited forms of hypertriglyceridemia. Clinically, alcohol abuse still needs to be ruled out as the cause of acute pancreatitis whenever hypertriglyceridemia is diagnosed [21,22]. Patients with familial chylomicronemia syndrome (FCS), a rare autosomal-recessive disorder characterized by a loss of lipoprotein lipase (LPL) activity due to inactivating mutations of the *LPL* gene or genes encoding for proteins that regulate LPL activity such as apolipoproteins C-II and A-5 (*APOC2*, *APOA5*), glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (*GPIHBP1*), and lipase maturation factor 1 (*LMF1*), have an increased risk of recurrent acute pancreatitis resulting from an excessive increase of plasma triglycerides by more than 10 to 100 times above the normal level [23].

Diagnosis of hypertriglyceridemia-induced pancreatitis needs to be established early after disease onset because serum triglycerides levels usually fall rapidly after fasting periods and hypocaloric intravenous volume therapy [21].

It still remains controversial whether hypertriglyceridemia-induced pancreatitis tends to have a more severe course. Some data indicate that severe acute pancreatitis and organ complications may be more frequent in the presence of hypertriglyceridemia [22].

Initial treatment of hypertriglyceridemia-induced pancreatitis is the same as for other etiologies and includes fluid resuscitation, analgesia, and controlled oral food intake. In cases of severe acute pancreatitis and sustained excessive elevation of triglyceride levels lipid apheresis might be considered as a therapeutic option but a clear benefit has not been consistently shown [24]. Emphasis should be laid on lifestyle modifications and lipid-lowering agents, fibrates in the first line, to prevent further attacks of pancreatitis [14]. In patients with FCS, a therapy with volanesorsen, an antisense oligonucleotide targeting APOC3 mRNA can be used as an adjunct therapy when conventional triglyceride lowering agents failed [23].

Diabetic Ketoacidosis

Acute pancreatitis can arise as a severe complication of diabetic ketoacidosis (DKA) with a risk of high mortality. Unfortunately, it is often overlooked because abdominal pain or peritoneal irritation can result from ketoacidosis and hyperlipasemia/-amylasemia might be unspecifically elevated. Acute pancreatitis occurs in at least

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10–15% of patients with DKA [20]. It has also been reported during non-ketoacidotic hyperosmolar coma but this is very rare. The pathogenesis of acute pancreatitis in DKA is often attributed to hypertriglyceridemia that frequently occurs in parallel. Normally, hypertriglyceridemia is transient and resolves once DKA is corrected [20]. Insulin, fluid resuscitation under control of glucose, and electrolyte balance are key elements in the management of DKA. Plasmapheresis is used in refractory cases complicated by severe hypertriglyceridemia.

Bariatric Surgery

The number of bariatric surgeries performed annually is constantly growing. Besides weight loss an improvement of obesity-associated metabolic diseases is becoming a relevant intention. In the context of acute pancreatitis, it is noteworthy that there is some evidence of so-called "post-bariatric pancreatitis." Currently, a few case reports of post-bariatric pancreatitis as an early complication following laparoscopic gastric bypass or sleeve gastrectomy exist. Consistently in these cases, pancreatitis developed within a few days after surgery. Intraoperative manipulation of peripancreatic tissue, compromised pancreatic microcirculation, edema, and spasm of major papilla as well as small bowel or outlet obstruction caused by blood clots have been suggested as triggers. Since pancreatitis as a short-term complication of bariatric surgery is rarely seen, the exact mechanisms remain to be elucidated. Data from a historical cohort of patients who underwent Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding, and revisional procedures showed a higher incidence of acute pancreatitis than in the general population [25]. The risk of acute pancreatitis is higher after vertical sleeve gastrectomy compared to Roux-en-Y gastric bypass surgery [26]. However, it is believed that this risk increase is primarily driven by biliary disease caused by sludge or gallstones as a result of rapid post-surgery weight loss, especially after sleeve gastrectomy. Hence, post-bariatric pancreatitis is likely seen exclusively as an acute complication after surgery, whereas in the longer term, pancreatitis may be caused by other and more common etiologies, first of all biliary.

Infectious Diseases

Data regarding the influence of microorganisms on acute pancreatitis and their incidence are rare and almost exclusively based on case reports. Sometimes it is not entirely clear whether other causes have been ruled out. Patients with acute pancreatitis based on an infectious agent often have a coexistent immunocompromising disorder or diabetes. The microbes involved include bacteria, viruses, fungi, and parasites (Table 22.1) [27].

Bacteria

Numerous bacterial pathogens have been mentioned as causing acute pancreatitis but mostly they are described in single case presentations. Reports exist on *Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*, *Campylobacter*, and *Brucella* species as well as *Mycobacteria tuberculosis*. The pathogenesis of acute pancreatitis is most likely related to released bacterial toxins. Antimicrobial treatment was initiated upon diagnosis of bacteria-related acute pancreatitis in the majority of cases. However, some reports mention a resolution of pancreatitis with only symptomatic treatment.

Viruses

Of all the infectious agents, most reports exist on mumps virus and its relation to acute pancreatitis. Paramyxovirus causes mumps and although this disease usually has a

Table 22.1 Infectious agents associated with acute pancreatitis.

Bacteria	Viruses	Fungi	Parasites
Mycoplasma pneumoniae	*Paramyxovirus*	*Candida* spp.	*Ascaris lumbricoides*
Legionella pneumophila	*Hepatitis virus A-C, E*	*Aspergillus*	*Toxoplasma gondii*
Salmonella enteriditis	*Human immunodeficiency virus (HIV)*		*Cryptosporidium parvum*
Campylobacter jejuni	*Varicella zoster virus* *coxsackie virus*		*Plasmodium falciparum*
Leptospira interrogans	*Herpes simplex virus*		*Strongyloides stercostalis*
Brucella melitensis	*Cytomegalievirus*		*Fasciola hepatica*
Mycobacterium tuberculosis	*Influenza virus (H1N1)*		
	Coronavirus (SARS-CoV-2)		

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mild course, pancreatitis was reported in around 4% of mumps patients [28,29].

The association between hepatitis A, B, and C viruses and acute pancreatitis has also been described. Hepatitis E infections are increasingly diagnosed in Western countries and reports on associated acute pancreatitis have been published [30]. Acute pancreatitis usually has a favorable outcome when related to viral hepatitis.

Human immunodeficiency virus (HIV)-positive patients with the diagnosis of acquired immune deficiency syndrome (AIDS) are also at risk for acute pancreatitis. So far, data are not conclusive whether these patients suffer from a more severe course of the disease. Severe acute pancreatitis was reported in 10–50% of patients with AIDS [31]. Modern therapeutic regimens for HIV/AIDS are associated with a much lower incidence of acute pancreatitis and a lesser degree of severity than earlier regimes that included the use of high pentamidine and didanosine concentrations.

In humans, group B coxsackie virus infections affect many organs including the heart, the central nervous system, and the pancreas. In addition, the association of this member of the picornaviridae family with acute pancreatitis has already been investigated in experimental animal models.

Gastrointestinal symptoms are observed in patients infected by severe acute respiratory distress coronavirus 2 (SARS-CoV-2). So far, small retrospective and case-control studies suggest that acute pancreatitis is an infrequent complication of COVID-19 infection and the proposed underlying pathomechanisms seem to make this association plausible. However, a true increase in the incidence of acute pancreatitis during the COVID-19 pandemic has not been firmly demonstrated [32]. Moreover, diagnosis of acute pancreatitis must be clearly differentiated from a sole elevation of serum pancreatic enzymes, which occurs more frequently [33]. Cytotoxic effects, disturbed immune reactions, a penetration of SARS-CoV-2 mediated by ACE2 receptors to the pancreas and virus-associated coagulopathies are currently being discussed as causative mechanisms.

Other suspected viruses include varicella zoster virus, causing chickenpox [34], influenza [35], herpes simplex, Epstein–Barr, and cytomegalovirus [27].

Fungi

Data on fungal infections causing acute pancreatitis are extremely rare; more often fungi manifest as a late infectious complication of severe acute pancreatitis with infected necrosis. Among them *Candida* spp. is the most common fungal microorganism that is seen secondary to pancreatitis [36]. *Aspergillus* species are discussed as a potential causative agent for pancreatitis as well [27]. Most fungal infections involving the pancreas are superinfections of pancreatic or extrapancreatic necrosis and thus secondary events. Once they occur they have a negative effect on outcome and mortality. Prior antibiotic treatment of (bacterially) infected necrosis does not appear to increase the rate of fungal infection of necrosis.

Parasites

Some case reports exist on acute pancreatitis caused by *Toxoplasma*, *Cryptosporidium*, *Ascaris*, *Plasmodium falciparum* infections, or helminths (*Strongyloides*). An immunomediated mechanism is discussed as being the underlying mechanism but even immunocompetent individuals can develop pancreatitis. For parasites such as *Ascaris lumbricoides*, *Fasciola hepatica*, and *Clonorchis sinensis* the disease mechanism is identical to that of gallstone-induced pancreatitis: impaction in the duodenal papilla and obstruction of the pancreatic duct. They account for up to 5% of cases of "biliary" pancreatitis in some parts of Asia and China and endoscopic removal of the parasite from the papilla remains the therapy of choice.

Drug-Related Diseases

According to the World Health Organization (WHO) more than 525 drugs have been reported to cause acute pancreatitis as a potential side-effect. It is expected that the number of medications will increase in parallel with the approval of new drugs and accumulating case reports [37]. However, the level of evidence differs as knowledge is essentially extrapolated from case reports with varying strength in quality [38]. By definition, case reports only produce the lowest level of evidence in epidemiologic studies. Moreover, drug-related acute pancreatitis is usually not accompanied by other clinical or laboratory signs of adverse drug reactions such as a rash, lymphadenopathy, or eosinophilia. Therefore diagnosis is often difficult to establish [39]. A rechallenge with the suspected drug and induction of an additional attack of pancreatitis (after initial withdrawal) allows researchers to conclude potential causality but is not definitive proof. Apart from this challenge, ethical considerations limit the use of re-exposure to a drug in order to trigger a second attack of pancreatitis with its potential complications. The incidence of drug-induced pancreatitis is low and is estimated to account for 0.1–2% of all cases [40,41]. Very young and older people, women, and patients suffering from immunosuppressive disorders (such as HIV) or inflammatory bowel disorders are at higher risk. Risk increases in these groups by up to fourfold and is most probably based on immune-mediated

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reactions and the type of drugs prescribed for these disorders [37,38,42].

There are many different ways currently in use to classify drugs according to their risk of causing adverse events. With regard to acute pancreatitis the classification model of Badalov and coworkers from 2007 is currently the most frequently used. It subdivides drugs into four groups (class I–IV), based on the quality of published evidence for each agent reported as having caused acute pancreatitis [43]:

- *Class I*: Group with highest level of evidence and the presence of a positive rechallenge test for the drug. Class I drugs can be further subdivided into those in which other potential causes for acute pancreatitis (i.e., alcohol, gallstones, hypertriglyceridemia) have been ruled out (Ia) and those where other causes were not excluded in the relevant reports (Ib).
- *Class II*: At least four case reports for the particular drug are required. In addition, ≥75% of the cases must show a consistent drug latency, meaning that time of onset of pancreatitis is within a reasonable time frame after drug consumption. The mean interval between initial drug intake and start of symptoms is around 5 weeks, with a wide range of 2 to 36 weeks [44].
- *Class III*: At least two case reports exist but there is neither a consistent latency among the cases nor a published rechallenge test.
- *Class IV*: Weakest level of evidence based on a single case report, no rechallenge test was done.

Alternatively, drug-related adverse effects are classified by application of the Bradford Hill criteria. Nine different criteria evaluate the evidence of causation and one of them is the claim for biologic plausibility, meaning that the proposed causality must have been shown in an experimental laboratory setting [45].

A third classification system groups drugs according to a definite, probable, or possible causality for an adverse reaction. The main characteristics include: (i) a reasonable temporal relationship from drug intake to onset of symptoms, (ii) a known underlying pharmacologic mechanism, (iii) presence or absence of other causes for the particular side-effect, and (iv) recurrent disease after rechallenge [46]. Depending on the quality of the case report, it can happen that a suspected medication might be classified once as a definite and once as a probable risk factor [38].

To assess the probability of a causal relationship between a drug and an adverse event, also the Naranjo criteria can be used. Besides questions on existing conclusive reports on the specific drug reaction, assessment of symptoms after drug discontinuation, and information on serum concentrations of the drug, this algorithm also considers whether alternate causes of acute pancreatitis have been excluded [47].

The underlying mechanism of drug injury on the pancreas is likely based on idiosyncratic reactions. This type of reaction is characterized as being unpredictable, dose-independent, and with varying latency. From a pathophysiologic point of view idiosyncratic reactions are often mediated by an immunologic or cytotoxic mechanism of the specific compound or its metabolites. Unfortunately, they are difficult to reproduce in experimental animal models, whereas effects of intrinsic toxicity are mimicked more easily. Intrinsic toxicity implies organ damage in a dose-dependent way and is usually seen as toxicity after drug overdoses. With regard to the pancreas there are only a few reports based on an intrinsic mechanism covering acetaminophen, erythromycin, and carbamazepine [43]. A list of drugs often named in association with acute pancreatitis is given in Table 22.2.

In addition, some of the most frequently cited drugs and their corresponding potential pathophysiologic mechanisms are discussed here.

Nonsteroidal anti-inflammatory drugs (NSAID) have been proposed to induce acute pancreatitis, probably due to inhibition of prostaglandins. Prostaglandins seem to have a protective and membrane-stabilizing effect on pancreatic cells, as shown in experimental models [37,48]. The highest risks were reported for diclofenac (odds ratio [OR] 5.0) and the lowest for naproxen (OR 1.1). Use of selective COX-2 inhibitors can lower the risk for acute pancreatitis [38,49]. Conversely, given prophylactically as suppositories unselective NSAID have been shown to lower the rate of endoscopic cholangiopancreatography (ERCP)-induced pancreatitis, at least in very high-risk patients.

Estrogens, which are also used in oral contraceptives, may induce acute pancreatitis by reducing lipoprotein lipase activity, which then increases serum triglycerides and fatty acids. These components are known to be precipitating factors for acute pancreatitis [50].

Angiotensin-converting enzyme (ACE) inhibitors such as captopril, enalapril, lisinopril, and others decrease degradation of bradykinins that are released during acute pancreatitis. Bradykinins cause a local angioedema that could favor tissue edema or pancreatic duct obstruction and subsequent organ damage. There is also evidence for a direct toxic effect of ACE inhibitors on the pancreas [51,52].

Several studies report on the side-effects of azathioprine and 6-mercaptopurine, and these include acute pancreatitis. Interestingly azathioprine-induced pancreatitis is nearly never reported outside the field of inflammatory bowel disease (IBD), especially Crohn's disease [38]. Presumably the drug's toxicity is associated with the underlying disease. Affected individuals carry an up to 8- to 13-fold increased risk of acute pancreatitis [53,54]. With regard to 6-mercaptopurine, 3.25% to 6% of patients with IBD being treated with that drug develop acute

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Table 22.2 List of drugs with association to acute pancreatitis.

Definite association	Probable association
Asparaginase	Cyclopenthiazide
Azathioprin	Oxaliplatin
Carbamazepine	Mesalazine
Cytarabine	Rifampin
Didanosine	Octreotide
Enalapril	Metformin
Erythromycin	Hydrochlorothiazide
Estrogens	Propofol
Furosemide	Tamoxifen
Lamivudine	
Mercaptopurine	
Mesalamine	
Opiates	
Pentamidine	
Pravastatin	
Steroids	
Sulfasalzine	
Trimethoprim/Sulfmethaxazole	
Tetracycline	
Valproic acid	
Immune checkpoint inhibitors	

Source: Adapted from Nitsche C et al., Curr Gastroenterol Rep 2012 and Hung WY et al., 2014.

pancreatitis [55,56]. It is noteworthy that 5-aminosalicylic acid (OR 0.7) and sulfasalazine (OR 1.5), which are also frequently used for IBD treatment, were not associated with significantly increased pancreatitis risk in a recent report [57].

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly known as statins), such as simvastatin, pravastatin, and atorvastatin are thought to have direct toxic effects and in a number of cases drug interactions involving cytochrome P450 3A4 (CYP3A4) seem to contribute to pancreatitis. However the overall risk for acute pancreatitis is rather low with an OR ranging from 1.01 to 2.02, so statins seem to be of low importance for drug-induced pancreatitis [58].

Nucleoside reverse transcriptase inhibitors such as didanosine, lamivudine, and stavudine have a toxic effect on the pancreas. In addition they cause metabolic disturbances [52]. HIV patients with a low CD4 count are at a higher risk [38].

Asparaginase is a cytostatic drug and commonly used for treatment of non-Hodgkin lymphoma and acute lymphoblastic leukemia. Asparaginase-associated acute pancreatitis was reported from 5–13 % in these therapies occurring in both children and adults with similar risk while pancreatitis-related complications were most frequently observed in adolescents. Re-administration of asparaginase is related with a high rate (up to 44%) of recurrence of acute pancreatitis and therefore should be carefully considered before rechallenging [59].

Consumption of valproic acid or other anti-epileptic drugs is associated with an increased risk for acute pancreatitis, presumably mediated by direct toxic effects and an increase of reactive oxygen species [38,52]. According to recent studies and in contrast to older reports, selective serotonin reuptake inhibitors (SSRI) do not increase the risk of acute pancreatitis [60].

Soon after introduction of incretin mimetics (glucagon-like peptide-1 [GLP-1] agonists) safety concerns arose about the potential of acute pancreatitis as a side-effect, especially for exenatide and sitagliptin. Reports were also released on dipeptidyl-peptidase-4 (DPP-4) inhibitors [61,62]. Recent analyses failed to find an unequivocal effect on the incidence of pancreatitis and were explained by the fact that people with diabetes already are at increased risk of developing acute pancreatitis [37,63,64]. A higher prevalence of gallstone disease or hypertriglyceridemia is also seen in this patient group [65]. Summing up, the role of incretin mimetics is not conclusively answered: preexisting risk factors such as diabetes mellitus and cardiovascular disorders explain most pancreatitis cases in this group and the large safety trials on DPP-4 inhibitors have largely calmed the initial concerns about an association with pancreatitis.

Immune checkpoint inhibitors are directed against cytotoxic T-lymphocyte-associated-antigen 4 (CTLA4), programmed cell death protein 1 (PD-1) or its ligand 1 (PD-L1), which are expressed on T cells, antigen presenting and tumor cells, respectively. They are increasingly used for treatment of a growing number of malignant tumors and for some entities combinations of checkpoint inhibitors exist. Due to the higher number of prescriptions immune-related adverse events are observed more frequently. Pancreatic injury is observed in up to 4% of patients being treated with immune checkpoint inhibitors [66], most often manifested by an asymptomatic increase of serum lipase and amylase but occasionally also by acute pancreatitis. Treatment consists of discontinuation and in severe cases of immune-mediated reactions steroid treatment is required.

Very few case reports exist on drug-induced acute pancreatitis after penicillin-type antibiotics and these

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belong to class IV group because usually no rechallenge has been done after discontinuation of the medication [67].

For all drug-associated forms of pancreatitis management consists of drug discontinuation and supportive care, as for other types of acute pancreatitis. If necessary, a drug of a different class will be selected for further therapy. However, drug-induced pancreatitis remains a rare entity and physicians should at first rule out other causes as at least one underlying condition predisposing to acute pancreatitis is found in almost half of the patients [68]. These include occult gallstone disease, immoderate alcohol consumption, and underlying genetic changes. A critical review of the patient's medication profile is mandatory before assuming a drug to be causative for pancreatitis.

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23

Radiologic Diagnosis and Staging of Severe Acute Pancreatitis

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Introduction

The role of imaging is important in diagnosis and evaluation of severity in patients with known or suspected acute pancreatitis. Common imaging techniques for the evaluation of the pancreas include transabdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Angiography and positron emission tomography (PET)-CT are sometimes used to diagnose special complications in acute pancreatitis patients. This chapter deals with these imaging techniques in the diagnosis of local and systemic inflammation associated with acute pancreatitis.

Classification of Acute Pancreatitis

Acute pancreatitis represents a spectrum of inflammatory disease ranging from clinically mild to severe acute pancreatitis [1]. In recent years a radiological approach has been commonly used to diagnose acute pancreatitis and evaluate severity. For these purposes, CT is one of the most popular methods. Abdominal CT has been commercially available since the 1970s.

In 1983, Kivisaari et al. reported that pancreatic necrosis in acute pancreatitis could be diagnosed using CT [2]. Bradley et al. [3] and Johnson et al. [4] also reported the usefulness of CT in diagnosis of pancreatic necrosis in acute pancreatitis patients, in 1989 and 1991, respectively. These studies regarded pancreatic necrosis as one of the most important factors in predicting a poor prognosis (Table 23.1).

In contrast, based on broadening of inflammation, Balthazar et al. [5] established a CT grading system to define the severity of acute pancreatitis in 1985. This is called Balthazar's CT grade, and it became one of the most popular image-based grading systems of severity of acute pancreatitis. It was partially modified in 2002 [6]. In 1985 the Balthazar system classified acute pancreatitis into five grades: A—normal, B—focal or diffuse enlargement of the pancreas, C—peripancreatic inflammation with intrinsic pancreatic abnormalities, D—intra- or extrapancreatic fluid collections, and E—two or more large collections of gas in the pancreas or retroperitoneum. In the 2002 version, grades D and E were modified: D—single fluid collection and E—two or more fluid collections and/or retroperitoneal air, respectively.

The two concepts that assist in diagnosis—local pancreatic damage and evaluation of broadening of inflammation—were combined into the CT severity index to predict prognosis (see section on CT severity index later in this chapter).

According to these moves to diagnose and evaluate acute pancreatitis using CT, a newer classification of acute pancreatitis was discussed at the Atlanta conference in 1992 [7]. In Atlanta, following previous symposia [8–10], severity of acute pancreatitis was classified into two grades: mild and severe. In this classification, severe acute pancreatitis was associated with organ failure and/or local complications, such as pancreatic necrosis, pancreatic fluid collection, acute pseudocyst, or pancreatic abscess. Since it was considered that CT could diagnose these local complications accurately, descriptions of the Atlanta classification were largely devoted to diagnostic criteria of local complications on CT. Following this symposium, radiological findings associated with acute pancreatitis were described in medical reports based on these terminological definitions.

The Atlanta classification was universally applied for two decades from 1992. During these two decades, two important insights were reported. First, Casas et al. reported that the early CT, which was performed within

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Table 23.1 Diagnostic criteria of pancreatic necrosis and their accuracy.

Study	*n*	Timing of performing CT	Scanning protocol	Diagnostic criteria	Accuracy for diagnosis of pancreatic necrosis	
					Sensitivity	Specificity
Kivisaari 1983 [2]	28	<1 day from administration	NC + CE-CT	<15 HU[a]	100	–
Block 1986 [29]	77	–	CE-CT	–	85	50
Nuutinen 1988 [30]	28	–	NC + CE-CT	<30 HU[b]	–	–
Bradley 1989 [3]	37	<2 days from administration	CE-CT	<40 HU[b]	–	–
Larvin 1990 [31]	60	<7 days from administration	CE-CT	<30 HU[b]	–	–
Johnson 1991 [4]	13	<3 days from administration	CE-CT	Lack of enhancement	100	100
Bradley 1993 [7][c]	–	–	CE-CT	<50 HU[b] or comparison to splenic enhancement	–	–
Casas 2004 [11]	184	<3 days from the onset	CE-CT	–	53	90
Takeda 2005 [27]	102	<7 days from the onset	CE-CT	Lack of enhancement	–	–
Tsuji 2007 [32]	30	<3 days from the onset	Perfusion CT	Comparison of hepatic perfusion	100	95.3
Spanier 2010 [33]	166	–	–	–	0	–
Tsuji 2014 [34]	48	<3 days from the onset	CE-CT	Lack of enhancement	74.5 (64–82)[d]	87.5 (78–97)[d]
			NC + CE-CT		77.5 (64–91)[d]	88 (81–97)[d]
			CE + sub-CT	<15 HU[a]	91 (82–100)[d]	94.7 (89–100)[d]
Yadav 2015 [35]	32	<3 days from the onset	Perfusion CT	PBF <23 mL/100 mL/min	87.5	100
Pienkowska 2016 [36]	79	<1 day from the onset	Perfusion CT	Permeability <40 mL/100 mL/min	100	84.2

NC: noncontrast; CE: contrast-enhanced; sub-CT: subtraction color map based on duel energy CT; PBF: pancreatic blood flow; –: not described.
[a] Difference of CT values between pre- and postinjection of contrast agent.
[b] CT values of postinjection of contrast agent.
[c] Atlanta criteria.
[d] Average values among three reviewer (minimum–maximum).

3 days from the onset, could not diagnose pancreatic necrosis accurately [11]. Second, a new concept, "walled-off necrosis (WON)," was proposed [12,13]. Early pancreatic complications (e.g., pancreatic and peripancreatic necrosis) could develop WON 4 weeks later than the onset. The concept of "WON" has made meanings of pseudocysts different (Table 23.2). Our improved understanding of the pathophysiology of organ failure and necrotizing pancreatitis and their outcomes, as well as improved diagnostic imaging, have made it necessary to revise the Atlanta classification.

The Atlanta classification was also revised in 2012 [14]. According to this classification of acute pancreatitis, known as the "revised Atlanta classification," the severity of acute pancreatitis is categorized into three groups: mild, moderate severe, and severe. In patients without local and systemic complication, the severity is judged to be mild. Patients with local complication without organ failure or transient organ failure which can be controlled within 48 hours from induction of treatment are classified in the moderate severe group. Patients with organ failure that resists treatment resulting in persistence for 48 hours or more are classified as severe (Table 23.2).

At the same time as the revised Atlanta classification, the determinant-based classification [15] was also published by another group. As with the revised Atlanta classification, the aim of this classification was to revise the original Atlanta classification. However, the determinant-based classification regards (peri)pancreatic necrosis as the more important factor to predict prognosis, compared to the revised Atlanta classification. According to determinant-based classification, the severity of acute

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Table 23.2 Diagnosis of local complications on criteria.

Terminology on			Image on CT						
Atlanta criteria	**Revised Atlanta criteria**	**Determinant-based criteria**	**Location**	**Density**	**Wall**	**perfusion**	**Time from onset**	**Pathology**	**Late complication**
Pancreatic necrosis	ANC	(Peri) Pancreatic necrosis	Pancreatic	Heterogeneous and nonfluid density	None	None or less	<3 days	Ischemic tissue	Healing without necrosis or WON
						None	<4 weeks	Pancreatic necrosis	WON
			Peripancreatic					Fat necrosis	
Pancreatic fluid collection								Inflammatory tissue	Resolving
	APFC	Not described		Homogeneous fluid density				Sterile fluid	PPC
Acute pseudocyst	PPC				Well defined		≥4 weeks		
Pancreatic abscess								Infected fluid	
	WON			Heterogeneous with fluid and nonfluid density				Sterile	WON
								Infected	

ANC, acute necrotic collection; APFC, acute pancreatic fluid collection; PPC, pseudocyst; WON, walled-off necrosis.

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pancreatitis is categorized into four groups: mild, moderate, severe, and critical. If the patient has neither (peri) pancreatic necrosis nor organ failure, severity is judged to be mild. The patient with sterile (peri)pancreatic necrosis and/or transient organ failure is classified as moderate. The patient with infected necrosis or persistent organ failure (more than 48 hours from start of treatment) is classified into the severe group. The patient with both infected necrosis and persistent organ failure is classified into the critical group (Table 23.2).

Between the revised Atlanta and determinant-based classifications, there is a difference with regard to the radiological definition of pancreatic necrosis. According to determinant-based classifications, (peri)pancreatic necrosis is nonviable tissue without a radiologically defined wall. In contrast, the revised Atlanta classification makes categorizes pancreatic necrosis into two types according to a diagnosis of well-defined wall: acute necrotic collection (ANC) and WON (Table 23.2). In the determinant-based classification, there is no description with regard to necrotic tissue with radiologically well-defined wall, which was categorized into "acute pseudocyst or pancreatic abscess" and "pancreatic pseudocyst or walled-off necrosis" in the Atlanta and revised Atlanta classifications, respectively. Thus, it appears that the concept of pancreatic necrosis in the determinant-based classification is not the same as that in the revised Atlanta classification.

In both the revised Atlanta and determinant-based classifications, the development of persistent organ failure (48 hours or more from start of treatment) is needed to diagnose severe or critical acute pancreatitis. Thus, in the emergency room we can use only two grades of severity: mild or moderate. From this point of view, a patient with moderate acute pancreatitis is potentially at high risk of developing severe or critical acute pancreatitis. Accurate diagnosis of pancreatic necrosis is one of the most important factors to perform in the emergency room for appropriate triage based on the severity of recent classifications.

Radiographic Diagnosis of Severe Acute Pancreatitis

Two major types of acute pancreatitis are known: acute edematous and necrotizing pancreatitis [14]. Since the prognoses and strategies of treatment of these two are totally different, it is necessary to diagnose them accurately.

Acute Edematous Pancreatitis

According to Klöppel [16], the pancreas is enlarged without necrosis on gross pathology in acute edematous pancreatitis, although microscopic areas of parenchymal fat necrosis may also be found. Lack [17] stated that hemorrhage and intraparenchymal necrosis is absent in the pancreas. Importantly, in acute edematous pancreatitis, where fat necrosis does not come into contact with a blood vessel, it does not damage the vessel wall, leading to macroscopic pancreatic necrosis [16]. Thus contrast enhancement of pancreatic parenchyma is usually normal on contrast-enhanced CT (CE-CT). In addition, the revised Atlanta classification [14] described that CE-CT shows pancreatic swelling with relatively homogeneous enhancement in acute edematous pancreatitis (Fig. 23.1).

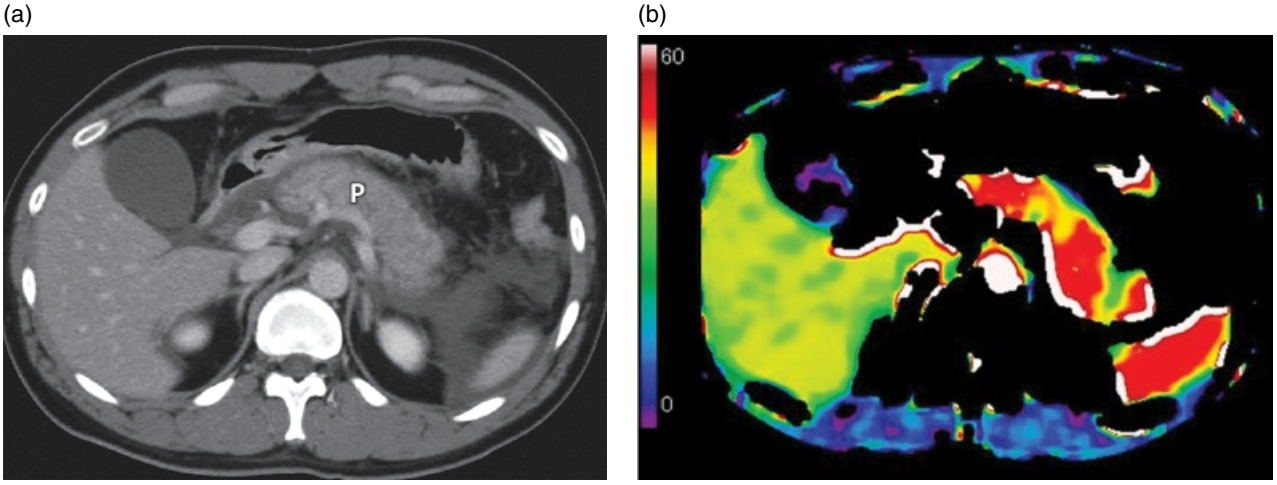


Figure 23.1 Acute edematous pancreatitis. (a) Contrast-enhanced CT shows enlargement of pancreas (P). At the same time as (a), perfusion CT was obtained. (b) Tissue blood flow was demonstrated based on the left-sided scale bar. Pancreatic blood flow was red-yellow (about 40 mL/100 g/min), which indicates that pancreatic blood flow was high.

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In the Atlanta classification [7], the macroscopic feature of mild acute pancreatitis was interstitial edema. Therefore, in those days, mild acute pancreatitis was nearly equal to acute edematous pancreatitis. One of the important things to note is that the revised Atlanta classification [14] changes the definition of mild acute pancreatitis to "pancreatitis with no organ failure and no local or systemic complications." In the revised Atlanta classification, local complications are redefined as acute peripancreatic fluid collection (APFC), pancreatic pseudocyst (PPC), acute necrotic collection (ANC), and walled-off necrosis (WOF). Thus, using the revised Atlanta, acute edematous pancreatitis with APFC, one of the local complications, is classified into moderate severe acute pancreatitis, not mild. The prognosis of patients with acute edematous pancreatitis is much better than that of those with local complication.

Acute Necrotizing Pancreatitis

Approximately 2–10% of acute pancreatitis patients develop necrosis of pancreatic parenchyma and/or peripancreatic tissue [14,18]. Both in the Atlanta and the revised, acute necrotizing pancreatitis is defined as "acute pancreatitis with pancreatic necrosis which involves pancreatic parenchymal necrosis and/or peripancreatic fat necrosis." Reports put the mortality rate for acute pancreatitis patients with pancreatic necrosis at roughly 30% [19].

Development of pancreatic parenchymal necrosis consists of three steps: acinar injury, vascular injury, and tissue injury. The initial pathway in the development of pancreatitis is ectopic activation of trypsinogen in acinar cells and/or activation of macrophages [20–23] or neutrophils [24]. The activation of trypsinogen in acinar cells leads to the acinar cells being destroyed, followed by releases of trypsin and damage-associated molecular pattern molecules (DAMP) [25] into the pancreatic vessels. Vascular epithelial cells are injured by the released trypsin and/or DAMP, resulting in damage to the coagulant–fibrinolytic system of the endothelial cells. In combination with this endothelial damage, periarterial fat necrosis, interstitial edema, and/or bleeding due to inflammation reduces tissue perfusion by compressing vessels. If this reduction of perfusion continues and/or ischemic–reperfusion damage occurs, serious tissue damage often develops, leading to acute necrotic collection (ANC) [26,27]. At 4 weeks or more later, ANC may develop WON. Since ANC and WON are irreversible, attempts to prevent the development of ANC or WON should be started based on a diagnosis of pancreatic ischemia [28] (see sections on acute necrotic collection and walled-off necrosis later).

To diagnose pancreatic necrosis (pancreatic ischemia, ANC, and WON), CE-CT, MRI, or CE-US are used. According to CE-CT criteria in the revised Atlanta classification, acute necrotizing pancreatitis is diagnosed based on lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or presence of peripancreatic necrosis (Table 23.1) [2–4,7,11,27,29–36].

Diagnosis of Local Complications of Acute Pancreatitis

As was described earlier, local complications are divided into four types: APFC, ANC, WON, and PPC in the revised Atlanta classification.

Acute Peripancreatic Fluid Collection

In the Atlanta classification [7], pancreatic fluid collections occurred early in the course of acute pancreatitis, were located in or near the pancreas and always lacked a wall of granulation or fibrous tissue. The precise composition of such collections was not known pathologically. Instead of the term "pancreatic fluid collections" [7], the use of the term APFC was suggested in the revised Atlanta classification [14]. APFC is peripancreatic fluid association with interstitial edematous pancreatitis and without necrosis. In CE-CT, APFC is a homogeneous collection with fluid density, without abnormal peripancreatic fascial planes, without defined wall encapsulating the collection, and without intrapancreatic extension (Table 23.2, Fig. 23.1).

Acute Necrotic Collection

ANC includes parenchymal necrosis of pancreas and peripancreatic fat necrosis. Thus, acute pancreatitis with ANC is the same as acute necrotizing pancreatitis. A collection contains variable amounts of both fluid and necrotic tissues. As was previously described, ANC is a pre-stage of developing WON. The border between ANC and normal tissue is gray (Fig. 23.2).

Parenchymal necrosis of pancreas appears as a low attenuation or non-enhancing area on CE-CT [4,5,37]. Early studies reported that CE-CT was highly accurate for the detection of pancreatic necrosis [3,4,29]. These studies mostly included surgical cases, so very few patients in the early stage of acute pancreatitis were included. Four previous studies reported the accuracy of CE-CT in predicting pancreatic necrosis in the early stages of acute pancreatitis [11,33,34,38]. One study showed that pancreatic necrosis was not detected in any of 49 patients with acute pancreatitis on CE-CT

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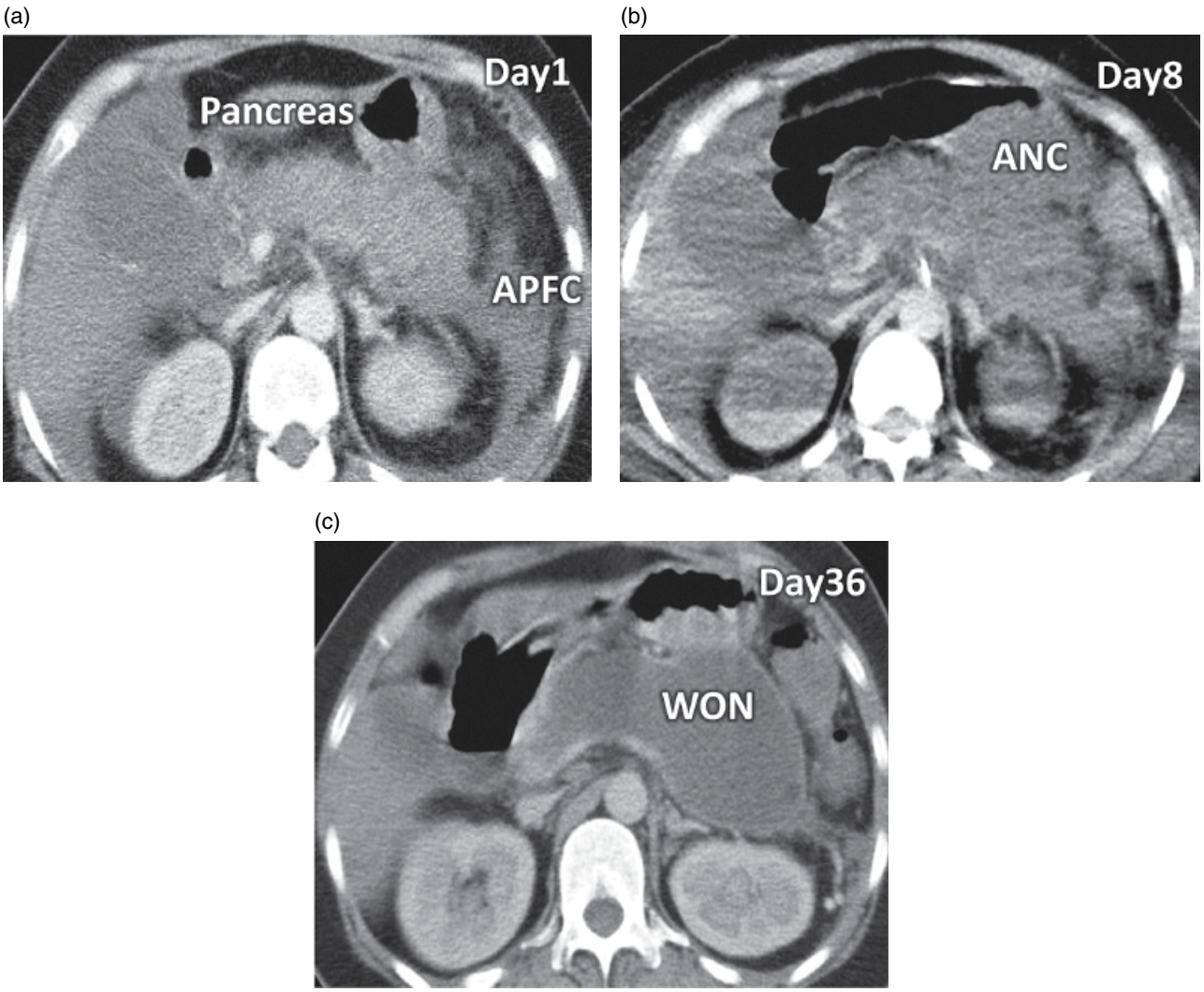


Figure 23.2 Acute necrotizing pancreatitis and its natural history. Due to serious complications of acute pancreatitis, this patient had three CT scans during the course of the disease. Contrast-enhanced CT shows homogeneous enhancement of pancreas at day 1 (a). On day 8 (b), enhancement of pancreas was markedly reduced, so this case was diagnosed as acute necrotizing pancreatitis. (c) On day 36, the scan shows acute necrotic collection (ANC) and altered walled-off necrosis (WON), which was surrounded by a well-defined wall.

performed within 72 hours of onset (sensitivity: 0%) [33], while the three other studies [11,34,38] showed that CE-CT had a sensitivity of 63%, 72%, and 75%, respectively, for the early phase of acute pancreatitis (within 1 day of admission or 72 hours of onset).

As Klöppel described previously [16], pancreatic inflammation can reduce pancreatic blood flow, resulting in development of pancreatic necrosis. Using angiography, Takeda also showed that pancreatic parenchyma with vasospasm of the intrapancreatic artery develops parenchymal necrosis with high ratio [27]. Perfusion CT [39,40], which can measure parenchymal blood flow accurately, has shown promise as a method that can accurately detect pancreatic necrosis at an early stage of acute pancreatitis with an estimated sensitivity of 88–100% and specificity of 84–100% [32,35,36] (Fig. 23.3). Perfusion CT can differentiate reversible from irreversible ischemic tissue, and thus has been used widely for diagnosing acute brain stroke (Fig. 23.1). According to Yadav et al. [35], pancreatic parenchyma with poor blood flow (cutoff value about 20 mL/100g/min or less and normal pancreas 100 mL/100g/min or more) could develop pancreatic necrosis with high ratio. At 24 hours from onset, Pienkowska et al. [36] showed that perfusion CT can predict development of pancreatic necrosis accurately. This suggests that the parenchymal blood flow is decreased even at an early stage of acute pancreatitis in areas of impending necrosis (Fig. 23.4 and 23.5).

Dynamic contrast-enhanced magnetic resonance imaging (CE-MRI) [41] may be an alternative to CE-CT

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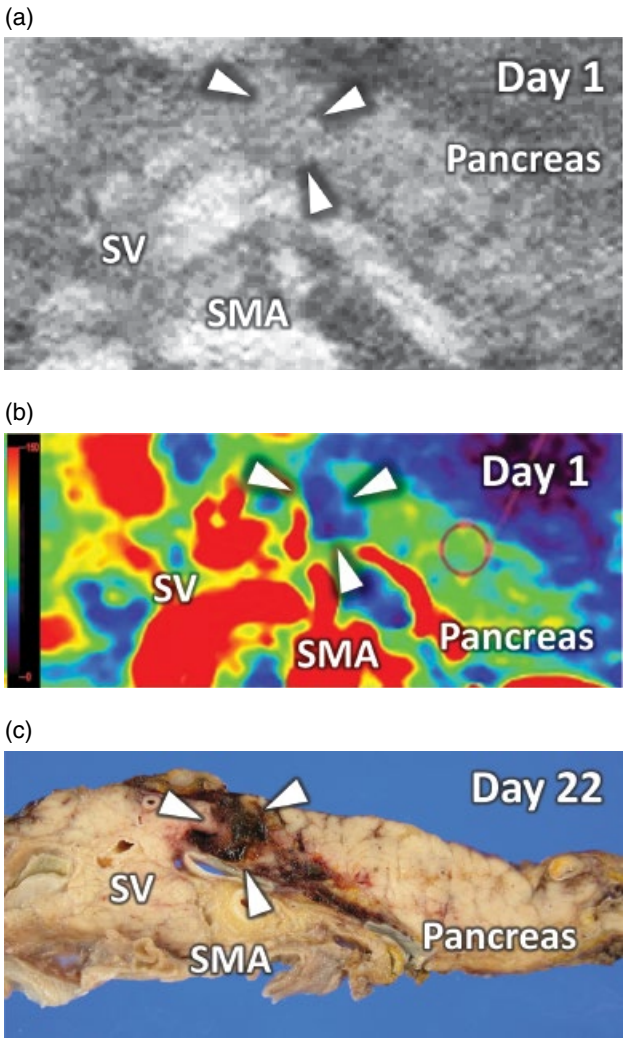


Figure 23.3 Difficulty in identifying pancreatic parenchymal necrosis using conventional CT. (a) Using contrast-enhanced CT (day 1), regional necrosis on the pancreatic head was not identified (arrowheads). (b) However, perfusion CT showed markedly reduction of pancreatic perfusion. (c) The poor perfusion area on perfusion CT (b) was concordant with an area of pancreatic necrosis at autopsy.

for detecting pancreatic necrosis. Indeed, MRI has certain advantages over conventional CE-CT, including greater sensitivity in detecting ischemia. Moreover, when MR angiography is performed in conjunction with MRI, assessment of vessel patency is also possible.

Walled-off Necrosis

WON is defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has a well-defined wall [12–14]. It arises secondary to ANC and usually occurs at >4 weeks after onset of acute pancreatitis. On CE-CT, WON often appears heterogeneous, with liquid and nonliquid density with varying degrees of loculations [14]. Ultrasound (both percutaneous and endoscopic) or MRI is better for diagnosing the heterogeneity of WON compared to CE-CT, because the identification of the liquid area in necrosis by MRI or ultrasound is more accurate than that by CE-CT.

Compared to ANC, WON has well-defined walls at marginal zone of necrosis, and therefore the border is clear. WON develops liquefaction of necrotic area heterogeneously and gradually [17]. Some areas of WON have inner walls, and WON can thus be separated into various sizes. In addition, WON develop in many areas, side by side or separately. Therefore, in acute pancreatitis patients with local complications, there is a possibility that many areas of WON will develop in the abdominal cavity.

In cases of suspected ANC/WON infection, rapid enlargement of the necrotic area, inflammatory changes in the neighboring fat, gas in the necrotic area, and surrounding paralytic ileus may help to diagnose the location of the infection (Fig. 23.6). One study suggests that PET-CT may be useful in identifying infected WON [42], although it is expensive.

Pancreatic Pseudocyst

It should be noted that the definition of the term PPC has recently changed. Previously, PPC included both WON and encapsulating fluid [7]. In the latest international classification, the revised Atlanta [14], PPC is redefined as an encapsulating collection of fluid with a well-defined inflammatory wall. PPC usually occurs more than 4 weeks after onset, as well as WON. Any solid region is not identified as PPC, thus (endoscopic) US or MRI is useful to diagnose it (Fig. 23.7).

Radiologic Staging of Severe Acute Pancreatitis

The concept of radiologic staging of severity of acute pancreatitis is based on two important findings: extent of inflammation and necrosis (ANC/WON).

CT Severity Index

Combining the findings of broadening of inflammation and local pancreatic damage on CT, the CT severity index (CTSI) was published in 2002. In the CTSI, Balthazar CT grade A (normal pancreas) scores 0, grade B (enlargement of pancreas) scores 1, grade C (inflammatory changes in pancreas and peripancreatic fat) scores 2, grade D (single fluid collection) scores 3, and grade E (two or more poorly defined fluid collections)

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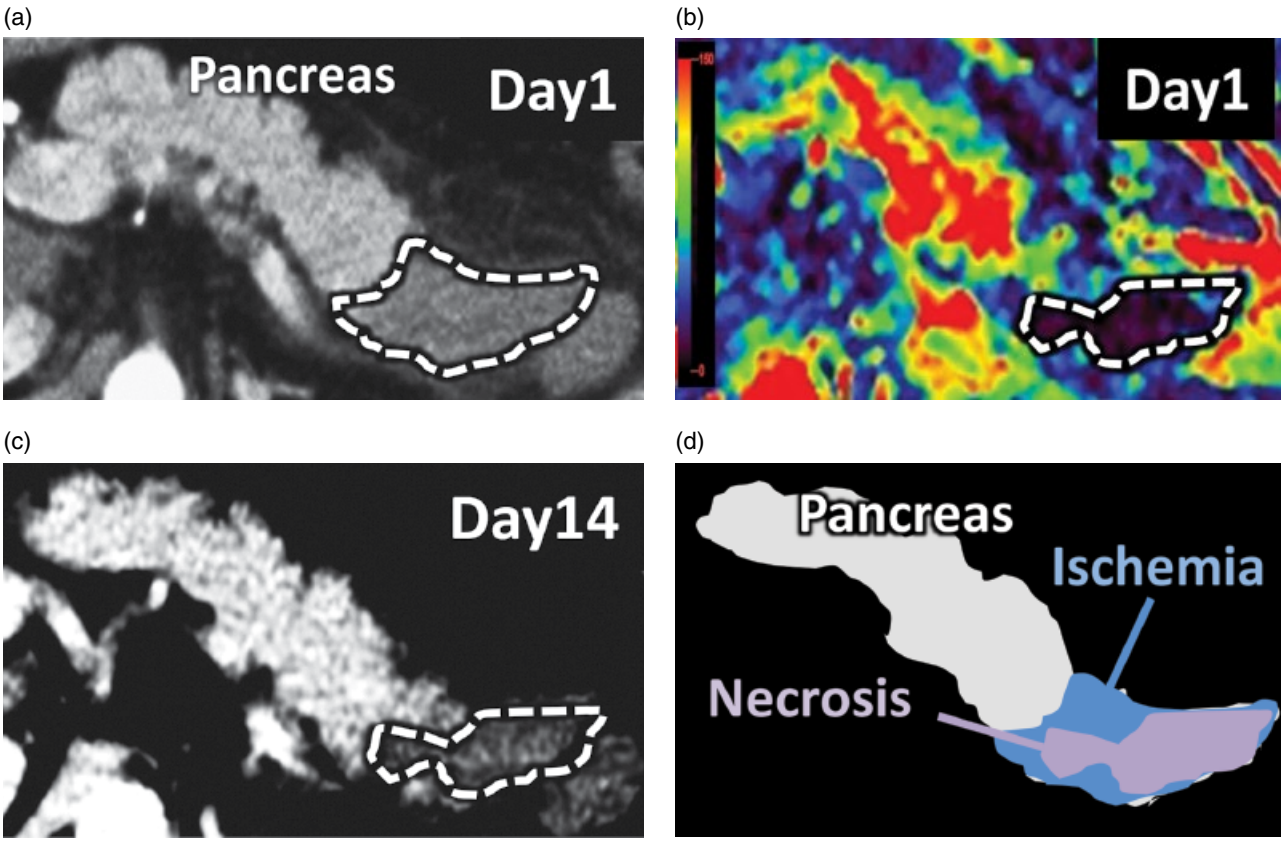


Figure 23.4 Reversible ischemia and necrosis in early stage of severe acute pancreatitis. (a) Contrast-enhanced CT (day 1) showed a lack of enhancement of the pancreatic tail (area surrounded by dotted line). (b) Perfusion CT showed a poorly perfused area in the pancreatic tail, which was smaller than the area with lack of enhancement on contrast-enhanced CT. (c) The area with poor perfusion in the perfusion CT developed pancreatic necrosis. (d) Based on these findings, the schema shows that the marginal zone of pancreatic necrosis could have been reversible ischemia.

scores 4. The pancreatic condition is independently evaluated: no pancreatic necrosis on CT scores 0, pancreatic necrosis less than/equal to 30% of pancreas scores 2, >30–50% scores 4, and >50% scores 6. Grading severity is based on a CTSI score of 0–10: mild (score 0–3), moderate (score 4–6), and severe (score 7–10) [5,6]. The CTSI was modified in 2004 by Mortele et al. (MD-CTSI) [43]. The MD-CTSI resulted in higher interobserver agreement ratio, correlation with length of hospital stay, need for invasive therapy, incident organ failure, and the occurrence of infection (Table 23.3).

Japanese CT Severity Index

In the latest Japanese definition of severe acute pancreatitis [44], Hiroto et al. established the JPN-CT severity score. In the definition, severe acute pancreatitis can be diagnosed either by the laboratory/clinical severity criteria or JPN-CT. The case mortality rate of patients with severe acute pancreatitis diagnosed by JPN-CT score was 14.8%. The case fatality of severe acute pancreatitis that fulfilled JPN-CT severity criteria (severity score ≥2 points) was as high as 30.8%.

Limitations and Pitfalls of Radiologic Diagnosis of Acute Pancreatitis

Diagnosis of Early Necrosis of Pancreatic Parenchyma

The accuracy of CE-CT to diagnose pancreatic parenchymal necrosis within 3 days of onset is not adequate [11,37]. One potential explanation for this disappointing performance of CE-CT is that the attenuation of pancreatic parenchymal necrosis is similar to that of viable enhancing parenchyma on CE-CT in the early stages of acute pancreatitis, and the CT attenuation of pancreatic necrosis decreases over time as nonviable parenchyma liquefies [12,31]. Moreover, because the CT

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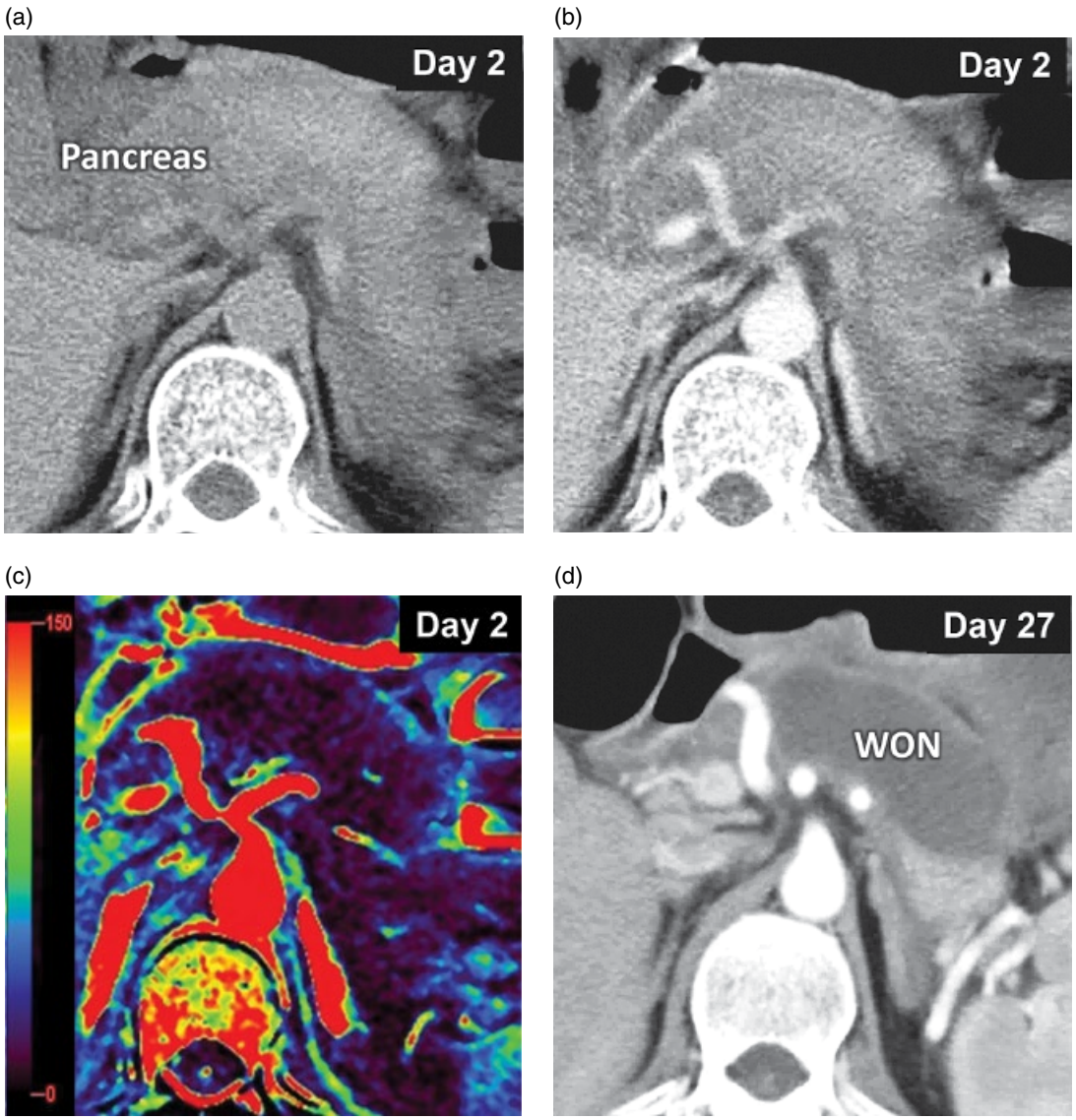


Figure 23.5 Tissue hemorrhage makes it difficult to diagnose necrosis using contrast-enhanced CT alone. (a) Noncontrast CT showed elevation of CT values in pancreatic body. (b) On CE-CT alone, it is difficult to judge whether the elevation of CT value of pancreatic parenchyma was due to hemorrhage or enhancement by contrast agent. (c) Perfusion CT showed that pancreatic blood flow of the whole pancreatic body was extremely low. These findings show that the pancreatic body had already developed necrosis on day 2. (d) The poorly perfused area with slight elevation of CT values on noncontrast CT was concordant with the area with later necrosis.

attenuation of pancreas may be altered by hemorrhage in necrosis or fatty infiltration, evaluation of regional variability in pancreatic enhancement becomes difficult with CE-CT. Another reason why CE-CT may not be accurate in predicting parenchymal necrosis in the early stages may involve the difficulty of evaluating the effectiveness of contrast-enhanced material. Since the border of early parenchymal necrosis that is included in the ANC is not clear, selecting specific of areas with suspicious parenchymal necrosis in the case of early acute pancreatitis poses difficulties, in contrast to analyses of enhancements in well-defined lesions, such as a WON.

Although the detection of pancreatic parenchymal necrosis with CT imaging has led to the improved prognostic stratification of patients using the CT severity index [45], the inaccurate prediction of parenchymal necrosis using CE-CT and its large interobserver variability [43,46] may also lead to recent recommendations questioning the routine use of CT at an early stage of acute pancreatitis [47,48].

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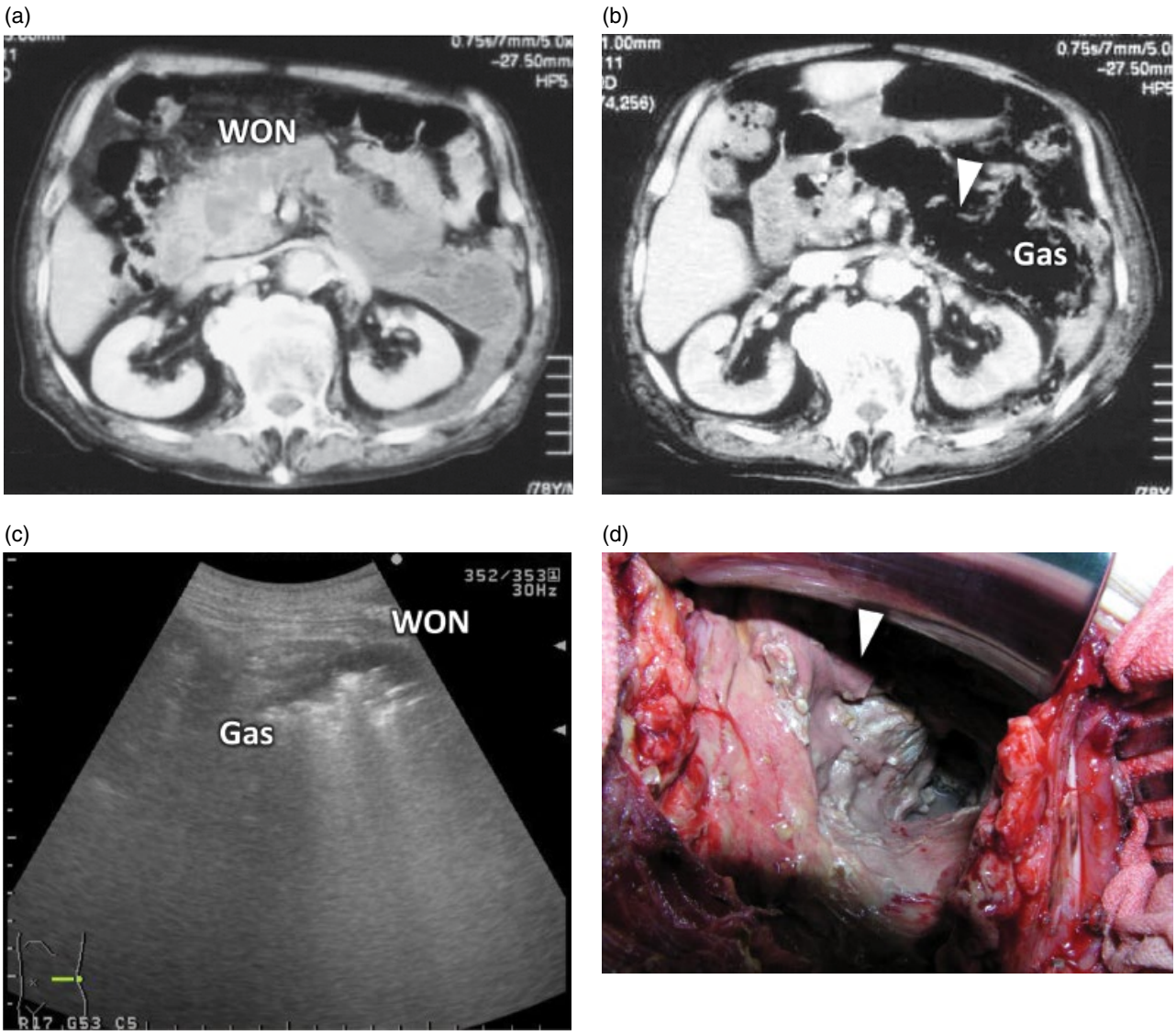


Figure 23.6 Infected walled-off necrosis (WON). (a) Presented case has WON on contrast-enhanced CT. (b) Most of the WON on the pancreas body and tail was replaced with gas, due to infection. In the gas cavity of WON, the inner wall (arrowhead) was detected. (c) Percutaneous ultrasound showed high spotty areas due to gas in WON. (d) Surgical treatment was performed and a part of the inner wall (arrowhead) was shown in the cavity. The patient recovered 6 months later.

Despite the advantages discussed earlier, MRI is underused in the evaluation of patients with severe acute pancreatitis. This underutilization can be attributed to practical considerations—patients with severe acute pancreatitis have difficulty withstanding the lengthy MRI procedure. In addition, removal of all the magnetic instruments (e.g., sphygmomanometer, saturation monitor, multiple infusion pumps, etc.), which cannot be taken away from patients with severe acute pancreatitis even for a short period, must be done before the procedure is performed.

Nephrotoxity of Contrast Material of CE-CT and CE-MRI

One of important systemic complications of acute pancreatitis is acute renal failure. Because CE-CT and dynamic CE-MRI has some nephrotoxicity, use of dynamic CE-MRI and CE-CT should be decided with care [41]. Perfusion CT is obtained from analysis of blood flow after a bolus injection of much less contrast materials (approximately 30–40%) than those used for conventional CE-CT [49]. Therefore, the nephrotoxity of

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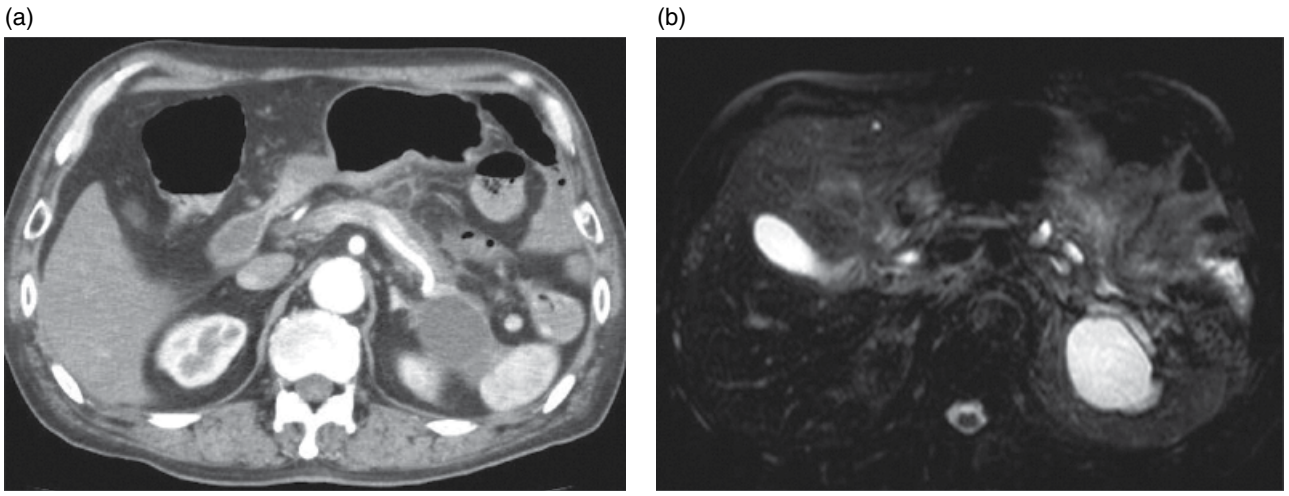


Figure 23.7 Pancreatic pseudocyst. (a) After 4 weeks from onset of acute pancreatitis, a low-density area with well-defined wall was identified by contrast-enhanced CT. (b) Using MRI (T2 weighted), a low-density area including liquid contents was identified, so the patient was diagnosed with pancreatic pseudocyst.

Table 23.3 Modified CT severity index.

Radiological findings	Points
Normal pancreas	0
Intrinsic pancreatic abnormalities with or without peripancreatic inflammatory change	2
Pancreatic/peripancreatic fluid collection or peripancreatic fat necrosis	4
Pancreatic necrosis	
None	0
≦30% gland necrosis	2
>30% gland necrosis	4
Extrapancreatic complications, i.e., pleural effusion, ascites, vascular or gastric involvement, parenchymal complications	2
CTSI score and disease severity of acute pancreatitis	
Score 0–3: mild	
Score 4–6: moderate	
Score 7–10: severe	

perfusion CT is lower than that of CE-CT and dynamic CE-MRI.

Rickes et al. have recently shown that CE-US [50], which does not have a bad effect on the kidney, can also be used to diagnose pancreatic parenchymal necrosis reliably. However, a whole pancreatic scan with ultrasound is often difficult, because a common complication of acute pancreatitis patients is paralytic ileus. Pancreatic parenchyma with inflammation is often surrounded by digestive canal with gas [14], and so the accuracy of ultrasound for evaluating severity of pancreatitis is limited.

Radiation Dose of CE-CT and Perfusion CT

The radiation doses of CE-CT and perfusion CT should not be ignored. However, recent techniques regarding noise reduction and registration make it possible to perform CE-CT and perfusion CT using much lower radiation dose protocols. Radiation doses used for recent pancreatic perfusion CT were lower than those used for triple phase CT [49,51].

Needs for Diagnosis of Pancreatic Necrosis in the Early Stage

As reported in a previous publication, neither APACHE II nor CE-CT give accurate predictions for patients in the early stages of acute pancreatitis [52]. Because of the absence of an ideal and established method for evaluating severity at an early stage, therapies often begin only after the patient has sustained serious damage. Since serious tissue damage (e.g., necrosis) may be irreversible, such treatments may be of limited benefit at later stages. Early and accurate predictions appear critical in establishing effective early care strategies. Accurate predictions of the severity may improve the accuracy of triage assignments and allow intensive treatment to begin earlier. Early inductions of aggressive fluid therapy [53] and enteral nutrition [54] may improve outcomes for patients with severe acute pancreatitis. Importantly, there is no strong evidence that early and accurate evaluations of severity can actually alter prognosis in acute pancreatitis. Prospective intervention trials based on early accurate predictive methods would be required to confirm this.

According to our study [55], new agent recombinant thrombomodulin could have reduce the risk of

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Table 23.4 Newer diagnostic instruction combining revised Atlanta criteria and JPN criteria.

	Edematous	APFC	ANC	WON > PPC	PPC > WON
CT	• homogenous-enhancing pancreatic parenchyma on CECT • no peripancreatic necrosis	• without defined wall encapsulating collection • homogenous collection with fluid density • without intrapancreatic extension • not stride peripancreatic fascial planes	• without defined wall encapsulating collection • heterogeneous with non-liquid density • continuous change from pancreas • homogenous collection in the early phase, occasionally	• mixed necrotic collection/fat necrosis as well as fluid collection • CT values are higher than water and heterogeneous • positive enhancement of wall high signal intensity • presence of parenchymal deformity	• mainly pancreatic fluid collection • CT values are close to water • often circular mass with low signal intensity
MRI		• high signal intensity on T2-weighted images	• low signal intensity on T1-weighted images	• heterogeneity signal intensity on T2-weighted images due to mixing of fluid and necrotic collection in MRI • septation • pancreatic duct discontinuity	• circular mass, low signal intensity on T1-weighted images, and high signal intensity on T2-weighted images • non-septational fluid collection • pancreatic duct dilation

APFC: acute pancreatic fluid collection; ANC: acute necrotic collection; WON: walled-off necrosis; PPC: pancreatic pseudocyst; CECT; contrast enhanced computed tomography CT: computed tomography; MRI: magnetic resonance imaging.

development of WON from ANC. Importantly, in this type of study, which investigated efficacy of early intervention, accurate diagnostic criteria of ANC would be needed in the early stage of acute pancreatitis. In this study, newer diagnostic instruction combining revised Atlanta criteria and JPN criteria was used (Table 23.4). This approach might be help to diagnose ANC early and accurately.

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24

Conservative Therapy of Acute Pancreatitis: Volume Substitution and Enteral and Parenteral Nutrition

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Introduction

Acute pancreatitis is an often devastating inflammatory condition of the pancreas that leads to extensive worldwide morbidity and mortality [1]. In fact, in the United States, acute pancreatitis is among the most common reasons for patients to be hospitalized for a digestive illness [2]. The substantial human costs of this disease, with billions in annual healthcare dollars spent worldwide, has led to extensive efforts to establish a pharmacologic treatment for this disease. Unfortunately, as of 2022, there is no specific medical therapy that specially targets acute pancreatitis or that has been useful to improve important clinical outcomes.

Over the past 50 years, extensive efforts have been made to develop targeted pharmaceutical therapies, but none have demonstrated benefit in randomized controlled trials. Agents directed at reducing pancreatic secretions, including histamine-2 blockers, such as cimetidine, glucagon, atropine, somatostatin and its analogue octreotide, do not reliably affect morbidity or mortality [3–5]. Antiprotease therapy with aprotinin and gabexate mesilate are equally ineffective, as is therapy with lexipafant, a platelet-activating factor antagonist [6,7].

Recently, as discussed elsewhere in this textbook, rectal nonsteroidal anti-inflammatory drugs (NSAID) have been demonstrated to be helpful in reducing the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis due to regulation of proinflammatory mediators. Rectal NSAID function by inhibiting phospholipase A2 activity, including arachidonic acid products and platelet-activating factors [8,9]. One NSAID in particular, rectal indomethacin, has been used extensively since 2012 following the publication of a randomized, placebo-controlled trial in patients undergoing ERCP considered to be at high risk for pancreatitis [9]. The trial found that a single 100 mg dose of rectal indomethacin significantly reduced the risk of pancreatitis from 16.9% in those receiving placebo to 9.2% in those receiving indomethacin.

However, with the exception of rectal indomethacin, there are currently no specific pharmacologic therapies advocated for the treatment of acute pancreatitis [10]. Supportive measures, including the use of fluid resuscitation, nutrition, and aggressive intensive care unit care, have become the cornerstone of conservative therapies in treating this disease.

This chapter focuses specifically on the conservative therapies of fluid resuscitation and enteral and parenteral nutrition. It will review the importance of the pancreatic microcirculation and its effects on the pathogenesis and prognosis of acute pancreatitis. It will discuss animal and human clinical trials that have evaluated the role of different types, volumes, and rates of fluid resuscitation. Finally, current recommendations in regard to administering fluids in acute pancreatitis will be provided. The latter aspect of the chapter will focus specifically on the role of enteral and parenteral nutrition in the treatment of acute pancreatitis, with a review of clinical trials and important recommendations for nutritional care on patients with this disease.

Fluid Resuscitation

The Pancreatic Microcirculation and Acute Pancreatitis

It is critically important to understand the intricacies of the pancreatic microcirculation when discussing the role of fluid resuscitation in acute pancreatitis. The arterial supply to the pancreas is derived from the two main proximal trunks of the aorta: the celiac trunk and superior

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mesenteric artery. The splenic and common hepatic arteries (as well as the left gastric artery, which does not supply the pancreas) arise from the celiac trunk. The splenic artery gives rise to the penetrating branches of the body and tail of the pancreas, while the common hepatic artery, via its branch the gastroduodenal artery, supplies the pancreatic head through the anterior and posterior superior pancreaticoduodenal arteries. The anterior and posterior inferior pancreaticoduodenal arteries, arising from the superior mesenteric artery, supply the head and neck of the pancreas, and form vascular anastomoses with the superior pancreaticoduodenal arteries. This vascular network features extensive collateralization, thus ensuring adequate pancreatic tissue perfusion.

From these large arteries arise the intralobular arteries, which run within the pancreas often parallel to the pancreatic ducts. The intralobular arteries give rise to the pancreatic microcirculation, a vast network of capillaries and venules that supply the pancreatic acinus with a rich blood supply [11]. An exocrine lobular plexus with multiple fine capillaries represents the basic vascular unit within the pancreas, and flow from the vascular plexus is almost 20 times more likely to prefer the pancreatic islet cells than the acinus. As a result, the pancreatic acinus is extremely prone to low vascular flow states when there is lack of circulating blood flow to the pancreas [12]. This susceptibility is why the pancreatic acinus can be so prone to damage with even a slight perturbation in systemic blood flow.

Disturbance to the blood flow within the pancreatic microcirculation due to acute pancreatitis can occur for several reasons: hypovolemia, increasing capillary permeability, and hypercoagulability causing microthrombi, among others [13–16]. The generation of oxidative free radicals with subsequent capillary endothelial damage has also been implicated. This alteration in microcirculation significantly increases the degree of pancreatic ischemia, irrespective of etiology, thus exacerbating the systemic inflammatory response syndrome (SIRS) and potentially leading to multisystem organ failure.

Once significant acinar blood flow has been disturbed, acinar cell injury occurs. Acinar cell injury then causes the release of multiple proinflammatory cytokines and vasoactive mediators, including tumor necrosis factor α, histamine, bradykinin, interleukin 1 (IL-1), IL-2, IL-6, platelet-activating factor, and endothelin-1, which are recruited to the pancreatic microcirculation and delivered to the acinar cells [17–19]. Once this proinflammatory cascade is set into motion, the systematic sequelae of acute pancreatitis, including the collapse of the systemic circulation leading to multisystem organ failure, can occur. Once initiated, this process is exceedingly difficult to reverse.

The role of aggressive fluid resuscitation is essentially to try to perfuse the acinar tissue sufficiently in the face of such overwhelming antagonism of the normal physiologic maintenance of adequate tissue perfusion pressure. Although fluid resuscitation by itself does not have an effect on the proinflammatory mediators leading to circulatory collapse, the sequelae of maintaining adequate tissue perfusion may seek to slow or ameliorate at least part of the inflammatory cascade. The hope for intravenous fluid resuscitation in acute pancreatitis is that adequate tissue perfusion will perfuse the pancreatic microcirculation so that pancreatic necrosis and its subsequent complications can be minimized or even prevented.

Animal Studies

There have been extensive animal studies in the pathophysiology and treatment of acute pancreatitis, specifically in regard to establishing a definitive pharmacologic therapy for blunting the proinflammatory content of this disease. However, despite the important role of fluid resuscitation in acute pancreatitis, relatively few animal studies have been exclusively devoted to this subject. The critical question asked by animal studies in acute pancreatitis are the same as in human studies: How much fluid should be given? What type of fluid should be given? Is colloid or crystalloid fluid a better choice? What are the complications of using overly aggressive fluid resuscitation?

Two animal studies have demonstrated the importance of aggressive fluid resuscitation, irrespective of the type of fluid utilized. Juvonen et al., using a pig model of Na-taurocholate-induced pancreatitis, showed that the signs of splanchnic hypoperfusion can be prevented with fluid resuscitation [20]. The investigators found that the PCO_2 gap increased and portal venous blood flow decreased in pigs with acute pancreatitis, but did improve significantly with resuscitation. Niederau et al. have also demonstrated in a choline-deficient, ethionine-supplemented diet mouse model that hydration by subcutaneous fluid markedly improved survival and normalized the hematocrit without having significant biochemical or morphologic effects [21].

Crystalloid resuscitation has been studied only sparingly in animal studies of acute pancreatitis. Knol et al. evaluated the effect of low and high infusion rates of lactated Ringer's solution in 14 dogs with bile trypsin pancreatitis [22]. They found that pancreatic blood flow decreased to a greater extent in the low infusion group compared to the high infusion group. Crystalloid resuscitation with a balanced salt solution adequately restored plasma volume, supported tissue perfusion and prevented excessive hemodilution without detrimental effects on pulmonary pressures or oxygenation in a canine model of acute hemorrhagic pancreatitis [23].

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The majority of animal studies dealing with fluid resuscitation have used colloid solutions, most notably dextran, and generally found improved outcomes compared with crystalloid resuscitation. One suspected reason for improved outcomes with colloids has been that they are not as permeable to leakage in the pancreatic microcirculation compared with crystalloids. By remaining in the luminal environment, circulatory blood flow is better maintained, and inflammatory mediators are less able to access the acinus [24–28].

Thus, in summary, animal studies have been relatively sparse, and the majority of these have been completed with colloid rather than crystalloid solutions. However, these studies have not been able to answer effectively the questions of which solution is most appropriate, what is the optimal rate of fluid resuscitation, and what are the consequences of overly aggressive resuscitation. Surprisingly, as detailed below, the clinical studies in humans have not appreciably answered these questions satisfactorily either.

Human Studies

Despite the universally accepted paradigm that aggressive fluid resuscitation is an important element of supportive care in acute pancreatitis that leads to improvements in important clinical outcomes, few studies and even fewer randomized controlled trials have been performed on this treatment. Questions about the rate of resuscitation, type of fluids, and consequences of over-aggressive resuscitation remain unanswered. However, in the last decade more attention had been focused on this important clinical area, and several randomized trials are planned to try to answer these critically important questions.

The original investigation in humans about the importance of aggressive fluid resuscitation was carried out by Baillargeon, Banks, and colleagues in the 1990s. They emphasized the importance of resuscitation in improving clinical outcomes. In a retrospective cohort study, they found that hemoconcentration with an admission hematocrit >47% or failure of admission hematocrit to decrease at approximately 24 hours were strong risk factors for the development of pancreatic necrosis [29]. Multiple subsequent studies have validated these findings, including the Banks group who performed a retrospective study to determine whether fluid resuscitation could prevent pancreatic necrosis among patients with hemoconcentration at the time of admission [30–35].

As these data suggest, inadequate fluid resuscitation leading to poor pancreatic microcirculatory perfusion has been associated with acute necrotizing pancreatitis [33]. Specifically, we now know that early fluid resuscitation has more of a therapeutic effect than delayed fluid resuscitation. Although early fluid resuscitation is generally agreed upon as an intervention of paramount importance, there are currently no standard guidelines on the optimal fluid type, volume, rate, or duration of treatment. Despite the lack of standard guidelines, studies on the rate and volume of fluid therapy suggest early aggressive fluid resuscitation results in the best outcomes. When compared to early nonaggressive (<500 mL) fluid resuscitation, early moderate (500–1000 mL) to aggressive (>1000 mL) fluid volume administration significantly reduces the need for invasive interventions, with some evidence suggesting a trend towards lower complications with early moderate to aggressive fluid resuscitation [36]. Although human studies on the rate of hydration consistently show decreased morbidity and mortality with aggressive hydration in the first 24 hours, the total volume of hydration at the 48-hour mark seems to have a limited effect on patient outcomes [36,37].

The current American College of Gastroenterology (ACG) guidelines recommend 250–500 mL/h of isotonic crystalloid solution in the first 12–24 hours, with frequent re-evaluation every 6 hours and an ultimate goal of decreasing the blood urea nitrogen (BUN) levels [38]. Some experts recommend that in addition to the 1–2 L fluid bolus given in the emergency department, the starting infusion should be at a rate of 250–300 mL/h or enough to produce a urine output of at least 0.5 mL/kg per hour [39]. The goal within the first 24 hours is a total infusion volume of 2.5–4 L, with adjustments to be made based on the patient's age, weight, physical exam, and comorbid conditions [40]. Similarly, the current American Gastroenterological Association Institute (AGA) guidelines advise using goal-directed therapy for fluid management but note to proceed judiciously so as to avoid potential complications from overly aggressive fluid resuscitation [41].

The type of resuscitation fluid has been minimally studied. However, in a widely cited manuscript, Wu et al. found that the use of lactated Ringer's solution, in place of normal saline, resulted in less SIRS and a decreased C-reactive protein at 48 hours [42]. However, the small sample size of 40 patients limits the study. Nevertheless, more recent randomized controlled trials substantiate these results. De-Madaria et al. compared lactated Ringer's solution to normal saline solution and found that lactated Ringer's led to less SIRS criteria and lower C-reactive protein levels than normal saline. *In vitro*, they also observed that lactated Ringer's inhibited both the activation of macrophages to their inflammatory phenotype and the activity of NF-κB, a transcription factor involved in inflammation, while normal saline and Ringer's solution without lactate did not inhibit such processes [43]. In another randomized controlled trial, Choosakul et al. revealed that lactated Ringer's solution significantly decreased SIRS compared to normal saline 24 hours after the development of acute pancreatitis but did not show any significant differences in SIRS at 48 hours [44].

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A meta-analysis conducted by Iqbal et al. confirmed these findings by demonstrating that lactated Ringer's solution resulted in lower rates of SIRS development compared to normal saline at 24 hours [45]. However, a randomized controlled trial conducted by Lee et al. found no significant difference in SIRS between normal saline and lactated Ringer's, but did reveal that lactated Ringer's resulted in a shorter length of stay and fewer ICU admissions than normal saline [46]. In patients undergoing ERCP, aggressive fluid resuscitation using lactated Ringer's solution has been demonstrated to be an effective deterrent for the development of post-ERCP pancreatitis [47]. Thus, although these patients are not in the same exact clinical scenario as patients not undergoing ERCP, these results do suggest that the use of lactated Ringer's solution has a beneficial effect.

The issue of over-aggressive hydration and risk of poor outcomes, particularly the development of abdominal compartment syndrome, has been highlighted by two studies. The first, a retrospective evaluation of 99 patients with severe acute pancreatitis in Sweden, determined that patients receiving 4000 mL or more of fluids during the first 24 hours ($n = 32$) developed more respiratory complications (66% vs. 53%; $P = 0.001$) than patients who received less than 4000 mL of fluid [48]. Mao et al. have also reported improved survival rates by controlling the amount of fluid resuscitation within the first 72 hours in 83 patients with severe pancreatitis [49]. In addition, in a randomized controlled trial of patients with predicted severe pancreatitis whose hematocrit was aggressively lowered upon admission, those with aggressive lowering of their hematocrit had greater morbidity and mortality [50]. A subsequent meta-analysis of aggressive vs. nonaggressive fluid therapy determined that although no statistically significant difference in mortality existed between the two groups, patients receiving aggressive fluid resuscitation possessed a higher risk for acute kidney injury, as well as acute respiratory distress syndrome [51].

Thus, although important inroads have been made into the role of aggressive fluid resuscitation in the critical issue of supporting the pancreatic microcirculation in acute pancreatitis, several questions remain—particularly how best to monitor the rate of resuscitation and at what point the critical juncture of over-resuscitation occurs. Lactated Ringer's solution appears to represent an important breakthrough in the type of crystalloid solution to be used in this regard but further randomized controlled trials stratifying by the type of crystalloid solution are necessary. Continued animal studies into the effects of crystalloid and colloid solutions on the pancreatic microcirculations are in order, as well as carefully designed human clinical trials using varying fluid solutions and rates with an emphasis on patient monitoring and safety (Table 24.1).

Table 24.1 Important human studies of fluid resuscitation in acute pancreatitis.

Study type	Number of patients	Comparison group	Outcome
Retrospective [29]	65	Aggressive (Hct <47) vs. nonaggressive	Hct >47 developed necrosis
Retrospective [48]	99	Aggressive (4 L) vs. nonaggressive	Aggressive with more respiratory complications and increased ICU care
Retrospective [34]	45	Early vs. late resuscitation	Increased mortality in late
Retrospective [35]	434	Early vs. late resuscitation	Less SIRS, organ failure, ICU admissions, LOS in early
RCT [47]	62	Aggressive (3 mL/kg per h) vs. nonaggressive using LR in ERCP	Less hyperamylasemia and abdominal pain in aggressive group
RCT [50]	115	Aggressive (<35 Hct in first 24 h) vs. nonaggressive	A higher incidence of sepsis and decreased survival in aggressive group
RCT [42]	40	LR vs. normal saline	LR had decreased SIRS and CRP at 24 hours
RCT [43]	40	LR vs. normal saline	LR led to decreased SIRS and CRP than normal saline
RCT [44]	47	LR vs. normal saline	LR significantly decreased SIRS at 24 hours compared to normal saline, but had no significant difference at 48 hours
RCT [46]	121	LR vs. normal saline	LR resulted in decreased LOS and ICU admissions but led to no significant difference in SIRS compared to normal saline

Hct, hematocrit; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; LOS, length of stay; LR, lactated Ringer's solution; CRP, C-reactive protein.

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Enteral and Parenteral Nutrition

Nutritional supplementation has long been an important component of conservative treatment in acute pancreatitis. Since most patients with acute pancreatitis must be "nothing by mouth" for at least part of their hospitalization, the mechanism of nutritional supplementation and type has been an active area of clinical research for many decades. Although the standard of care for many years included nothing per mouth and "resting" the pancreas by limiting enteral intake, recent studies have proved that early enteral feeding appears to be of significant benefit to clinical outcomes.

The disadvantage of maintaining patients nothing by mouth is that bowel rest is associated with intestinal mucosal atrophy and increased infectious complications due to bacterial translocation [52]. In order to maintain gut barrier function, therefore, enteral feeding is preferred over parenteral feeding in the management of acute pancreatitis. This preference has been proven in multiple randomized controlled trials dating back to the early 1990s, and meta-analyses have consistently demonstrated the importance of enteral versus parenteral nutrition in both interstitial and predicted severe acute pancreatitis [53–57]. Currently there is no rationale to use parenteral over enteral nutrition in the setting of acute pancreatitis. Even in patients who cannot tolerate a full enteral diet, at least some degree of enteral nutrition should be provided to maintain gut barrier function. Early enteral nutrition (within 48 hours) after admission has been found to reduce mortality, multiple organ failure, operative interventions, and infections when compared to late enteral nutrition and parenteral feeding [58,59]. Current AGA guidelines corroborate these findings, as the AGA advising panel strongly recommends early (within 24 hours) oral feeding and, in patients who cannot feed orally, enteral rather than parenteral nutrition to generate the best outcomes [41].

In mild acute pancreatitis, early initiation of oral intake with a low-fat soft solid diet is often tolerated and has been demonstrated to be just as efficacious as tube feeding [60]. Further study has also demonstrated that even in patients with predicted severe acute pancreatitis, early oral vs. on-demand tube feeding has demonstrated equivalent efficacy in a randomized controlled trial [61]. Enteral feeding is recommended within 3 days of hospitalization, typically after cessation of nausea, vomiting, discontinuation of parenteral analgesics, reduction in abdominal pain, and return of bowel sounds. However, one study suggests that early oral refeeding based on hunger rather than on clinical and laboratory measures proves effective for introducing nutrition earlier to patients with acute pancreatitis without more complications than conventional refeeding based on clinical parameters, and it reduces length of stay compared to conventional refeeding [62]. Moreover, feeding can be started with a low-fat solid diet and does not need to be initiated using the archaic clear liquid, mechanical soft, and low-fat method [63]. Moraes et al. found in a randomized controlled trial that patients who received a full solid diet as opposed to either a clear liquid diet or a soft diet and who had no abdominal pain relapse had the shortest length of stay (median 1.5 days shorter). However, when considering patients who had abdominal pain relapse, the length of stay was similar among the three groups, and the authors found no difference in pain relapse between the three different diets [64].

The choice between nasojejunal or nasogastric feeding has been debated for quite some time with nasojejunal feeding being favored—again because of the issue of achieving pancreatic rest. However, recent studies have suggested that nasogastric feeding may be just as efficacious and well tolerated as nasojejunal feeding when evaluated in a randomized controlled setting and demonstrate benefits when compared to nil per os [65,66]. Because of no apparent mortality benefit of one over the other, the AGA guidelines recommend either nasogastric or nasojejunal feeding [41].

The issue of type of feeding has been inadequately studied, but there has been a meta-analysis evaluating 20 randomized controlled trials comparing different formulations [67]. The authors concluded that the use of polymeric, rather than (semi)elemental, formulation does not lead to a significantly higher risk of feeding intolerance, infectious complications, or death in patients with acute pancreatitis. Neither the supplementation of enteral nutrition with probiotics nor the use of immunonutrition significantly improved the clinical outcomes. A Cochrane Database review also found similar low-quality evidence differentiating the types of formulations and their benefit in acute pancreatitis [68]. In addition, a recent study of the use of probiotics in acute pancreatitis demonstrated worsening mortality due to bowel ischemia in the group receiving probiotics, and it is thus advised that probiotics should not be used in patients with acute pancreatitis [69].

Thus, in summary, enteral feeding is favored over parenteral feeding in acute pancreatitis based on improvement in important clinical outcomes. Oral feeding should be initiated within 72 hours of admission in all patients using a low-fat diet. If patients cannot tolerate oral feeding, nasoenteric feeding, usually with a nasogastric feeding tube, can be employed. In those patients in whom appropriate enteral feeding is not tolerated, low-level "trickle" feeding should be used to help prevent gut translocation of bacteria, which can lead to infected necrosis. Patients should not be given probiotics, as these formulations have demonstrated an increased risk of mortality due to mesenteric ischemia.

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Conclusions

Supportive care in acute pancreatitis is critical to achieving optimal patient outcomes in the context of no targeted pharmacologic options in this disease. Aggressive fluid resuscitation and the initiation of early enteral feedings have revolutionized the care of patients with acute pancreatitis. Further studies—specifically targeting the type of fluids and enteral nutrition formulations in randomized controlled trial format—are needed, however, in order to optimize further conservative care for these patients.

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ICU Treatment of Severe Acute Pancreatitis

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Introduction

Acute pancreatitis remains a complex, progressive, and variable acute inflammatory syndrome of the pancreas. In some cases, the inflammatory response is so severe that a sequence of systemic inflammation defined by the systemic inflammatory response syndrome (SIRS), capillary leak syndrome (CLS), multiorgan dysfunction, shock, and death may occur. Patients with life-threatening complications should be managed in the intensive care unit (ICU), where early intervention and support may result in better outcomes. This chapter will focus on management following a general clinical pathway to emphasize the sequence of common events and evidence behind clinical decisions.

Pre-ICU Management

Optimal treatment begins in the clinic or emergency department (Fig. 25.1). The primary goals in early evaluation include confirming the diagnosis, detecting early signs of organ dysfunction, and initiating fluid resuscitation. Fluid resuscitation (see Chapter 26) may be the most important early intervention for stabilizing and treating patients with evolving severe acute pancreatitis.

The initial physical examination is central to assessment and proper triage. The clinical histories are variable, but sudden onset of severe, sharp, unrelenting pain with nausea and vomiting is common. In addition to a routine physical examination the clinician should focus on early signs of severe acute pancreatitis, including severe pain, anxiety, confusion, scleral icterus, diaphoresis, dry mouth, tachycardia, thready pulses, acrocyanosis, tachypnea, lung rales, and abdominal tenderness with or without rebound pain. Postural changes (e.g., supine to standing) resulting in dizziness or tachycardia suggest significant intravascular hypovolemia.

The initial laboratory assessment should include standard diagnostic tests in addition to standard laboratory tests (Box 25.1). These tests serve both as baseline values for future comparisons and early biomarkers of organ dysfunction that may require ICU management. A chest X-ray may provide early evidence of pulmonary edema and/or plural effusions [1].

Early morbidity and mortality are heralded by SIRS, as it often leads to endothelial stress [2], CLS [3] and organ dysfunction involving the lungs, cardiovascular system, intestines, and kidneys, and damage to the pancreas [4–7]. Early management focuses on fluid resuscitation and oxygenation. Patient comfort centers on treatment of pain and nausea.

Life-threatening hypovolemia in acute pancreatitis develops because of CLS, which occurs in an unpredictable subset of patients. The mechanism of hypovolemia in acute pancreatitis appears to overlap with trauma and involve epithelial cell damage, CLS, and loss of large and small proteins from the circulation into interstitial and third spaces [2,3,8]. Blood pressure may not become significantly decreased until the patient has lost 30–40% of circulating blood volume [9]. Therefore, blood pressure correlates poorly with both blood volume and cardiac output. Furthermore, the severity of the hypovolemia may be masked by splanchnic vasoconstriction and shunting of blood from the viscera to maintain circulation to the brain and peripheral organs. Hypovolemia may also be overlooked by focusing on criteria designed for sepsis or multiple trauma such as systolic blood pressure <90 mmHg [7,10].

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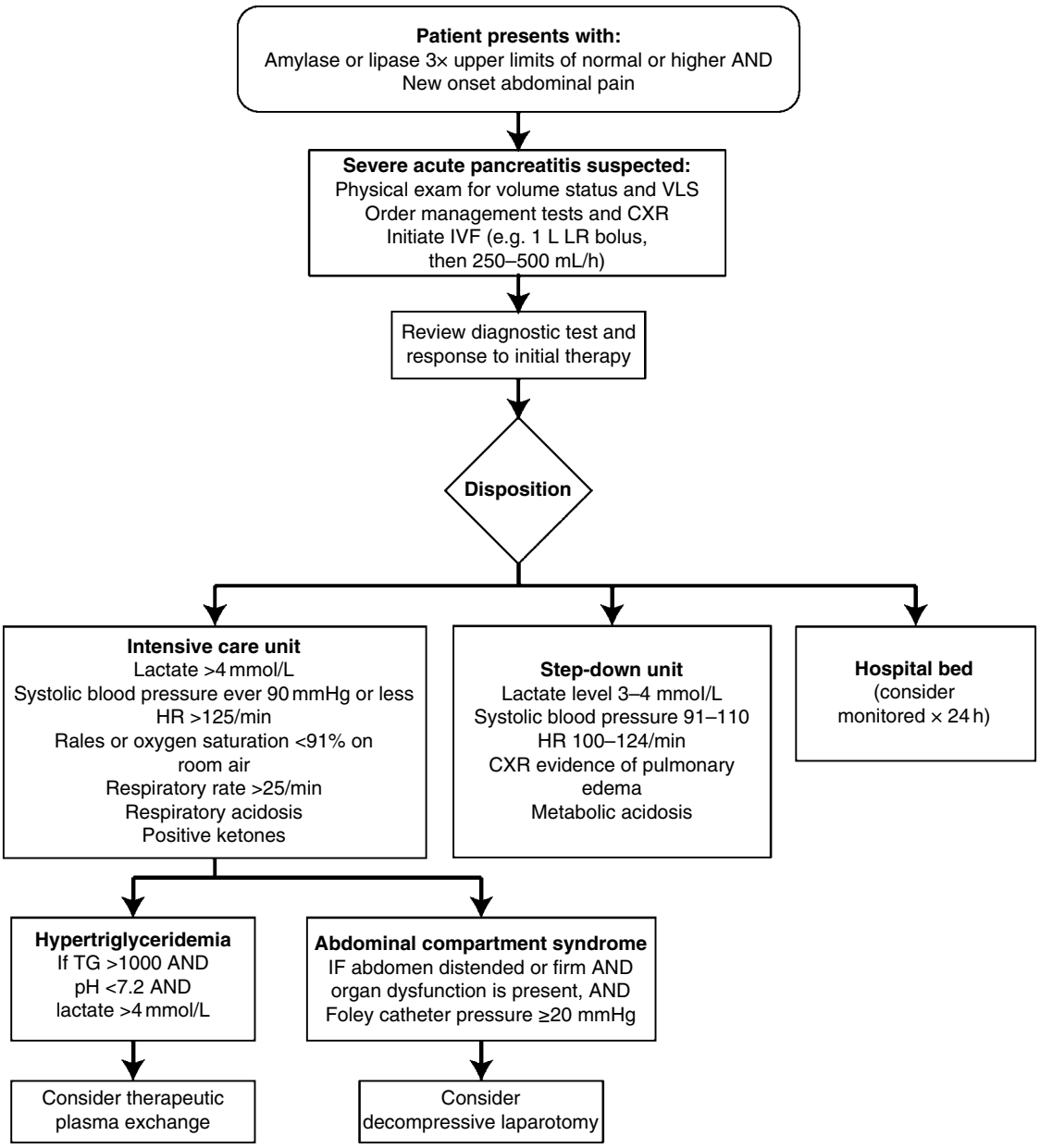


Figure 25.1 An illustrative clinical pathway for managing patients during the initial evaluation and possible admission into the intensive care unit. See text. CXR: chest x-ray; HR: heart rate; LR: lactated Ringer's solution; TG: triglyceride level; CLS: capillary leak syndrome.

Hypoperfusion and/or ischemia of visceral organs create two additional challenges to the problem of generalized tissue ischemia. First, hypoperfusion may continue long after systemic volume resuscitation has occurred, resulting in continued ischemic stress on intestinal mucosal epithelial cells, the most vulnerable cells of the gut. Second, mucosal epithelial cell injury results in breakdown of the mucosal barrier and translocation of bacteria and toxic factors that enter the circulation via the mesenteric lymphatics and drive SIRS [11,12]. Thus, in some patients, a vicious cycle develops with systemic inflammation leading to CLS, which causes intravascular hypovolemia and splanchnic vascular bed ischemia, leading to translocation of proinflammatory toxins from the gut lumen into the lymphatics that further drives systemic inflammation. Interruption of this cycle should begin with minimizing or preventing intravascular hypovolemia.

The usual systolic blood pressure of adults varies widely, so the relative change in both blood pressure and heart rate may be more important than an absolute value. A systolic blood pressure <90 mmHg, however, is likely

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Box 25.1 Baseline blood-based laboratory tests

Diagnostic tests [on admission]

- Amylase level
- Lipase level
- Triglyceride level
- Calcium level

Management tests [on admission and every 6–24 hours as needed]

- Electrolytes (sodium, potassium, chloride, bicarbonate)
- Blood urea nitrogen (including pre-acute pancreatitis levels)
- Creatinine (including pre-acute pancreatitis levels)
- Blood glucose
- Complete blood count (for white blood cell count and hematocrit)
- Liver injury tests (for bile duct obstruction and aetiology)
- Albumin (including pre-acute pancreatitis levels)
- Total Protein (including pre-acute pancreatitis levels)
- Serum lactate
- Serum LDH (optional)
- Arterial blood gas (optional)

to be a *late* sign of severe intravascular hypovolemia [13]. An elevated hematocrit indicates hemoconcentration and implies significant extravasation of serum and protein-rich plasma from the bloodstream and is a harbinger of impending organ failure [3]. Elevated lactate levels also suggest that tissues may already be in shock [14]. We believe that optimal treatment includes the prevention of hypotension and shock, and resuscitation should not be delayed until signs of hemoconcentration, and shock develop.

Treatment and prevention of progressive intravascular hypovolemia must begin before the patient is transferred to the ICU. Although acute pancreatitis has been compared with septic shock and similar resuscitation algorithms suggested, the current evidence supporting goal-directed therapy, using parameters to guide either rate or total volume of resuscitation, to reduce morbidity or mortality is limited [10]. We recommend that resuscitation with balanced salt solution should be given rapidly, as soon as the diagnosis of acute pancreatitis is made, with modifications for patients with existing comorbidities [4,10]. Further research on the resuscitative strategies may help guide our approach [15].

Early use of supplemental oxygen is warranted with continuous monitoring of oxygen saturation via pulse oximetry or intermittent arterial blood gas analysis. The pulmonary edema seen in patients with severe acute pancreatitis and CLS is usually due to endothelial cell injury and extravasation of plasma, not fluid overload. Therefore, the treatment should be positive pressure ventilation and not diuresis, unless the patient is absolutely volume overloaded.

For pain we recommend hydromorphone 0.5–2.0 mg intravenously every 15 minutes while the respiratory rate is >10 and systolic blood pressure is >90 mmHg. However, no differences between opiates were demonstrated in systematic reviews of variable quality clinical studies [16,17]. Opiates primarily used in the United States and new studies are needed to determine necessity and utility. For nausea we give ondansetron 4–8 mg intravenously every 6 hours as needed.

Special Considerations

As in trauma, management decisions made in the early minutes and hours of care have significant downstream consequences. The emergency in severe acute pancreatitis is fluid management and tissue oxygenation within the context of systemic inflammation. But unlike trauma where the insult is rapid and finite, the systemic inflammation of acute pancreatitis evolves, so continued attention to the evolution of the process over the first 24 hours is critical.

We strongly discourage the use of contrast computed tomography (CT) scan in early severe acute pancreatitis. The diagnosis can almost always be made by the combination of typical pain and elevated serum levels of pancreatic digestive enzymes [5,7]. Although contrast-enhanced CT scan remains useful for detecting and quantifying pancreatic necrosis and/or fluid collections, there are no urgent interventions, and the evaluation can be delayed for days. Early contrast CT poses at least two risks. First, the contrast may worsen the severity of pancreatic necrosis, as well as kidney injury in patients, especially if there is poor perfusion from hypovolemia and/or shunting of blood from visceral organs. Second, the process of obtaining a CT may interrupt evaluation and treatment, or delay transfer to the ICU. However, CT or other abdominal imaging modalities may be required if the diagnosis is in question.

Gallstone pancreatitis occurs when small gallstones become lodged at the sphincter of Oddi and trigger intrapancreatic digestive enzyme activation and acute pancreatitis. In some cases, the gallstone remains lodged, whereas in others the stone passes on its own. Although there used to be great enthusiasm for urgent endoscopic retrograde cholangiopancreatography, biliary sphincterotomy, and stone removal, randomized studies failed to demonstrate a benefit for early intervention [18]. The

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exceptions are cases where an impacted gallstone results in ascending bacterial cholangitis [18]. This condition represents an urgent complication that requires a therapeutic intervention. In this setting, antibiotics should be started immediately. However, the priority of an ERCP is secondary to fluid resuscitation, airway management, and patient stabilization.

Indications for ICU Admission

Early and appropriate treatment of patients with acute pancreatitis may result in rapid resolution of signs and symptoms of more severe disease. In these cases, it is reasonable for patients to be treated and monitored on a step-down unit until the clinical course of the patient dictates a change in care level.

The severe early consequences of acute pancreatitis are related to organ dysfunction and damage rather than SIRS itself. The recommendations of the Revised Atlanta Criteria recommends that patients with SIRS be considered as high risk for organ failure, but that severity is based on organ failure that persists for at least 48 hours to classify patients as truly severe [7]. The Revised Atlanta Criteria defines organ failure based on the Modified Marshall Score of 2 or more in the respiratory system (PaO2/FiO2 of ≥300), renal system (serum creatinine of ≥170 μmol/L or ≥1.9 mg/dL) or cardiovascular system (systolic blood pressure of <90 and not fluid responsive) [7]. However, we are concerned that the criteria are too severe and too late for early triage, increasing risk of avoidable organ damage and unexpected cardiopulmonary arrest of patients admitted to unmonitored regular hospital floors or at home.

The problem with the Modified Marshall Score criteria is that they do not account for the baseline state of the patient and reflect the eventual development of severe organ dysfunction and failure to meet criteria. In the early hours of acute pancreatitis evaluation, it is most important to determine which patient is evolving into organ failure and initiate mitigation strategies such as early fluid resuscitation which may prevent hypotension despite severe underlying pathophysiology. We recommend early identification of patients with evolving organ failure using the Komara criteria [3], which considers pre-acute pancreatitis biomarker status and more accurately distinguishes patients with more severe disease. Specifically, early organ failure (e.g., within the first 72 hours) is likely if the patient has a rise of haematocrit from baseline of >3 (odds ratio 17.7, $P = 0.014$), if both BUN and creatinine levels are increasing from pre-acute pancreatitis levels (and continue rising), and if serum albumin and total protein are dropping. The drop in albumin, and especially total protein appear to reflect endothelial cell stress or injury with CLS, which takes 24 hours to develop [3]. Multiple studies now demonstrate that dropping and low serum albumin are associated with multiorgan failure and severe outcomes [3,19–21]. Multiple prognostic scores may also be useful for predicting later organ failure [22].

We recommend ICU admission for patients with evolving or persistent organ dysfunction who require a high level of care with frequent adjustments to the care plan. Examples include patients with lactate >4 mmol/L, systolic blood pressure at any time <90 mmHg, need for vasopressors, an ongoing heart rate of >125 per minute, rales on lung exam or oxygen saturation <91% on room air, a respiratory rate >25 per minute, any respiratory acidosis or positive serum ketones. In addition, patients with SIRS and CLS (based on Komara Criteria above) may require ICU admission for invasive monitoring of intravascular volume, and impending cardiac and/or pulmonary dysfunction.

ICU Treatment of Severe Acute Pancreatitis

The evolution of severe acute pancreatitis dictates the concerns and management strategies over the first days of disease. The initial phase (0–48 hours after onset of pain) reflects the magnitude of the acute inflammatory response with SIRS, CLS, and early organ dysfunction of the cardiovascular system, lungs, and kidneys. The second phase (48–120 hours after onset of pain) focuses on managing recovery of organ systems from injury and preventing secondary problems such as infection in immunocompromised patients from the compensatory anti-inflammatory response syndrome (CARS) (23).

Early ICU Management (0–48 Hours from Onset of Pain)

Managing patients with acute pancreatitis who require ICU admission is best done by a multidisciplinary team including intensivists and specialists in the medical and surgical management of pancreatitis.

Management of Cardiovascular Dysfunction

Hypotension may be the result of inadequate cardiac output from intravascular volume depletion, reduced systemic vascular resistance, or both. Early therapy

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should center on restoration of adequate circulating blood volume to ensure adequate oxygen delivery while simultaneously avoiding exuberant fluid administration, which leads to volume overload and potentially worse outcomes [24]. Ongoing hypotension despite volume resuscitation will require vasopressor support. We guide our volume resuscitation and the initiation of pressors based on repeated physical exam, biochemical markers of perfusion (lactate and mixed venous oxygen saturations), and dynamic measures of preload responsiveness, such as pulse pressure variation on the arterial line of intubated patients [25–27].

If the patient remains hypotensive after preload is optimized, we initiate pressors for maintenance of perfusion pressure. We target a mean arterial pressure of ≥65 mmHg. Once again, there are few study results to guide us in our choice of pressor. The literature suggests that neither norepinephrine nor epinephrine have a mortality benefit for patients with septic shock [14,28]. However, epinephrine may increase lactate levels despite achieving adequate perfusion pressure, so we start with norepinephrine. We do not routinely add vasopressin unless the patient exhibits significant complications from high-dose catecholamine therapy such as tachyarrhythmias [29]. Careful documentation of both fluid input and output is useful for gauging overall fluid balance and the magnitude of CLS.

Management of Pulmonary Dysfunction

Acute respiratory distress syndrome (ARDS) is a well-recognized complication of acute pancreatitis. Initial management with supplemental oxygen may prove inadequate and many patients with ARDS will require more aggressive care. High-flow oxygen through a nasal cannula provides heated and humidified oxygen at flow rates high enough to develop some continuous positive airway pressure. In addition, high-flow oxygen may be more comfortable than noninvasive ventilation [30].

All patients who require intubation and mechanical ventilation for ARDS should be initially managed with a tidal volume of 6 mL/kg predicted body weight. Respiratory rates are adjusted to achieve a pH between 7.30 and 7.45 if possible. Positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FiO_2) should be titrated to maintain an arterial PaO_2 of between 55 and 80 mmHg (31). Titrating PEEP or FiO_2 to achieve a $PaO_2 > 80$ mmHg may improve arterial blood gas values but has not been shown to improve survival [32]. If hypoxia persists (i.e., a PaO_2/FiO_2 ratio of <150 mmHg) and PEEP and FiO_2 levels exceed 10 and 0.6, respectively, we consider neuromuscular blockade [33] and initiate prone position ventilation [34] early.

Management of Abdominal Compartment Syndrome

Abdominal compartment syndrome is a pathophysiologic process arising from increased tissue fluid within the peritoneal and/or retroperitoneal space. Like other compartment syndromes, when the abdominal cavity can no longer expand, further fluid collection results in increases in abdominal pressure with subsequent decreases in perfusion and ischemia to intra-abdominal organs. In patients with acute pancreatitis, swelling from pancreatic necrosis, ileus with gas distension, fluid collections, and volume overload from resuscitation may lead to abdominal compartment syndrome. Abdominal compartment syndrome is suspected on physical examination when the abdomen is firm and/or distended.

Intra-abdominal pressure is the steady-state pressure within the abdominal cavity and is measured by instilling 25 mL of sterile saline through the Foley catheter and measuring the resultant pressure at end expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line [35]. A normal intra-abdominal pressure in critically ill adults is 5–7 mmHg. Intra-abdominal hypertension is a sustained pressure ≥12 mmHg.

Abdominal compartment syndrome is a sustained intra-abdominal pressure of ≥20 mmHg with new organ dysfunction or failure. Although some patients may respond to a trial of sedation and neuromuscular blockade (relaxing the abdominal wall and thereby decreasing intra-abdominal pressure) and nasogastric tube decompression, many patients with acute pancreatitis and abdominal compartment syndrome will need a decompressive laparotomy.

Management of Metabolic Derangements

Hypertriglyceridemia

Hypertriglyceridemic acute pancreatitis represents a spectrum of underlying genetic disorders and metabolic risks such as diabetes mellitus and obesity. Triglycerides alone are inert. However, it is believed that in the presence of lipase(s), the triglycerides are hydrolyzed to free fatty acids (FFA), and it is the FFA that are toxic, especially unsaturated FFA [36–38]. Hypertriglyceridemia is associated with more severe acute pancreatitis and persistent organ failure [39] and may require special attention. Thus, while the focus of physicians treating hypertriglyceridemic acute pancreatitis in the past has often been on reducing the triglyceride levels, the focus should be on clearing FFA [39]. Serum concentrations of

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FFA are a function of production and clearance. The lipolysis of triglycerides normally occurs within tissues such as muscle, fat, and visceral organs by lipoprotein lipase (LPL), a regulated enzyme. FFA are cleared by these tissues, with excess FFA binding to albumin and transported to the liver where FFA are transferred from albumin to the hepatocytes. In acute pancreatitis, the controlled hydrolysis of triglycerides by LPL is disrupted with the addition of pancreatic lipase(s) that also catalyzes triglycerides to FFA in an unregulated way, overwhelming the capacity of the body to manage the FFA pool generated by LPL, and leading to lipotoxicity. In this case, management of the FFA-associated toxicity should focus on prevention of hydrolysis of triglycerides by LPL (e.g., fluid resuscitation and maintaining good hydration, avoiding heparin) by (theoretically) inhibiting pancreatic lipases [36], and by facilitating clearance of FFA from the serum with insulin infusion or apheresis/plasma exchange [40]. In addition to driving SIRS, FFA can block mitochondrial function, leading to lactic acidosis (pH <7.2, lactate >4 mmol/L), often seen with low calcium (e.g., calcium <8.3 mg/dL) [41]. This requires emergency intervention in the ICU, especially in the presence of liver and/or kidney dysfunction. Note that a similar syndrome of lactic acidosis occurs with complications of metformin use.

Diabetic Ketoacidosis with Acute Pancreatitis

Acute pancreatitis often develops in patients with diabetic ketoacidosis (DKA). The mechanism triggering acute pancreatitis appears to be linked to low pH. In a study of 100 subjects with DKA the subjects with coexisting acute pancreatitis had more severe metabolic acidosis (mean pH 7.15 vs. 7.31; $P = 0.0001$) and higher anion gap (38.17 mEq/L vs. 25.16 mEq/L; $P = 0.0001$) [42,43]. These patients may also have hypertriglyceridemia [44]. In these cases, addressing insulin deficiency, acidosis, and hydration results in rapid improvement.

Nutrition Support

Early nutrition support is associated with improved outcomes in patients with acute pancreatitis, and enteral feeding is superior to total parenteral nutrition (TPN) when feasible [45,46]. However, ICU patients are typically complex with confounding medial conditions, each case is unique, and multidisciplinary management may be required. Nutrition support is covered in Chapter 26.

Late ICU Management (>48 Hours after the Onset of Pain)

Visceral organs share a compartment and regulation of blood flow. Thus, damage to one organ should raise awareness of damage to others. The easiest organ to monitor is the kidney by following serum creatinine levels and blood urea nitrogen (BUN). The increase of serum creatinine and BUN levels over the first 24–72 hours usually indicates pre-renal azotemia [3] and remains among the best predictors of pancreatic necrosis and persistent organ failure [47,48]. Acute kidney injury in acute pancreatitis represents one component of a common mechanism of injury for multiple visceral organs (i.e., kidneys, pancreas, and intestine) that are damaged by hypoperfusion and ischemia [3]. Intestinal ileus may be a parallel sign of visceral organ ischemia. Early recognition of high risk for pancreatic necrosis determines future management strategies, and thus further evaluation is warranted.

After resuscitation and stabilization, abdominal imaging remains central to the eventual evaluation of pancreatic morphology, intra-abdominal fluid collections, and other complications. The radiologic evaluation and staging of severe acute pancreatitis are covered in Chapter 25.

Alcohol Withdrawal Syndrome

Alcohol abuse is a common cause of severe acute pancreatitis and alcohol withdrawal may be a complication encountered in the late ICU phase. We start treatment with escalating doses of benzodiazepines [49]. Maximal doses of benzodiazepines are defined by their diluent, propylene glycol, which can have potentially toxic effects. For benzodiazepine-resistant alcohol withdrawal syndrome, we add either phenobarbital or ketamine.

Management of Infectious Risks

The use of antibiotics is discussed in Chapter 28. The management of infected pancreatic necrosis is discussed in Chapters 29–31.

Transition Planning

As the clinical course of the patient becomes clear and the intensity of organ support is reduced, transition out of the ICU must be considered. We consider transfer out of the ICU when the organ system dysfunction that necessitated ICU admission has resolved.

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26

Clinical Course and Medical Treatment of Acute Pancreatitis—Use of Antibiotics in Severe Acute Pancreatitis: Indications and Limitations

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Introduction

Although 85% of the patients with acute pancreatitis experience an uneventful recovery, this disease bears a high risk for severe and even lethal complications. Cardiocirculatory, pulmonary, or renal failure, alone or in combination are common problems in patients with severe acute pancreatitis. The treatment is conservative, including mechanical ventilation, hemofiltration or hemodialysis as well as cardiocirculatory support, if required. The majority of patients respond to such an approach. Nevertheless, mortality of severe acute pancreatitis remains at about 10%.

The poorest prognosis is observed in patients with necrotizing pancreatitis who develop local bacterial infection. Surgical or interventional management is generally required in these cases and mortality rates exceeding 30% been reported [1,2]. Despite progress in our understanding of the pathology of pancreatic sepsis and in intensive care treatment, the mortality rates of infected pancreatic necrosis have not changed in recent decades. Recent attempts with nonsurgical or interventional treatment have been promising [1,3] but there is no doubt that bacterial infection will remain a life-threatening complication in patients with necrotizing pancreatitis.

The recently revised Atlanta classification of acute pancreatitis discriminates between mild acute pancreatitis, moderately severe acute pancreatitis, and severe disease, depending on the occurrence of organ failure and/or local and systemic complications [4]. In contrast to former classification systems, where the term "infected pancreatic necrosis" has been used for all locally infected pancreatic entities, the revised classification distinguishes between morphologically different local infectious complications.

Infectious Complications

During the course of acute pancreatitis, either systemic or local pancreatic infections may occur. The incidence of these complications varies widely, depending on definition and patient selection.

Local Pancreatic Infection

In approximately 30–40% of the patients with necrotizing pancreatitis local infections of the necrotic areas develop [5]. Bacterial infection of pancreatic necrosis is the most important determinant of outcome [6]. The revised Atlanta classification discriminates between different morphological entities and comprises acute peripancreatic fluid collections (APFC), pancreatic pseudocysts, acute necrotic collections (ANC), and walled-off necrosis (WON). These morphologic entities have a variable potential for bacterial infection (Table 26.1) with pancreatic necrosis and WON bearing the highest risk. For our understanding of relevance of infectious complications and the role of antibiotics in the treatment algorithm, discrimination between these morphologies is therefore important. Irrespective of the morphologic differences, bacterial infection is a phenomenon of the later phase of acute pancreatitis, commonly observed after the third or fourth week after onset of the disease. This might be one of the reasons why all efforts to reduce the infection rate by prophylactic antibiotics have failed. There is a wide time frame for infection and it is difficult to impossible to define the exact period when prophylactic antibiotics might be effective.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Table 26.1 Complications of severe acute pancreatitis with the potential risk of bacterial infection, according to the current revised Atlanta classification [4].

	Characterization	Estimated potential for infection
Necrotizing acute pancreatitis	Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis	High
Walled-off necrosis (WON)	Necrotic tissue surrounded by a wall of tissue, usually >4 weeks after onset of pancreatitis	High
Acute necrotic collection (ANC)	Collection of necrosis and fluid during the first 4 weeks of AP	Moderate
Pancreatic pseudocyst	Walled-off fluid collection weeks after AP. May require surgical drainage if persistent	Low-moderate
Acute peripancreatic fluid collection (APFC)	During the early phase of AP, resolve spontaneously	Low

AP: acute pancreatitis.

Systemic Bacterial Infection

Extra-abdominal bacterial infection is a common finding during severe acute pancreatitis. Its incidence varies widely in different studies. In a multinational European study, more than 40% of the patients had extra-abdominal infections, with respiratory tract infections being the most frequent (28%), followed by bloodstream infections (14%), and catheter-related infections as well as genito-urinary tract infections (4%) [7]. In the authors' own investigation, 25% of the patients of the control group (not treated with antibiotics) had extrapancreatic infection, with pneumonia being the most frequent [8].

The clinical relevance of extrapancreatic infection has been clearly demonstrated: it increases mortality and adversely affects the outcome of acute pancreatitis [9]. Whether its relevance is equal to that of pancreatic sepsis is subject to discussion.

Spectrum of Bacteria

In the first description of infected pancreatic necrosis in the 1980s, the bacterial spectrum of infection was dominated by gram-negative enteric germs [5]. During the past three decades, there has been some change, but gram-negative bacteria still play a predominant role in the bacterial spectrum. Nevertheless, gram-positive microorganisms, especially *staphylococci* and *enterococci* are increasingly coming into focus. The bacterial spectrum is polymicrobial and comprises anaerobic bacteria, as well (Table 26.2).

The role of multidrug resistance among these germs has been recently addressed. Many gram-positive species are resistant to methicillin, as are many extended spectrum beta-lactamase (ESBL)-producing gram-negative germs. In one recent study, 63% of the patients with infected pancreatic necrosis were infected with multiresistant germs [12]. As in other infectious pathologies, these multiresistant germs are of therapeutic and prognostic importance. Their isolation should prompt treatment with an adequate antibiotic drug according to the tested bacterial susceptibilities.

In addition, a considerable percentage of patients with necrotizing pancreatitis develop fungal infection. Its prognostic impact has been a matter of discussion over the past decade. Most often, fungal infection is caused by *Candida* species and is considered to be a predictor of worse outcome. It is generally accepted that antibiotic treatment promotes overgrowth of unaffected or resistant pathogens and is thus considered to be a risk factor for both fungal and multiresistant infection [13,14].

Rationales for Antibiotics in Acute Pancreatitis

The use of antibacterial agents in acute pancreatitis has been debated since the 1970s. At first, antibiotics were regarded as a part of the treatment regime without clear definition of their indication. Our increasing knowledge about the impact and relevance of infection has defined two potential settings for the use of antibiotics.

Prevention of Infection

The clinical relevance of bacterial infection with its poor prognosis supports treatment algorithms for its prevention. This led to the idea of prophylactic administration of antibiotics with the intention of preventing bacterial

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Table 26.2 Development of the bacterial spectrum of infected pancreatic necrosis over the past 30 years. Given are selected strains from different studies. Note the increase in the incidence of enterococci and fungi.

	Beger 1986 [5]	Isenmann 2004 [6]	Dellinger 2007 [10]	Schmidt 2014 [11]
No. of isolates	75	19	30	88
Percentage of strains				
Enterococci	8%	11%	23%	28%
E. coli	32%	32%	7%	26% (Enterobacteriaceae)
Pseudomonas	7%	–	10%	7%
Anaerobic bacteria	7%	–	3%	n.d.
Fungi	4%	10%	10%	14%

n.d.: no data.

superinfection. In recent years there has been considerable scientific effort to prove such a concept as discussed later in this chapter.

Treatment of Infection

In combination with surgical debridement, antibiotic treatment is the mainstay in the treatment of any intra-abdominal infection, including infected pancreatic necrosis. It is well known that inappropriate antibiotic treatment in severe sepsis results in a fivefold increase in mortality [15]. For acute pancreatitis a selective uptake of antibiotics into the pancreas has been described [16], which should be taken into account. As a consequence the antibiotics for treatment of pancreatic infection should not only be chosen according to the bacterial spectrum and their antibacterial activity, but also according to their ability to penetrate into the infectious focus [16,17].

Clinical Studies with Antibiotics

During the past 20 years, there have been numerous controlled and uncontrolled, blinded and unblinded studies addressing the issue of whether early administration of antibiotics in severe acute pancreatitis could reduce the incidence of local bacterial infection and consequently could improve the prognosis of the disease (Table 26.3). Among those, four had adequate scientific power for meaningful conclusions [10,18,19]. None of them has been able to give a definite answer to this question and according to the latest meta-analyses, there is no evidence to support the routine use of prophylactic antibiotics in patients with severe acute pancreatitis [20,21,22].

Consequently, the overwhelming majority of current guidelines and expert reviews do not recommend the routine administration of broad-spectrum antibiotics in patients with severe acute pancreatitis or pancreatic necrosis [34,35,36].

What are the reasons for our inability to demonstrate a beneficial effect of prophylactic antibiotics on the infection rate in acute pancreatitis? First, acute pancreatitis is a heterogeneous disease with a highly variable course ranging from mild and self-limiting to devastating with severe septic complications. The majority of patients with acute pancreatitis will never develop infectious complications. To date, there are no reliable parameters that allow the identification of patients at risk for developing pancreatic sepsis. Second, pancreatic infection is a phenomenon of the later course of the disease. Thus the ideal timing and optimal duration of antibiotic administration as prophylaxis is not clear. Antibiotics given too early and too long may be ineffective and promote bacterial resistance. Third, new concepts in the therapy of acute pancreatitis such as early enteral nutrition and treatment of organ dysfunctions may directly or indirectly affect the incidence of septic complications.

These facts, together with others, make it unlikely that we will ever be able to elaborate pathways for the prophylactic use of antibiotics in severe acute pancreatitis [37].

Indications for Antibiotic Treatment

The main indications for initiation of antibiotic treatment in acute pancreatitis are evidence or strong suspicion of local and/or systemic bacterial infection. Therefore, all current guidelines aim at the timely identification of infected necrosis. The recommended standard comprises close monitoring of infectious parameters, imaging by contrast-enhanced computed tomography and, in cases with strongly suspected bacterial infection, the fine-needle aspiration for Gram-stain and culture [35].

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Table 26.3 Studies on antibiotic prophylaxis in severe acute pancreatitis. Note that only a few had adequate scientific power for meaningful conclusions.

Author			Double-blind	Patients	Effect on infected necrosis	Effect on mortality
Pederzoli [23]	1993	Imipenem vs. none	No	41/33	Reduction in imipenem group	No
Delcenserie [24]	1996	Ceftazidime + amikacin + metronidazol vs. none	No	11/12	Reduction in antibiotic group	No
Schwarz [25]	1997	Ofloxacin + metronidazol vs. none	No	13/13	no	No
Nordback [26]	2001	Early imipenem vs. imipenem delayed	No	25/33	Reduction in early treatment group	No
Spicak [27]	2002	Ciprofloxacin + metronidazol vs. ciprofloxacin + metronidazol on demand	No	33/30	No	No
Spicak [28]	2003	Meropenem vs. meropenem on demand	No	20/21	No	No
Rokke [29]	2007	Imipenem vs. none	No	36/37	No	No
Barreda [30]	2009	Imipenem vs. none	No	24/34	No	No
Xue [31]	2009	Imipenem vs. none	No	29/27	No	No
Yang [32]	2009	Imipenem vs. none	No	28/26	No	No
Randomized/placebo-controlled with the best scientific power						
Sainio [18]	1995	Cefuroxime vs. none	No	30/30	No	Reduction in the cefuroxime group
Bassi [19]	1998	Pefloxacin vs. imipenem	No	30/30	Reduction in the imipenem group	No
Isenmann [13]	2004	Ciprofloxacin + metronidazol vs. placebo	Yes	58/56	No	No
Dellinger [10]	2007	Meropenem vs. placebo	Yes	50/50	No	No
Garcia-Barrasa [33]	2009	Ciprofloxacin vs. placebo	Yes	22/19	No	No
Poropat [41]	2019	Imipenem vs. placebo	Yes	49/49	No	No

Pancreatic infection should be suspected in patients with pancreatic or extrapancreatic necrosis and clinical deterioration or failure to improve over 7–10 days.

Antibiotic Treatment on Demand

The experience from the ASAP-study [8] showed that antibiotic treatment was initiated in a considerable percentage of patients with clinical deterioration. The criteria for initiating this so-called "antibiotic treatment on demand" in this study were:

- newly developed sepsis/SIRS;
- newly developed organ failure (pulmonary, renal, cardiocirculatory);
- increase in serum C-reactive protein and strongly suspected/proven extrapancreatic infection;
- increase in serum C-reactive protein and strongly suspected/proven pancreatic infection.

In 37% of the patients of this study, the double-blind study medication was terminated and switched to open antibiotic treatment. The low rate of infected pancreatic necrosis (10.5%) as well as the favorable outcome (mortality 6% in the overall study) can be taken as rationale to initiate antibiotic treatment at these given indications. In patients fulfilling these criteria, sepsis and bacterial infection (pancreatic and/or extrapancreatic) are most likely present and they should thus be candidates for antibiotic treatment [22].

Choice of Antibiotics

For the choice of antibiotics in necrotizing pancreatitis, the following should be taken into consideration:

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- the bacterial spectrum,
- the antibiotic concentrations at the site of infection,
- the results of clinical studies.

Based on these criteria, carbapenems, chinolones, and broad-spectrum cephalosporins are first-choice drugs for the initial treatment of pancreatic infection. The last two should be combined with metronidazole as they lack sufficient antibacterial activity in the anaerobic spectrum. Based on their pharmacokinetic properties, acylaminopenicillins beta-lactamase inhibitor combinations can also be regarded as effective, although there are no clinical studies with these drugs.

Following initiation of an empirical antibiotic therapy, a step down should be followed as soon as the results of bacterial susceptibility testing are available.

Up to now, there is no rationale to initiate a "blind" antifungal therapy. Antifungal agents should only be given when bacterial smears yield fungal infection.

Limitations of Antibiotic Treatment

Antibiotic treatment is an essential part of the therapeutic regime in patients with infected pancreatic necrosis, but it is not enough on its own for successful treatment of these critically ill patients. The mainstay for success is source control of the infectious focus, and debridement of the infectious material is an essential part of the treatment regime.

Today open or laparoscopic surgical debridement and interventional drainage are subject to debate. Scientific evidence suggests that a "step-up approach" might provide favorable results as the best surgical approach in pancreatic infection [1]. Following such an approach, the patient is managed by conservative treatment for as long as possible. In case of strongly suspected or proven pancreatic infection percutaneous drainage is used as an initial approach for source control. If this fails surgical necrosectomy (minimally invasive or open) follows [38].

Whether or not pancreatic infection can be treated with antibiotics alone and without debridement is under current investigation. The first studies following such an approach have been criticized [39], but a recent meta-analysis shows that in selected patients this can be safely done with low mortality [3]. Nevertheless it is necessary to define criteria that characterize the group of patients who are eligible for such a conservative approach.

A global overview on the use of antibiotics among physicians indicated that their use, both as prophylaxis and as treatment in acute pancreatitis is widespread [40]. Irrespective of the national treatment guidelines of the disease, antibiotics are frequently given without clear indication, even in mild pancreatitis or when pyrexia is present. This overuse poses not only healthcare problems in terms of unnecessary expense, but also risks for the patients: antibiotic-associated side effects and a selection of multiresistant bacteria.

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Indications for Interventional and Surgical Treatment of Necrotizing Pancreatitis

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Introduction

Whereas interstitial acute pancreatitis is typically a self-limited disease process that usually responds to supportive care, more severe necrotizing pancreatitis can be seen in approximately 20% of patients. This is characterized by necrosis of the pancreatic parenchyma or peripancreatic tissue, manifestations of the systemic inflammatory response syndrome (SIRS), with risks for infection and multiorgan failure [1]. High rates of morbidity are associated with mortality of up to 15% in the setting of necrotizing pancreatitis and as high as 30% in the subset of patients who develop infected pancreatic necrosis [2,3]. A variety of surgical and interventional approaches have been used in an attempt to limit the substantial morbidity and mortality of necrotizing pancreatitis.

Over the last few decades, there has been a significant change in the indications for intervention in necrotizing pancreatitis, timing of intervention, and methods of surgical, minimally invasive, radiologic, and endoscopic intervention. Revision of the 1992 Atlanta classification of acute pancreatitis [4] to describe the clinical behavior and imaging characteristics more precisely [5] has occurred in parallel with a progressively less interventional and less invasive approach to necrotizing pancreatitis. Although no universally accepted management algorithm exists to guide management, evidence-based consensus continues to develop [6,7].

Interventions for Pancreatic Necrosis: Historical Perspective

Just a few decades ago, the association of pancreatic necrosis with systemic inflammation and secondary infection led to the goal of surgically removing all necrotic pancreas regardless of the presence of infection [8–10]. In 1991, Bradley and Allen published a small series of 11 patients successfully managed nonoperatively with sterile pancreatic necrosis [11]. The general acceptance of nonoperative management for sterile pancreatic necrosis was facilitated by the publication of a large series demonstrating favorable overall mortality and complications [12,13]. In this new paradigm, intervention was primarily limited to surgical debridement for cases of infected pancreatic necrosis as demonstrated by computed tomography (CT)-guided fine-needle aspiration (FNA) of the pancreas. Banks et al. showed a sensitivity and specificity of 96.2% and 99.4%, respectively, for detection of infected necrosis, with a positive predictive value of 99.5% and a negative predictive value of 95.3% [14]. The presence of infection or positive Gram stain on CT-guided pancreatic aspiration was considered an absolute indication for debridement, as superinfection of the necrotic parenchyma had been associated with a mortality of virtually 100% without debridement [15].

The absolute necessity of surgical debridement for infected necrosis was subsequently questioned with the demonstration of successful nonoperative management in some patients. Runzi et al. [16] showed in a series of over 80 patients with documented infected pancreatic necrosis that initial conservative therapy can be instituted, including antibiotic therapy and maximal supportive care. Mortality in patients managed with surgery was identical to that in those managed nonoperatively. Surgical therapy, when required, was often delayed to a later stage of disease, when the systemic inflammatory response stabilized, and necrotic pancreas had become demarcated. In other patients, surgical therapy was avoided altogether. Subsequent studies have confirmed this strategy: Garg et al. describe a 10-year series of 80 patients with infected pancreatic necrosis in whom 47 were treated with

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antibiotics alone [17]. The paradigm of urgent surgical debridement for all patients with infected pancreatic necrosis is therefore no longer considered valid.

Definitions and Classification of Pancreatic Necrosis

A classification system for acute pancreatitis was first proposed at the Atlanta Symposium in 1992. This system defined acute pancreatitis as an acute inflammatory process, associated with elevated pancreatic enzymes, with variable involvement of other organ systems [4]. A further distinction was made between acute interstitial pancreatitis and sterile or infected necrotic collections [18]. Unlike the prior delineation of pancreatic necrosis to infected and sterile versions, the revised Atlanta classification, introduced in 2012 [5], divided collections associated with necrotizing pancreatitis according to time of disease onset. A collection that develops early and lacks a discrete wall is referred to as an acute necrotic collection (ANC), whereas a collection that persists after 4 weeks is referred to as walled-off necrosis (WON). Both forms may be sterile or infected, although no correlation exists between extent of necrosis and risk of infection [5].

Indications and Timing of Intervention

In principle, interventions for pancreatic necrosis intend to control organ damage by removing necrotic tissue while maintaining functional pancreas. These interventions may be considered in patients with infected pancreatic necrosis or symptomatic sterile necrosis. Although the presence or absence of infection is crucial for prognosis and affects management decisions, the presence of clinical symptoms rather than suspicion of infection is considered paramount for intervention. It should be noted that the management of pancreatic necrosis requires a multidisciplinary approach with clinical expertise from gastroenterologists, surgeons, interventional radiologists, critical care physicians, and dietitians. As such, clinical guidelines recommend transfer to a tertiary care center for management of these patients.

Timing of intervention is dependent on patient factors and clinical stability. Early resuscitative efforts, including fluid resuscitation, initiation of enteral nutrition, and reversal of organ failure, are critical, with most data and practice guidelines recommending delaying intervention for 3–4 weeks after onset of acute pancreatitis. In one retrospective series of 305 patients with necrotizing pancreatitis, early intervention (defined as <4 weeks from disease onset) was associated with longer hospitalization (37 vs. 26 days, $P = 0.01$) and higher mortality (13% vs. 4%, $P = 0.02$), compared to delayed (≥4 weeks) treatment [19]. A randomized trial has shown that early surgical intervention is associated with higher morbidity and mortality, compared to intervention at least 12 days after onset [20]. Other reviews have confirmed lower mortality with delayed surgical intervention [21,22] with data suggesting that early surgery is an independent predictor of poor outcome in necrotizing pancreatitis [23]. More recently, a randomized, multicenter, superiority trial (POINTER), comparing immediate and postponed intervention in patients with infected pancreatic necrosis, observed more interventions in the immediate drainage group, compared to the postponed drainage group, with no difference in adverse events [24].

Significant retroperitoneal inflammation, mediated by cytokine release, is hypothesized to contribute to these observed differences in outcomes. Moreover, early debridement may lead to incomplete excision of necrotic tissue and increased risk of injury to surrounding normal tissues, with associated increases in morbidity and mortality. Conversely, increasing time for clinical stabilization and decreased inflammatory response by delaying debridement improves outcomes for these patients.

Pancreatic Necrosis with Infection

Mortality rates for patients with pancreatic necrosis and superimposed infection approach 30%. Pancreatic infection occurs via bacterial translocation or seeding from bacteremia, and is most commonly caused by gut bacteria, including *Escherichia coli*, *Enterobacter*, *Enterococcus faecalis* and *faecium*, and anaerobes [25]. Infected necrosis is suspected with clinical deterioration of a previously stable patient with pancreatic necrosis. These patients may present with one of the following clinical features: fever, bacteremia, worsening leukocytosis or organ failure, or hemodynamic deterioration. Abdominal imaging in these patients may demonstrate gas within necrotic debris due to the presence of gas-forming organisms or via a fistula to the colon, small bowel, or stomach. Alternatively, infection may be proven by culture or Gram stain obtained by image-guided FNA [26]. Although a Gram stain positive for organisms was previously thought to mandate early surgical intervention [12], patients with suspected infection are increasingly managed with antibiotics and supportive care to allow less invasive and delayed management of a walled-off collection [3]. Diagnostic FNA is therefore used less routinely in the management of suspected infection.

Currently, first-line treatment for patients with infected pancreatic necrosis includes the initiation of

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broad-spectrum antibiotics with high penetration into the pancreas, such as carbapenems, quinolones, and metronidazole. Empiric fungal coverage is not routinely recommended. Notably, while antibiotics are critical in the management of pancreatic necrosis with infection, empiric use of antibiotics for prevention of infected necrosis is not supported. Multiple prospective, randomized trials have concluded that the administration of prophylactic broad-spectrum antibiotics does not impact rates of developing infected necrosis, systemic complications, or mortality [27,28]. As such, prophylactic use of antibiotics is discouraged.

Despite demonstrated success with nonsurgical management for infected necrosis, many if not most patients with infected pancreatic necrosis require some form of intervention. Some series suggest that clinically stable and relatively asymptomatic patients with infected necrosis can be managed with antibiotics alone [16,17,29]. Nonetheless, patients with infection are prone to clinical decline and require surgical, endoscopic, or radiographic intervention with the onset of clinical signs not responding to medical management. As mentioned above, in the era of surgical management, delayed intervention is far preferable to early surgery for patients with infected necrosis. Expedited intervention may be required in patients demonstrating progressive systemic sepsis or hemodynamic instability. In the absence of such systemic signs, clinically stable patients may generally be managed at least temporarily with antibiotics to allow further organization of the inflammatory process. Delayed surgical, endoscopic, or radiologic management may then proceed if clinical symptoms do not improve [6].

Delayed surgical intervention of infected pancreatic necrosis has been facilitated by the use of percutaneous catheter drains. A 1998 series by Freeney et al. [30] demonstrated that some patients with infected pancreatic necrosis might have surgical management delayed or potentially avoided altogether with the use of large-bore percutaneous catheters placed under CT guidance. This strategy was validated in a multicenter trial in which patients were randomized to standard pancreatic debridement versus a "step-up" approach in which debridement was used only if necessary [31]. Using a "step-up" approach, complications were significantly lower, and about one-third of patients were treated with catheter drainage alone.

Sterile, but Symptomatic, Pancreatic Necrosis

The precise role of radiographic drainage, endoscopic or surgical debridement in sterile pancreatic necrosis is less clear. Although most patients with sterile pancreatic necrosis respond to supportive care without the need for intervention, others will experience clinical decline, including organ failure despite the absence of demonstrable infection. Historically, some authors had therefore suggested the need for surgical debridement in patients with progression of disease or failure to improve, regardless of the status of infection [32,33]. Unfortunately, no uniform criteria have defined which patients with sterile pancreatic necrosis might benefit from debridement. In the era of surgical debridement as the primary intervention for necrotizing pancreatitis, some authors suggested criteria for intervention including the extent of necrosis of more than 50% of the pancreatic parenchyma [32], rapid clinical deterioration with multiple organ failure [34], or the presence or persistence of organ failure [35,36]. However, evidence is lacking to support the use of these criteria as an absolute indication for debridement or drainage. Close analysis of one study of 89 patients with severe sterile necrosis identified only two patients who died that might have theoretically benefitted from earlier surgical debridement, though no clinical parameters were able to easily differentiate these patients from others with severe sterile necrosis [13].

As noted above, in the absence of clinical confirmation of infection by image guided FNA or suggestive imaging, intervention is typically based on the clinical course and trajectory. Patients are therefore often brought to intervention for not just documented infection, with positive pancreatic FNA, but also for suspected infection based on persistent sepsis or progressive clinical deterioration [36]. Given the additional morbidity and mortality associated with open surgery, radiologic or endoscopic drainage is used prior to surgical intervention [37].

The process of walled-off pancreatic necrosis recognized in the revised Atlanta classification was previously described by Baron as "organized pancreatic necrosis" [38]. In this condition, an intrapancreatic or extrapancreatic heterogeneous semisolid collection develops in the context of acute necrotizing pancreatitis and has an encapsulated wall [5]. A subset of patients with WON may experience a prolonged clinical course marked by persistent pain, malaise, and inability to eat. This symptom complex was described by Warshaw as "persistent unwellness" [39]. The precise indications and timing of intervention are not precisely defined for these patients.

Asymptomatic WON does not require intervention regardless of the size of the collection and may resolve with conservative management (Fig. 27.1). Symptomatic WON, however, can be marked by pain, intestinal, or biliary obstruction, or later infection. In one series, approximately 10% of patients with sterile pancreatic necrosis underwent surgery for persistent pain and organized necrosis at a mean of 29 days after initial presentation [13].

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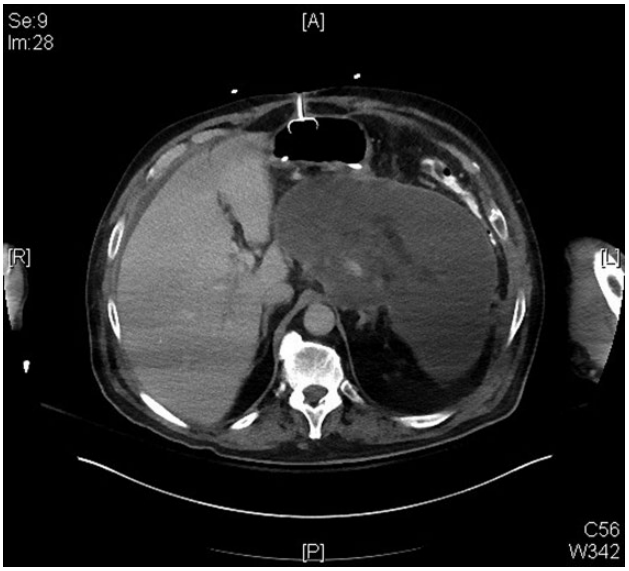


Figure 27.1 Walled-off necrosis. A 55-year-old man presented with severe acute pancreatitis and an acute necrotic collection. He was managed conservatively, and imaging 6 weeks after presentation revealed a large area of walled-off necrosis involving the entire body and tail of the pancreas. The patient remained asymptomatic, and no intervention was pursued.

Preoperative Evaluation and Imaging Considerations

The approach to debridement is dependent on imaging characteristics, including the extent and pattern of pancreatic necrosis. Involvement of the mesenteric root or extension down the paracolic gutter have historically been challenging to treat endoscopically. While some techniques have been described [40], wide surgical debridement and drainage is routinely employed in these cases to ensure adequate debridement. Extension of pancreatic necrosis into the mesocolon presents an additional challenge, as debridement of these tissues may compromise colonic blood flow. Patients with extensive colonic or mesenteric involvement may require partial colectomy at the time of surgical debridement.

Close examination of the pancreas on CT imaging is also key, as patients with isolated necrosis of the pancreatic neck or body may be at an increased risk for developing disconnected pancreatic duct syndrome (DPDS). In this condition, the disconnected pancreatic segment continues to secrete pancreatic fluid, which can in turn lead to the development of new pancreatic collections, fistula formation and recurrent pancreatitis [41]. In one retrospective series, fluid collections recurred in 42% of patients with DPDS, despite endoscopic drainage [42]. While rare with a reported prevalence of 10% to 31% [42], prompt diagnosis of DPDS is key to reducing morbidity. Diagnosis requires necrosis of at least 2 cm of pancreas and viable upstream pancreatic parenchyma [41]. While imaging modalities can be suggestive of DPDS, ERCP, which may visualize extravasation of contrast from the pancreatic duct, remains the gold standard for diagnosis.

Management includes conservative therapy with nutritional optimization, endoscopic treatment, and/or surgery. The routine use of octreotide in these patients is not supported [43]. While surgery was once considered the mainstay of treatment for these patients, advances in endoscopic treatment modalities have provided less-invasive alternatives for select patients. Transpapillary pancreatic duct stent placement has been previously described with successful outcomes [44,45]. In a series of 43 patients, 58% had resolution of the disruption after stent placement. Stents bridging the disruption and longer duration of stent therapy were associated with improved outcomes. In another series endoscopic treatment improved outcomes for patients with DPDS with a failure rate of 23% [42]. While long-term plastic stent placement has been associated with improved outcomes, risks include stent migration and infection. The prophylactic use of pancreatic stents in acute necrotizing pancreatitis remains controversial, with data from a recent prospective randomized superiority trial suggesting a high risk of infection in these patients and advising against routine prophylactic use [46].

Although DPDS can be temporized with EUS-guided transmural stenting [47], many patients may ultimately require consideration of definitive surgical management. Surgical options include distal pancreatectomy for removal of the viable distal segment or internal drainage procedures such as cyst-gastrostomy, which may better preserve pancreatic function.

Surgical and Interventional Procedures

The use of various radiologic, surgical, and endoscopic interventions for necrotizing pancreatitis will vary among institutions [6]. Although open surgical necrosectomy was previously considered the definitive management, a number of minimally invasive techniques have been developed. As noted above, delayed intervention is preferable in all patients, if possible, particularly when open surgical management is used [48]. However, interventional radiologic techniques may be performed earlier with suspected infection [22]. Even in the setting of suspected or known infection, there is a growing trend to treat with supportive care and antibiotics unless there are signs of sepsis, until the pancreatic collection becomes walled off [3].

Owing to the efficacy of minimally invasive approaches and associated reductions in mortality, the

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treatment paradigm for necrotizing pancreatitis has shifted to a predominantly nonsurgical approach. The original "step-up approach" to management of infected pancreatic necrosis was popularized by randomized data suggesting that percutaneous drainage followed by minimally invasive retroperitoneal necrosectomy improved morbidity and mortality [31]. This has further evolved based on a recent multicenter, randomized trial assessing an endoscopic step-up approach, defined as transluminal drainage followed by endoscopic necrosectomy. When compared to patients treated with the traditional "step-up" approach, patients in the endoscopic group were found to have lower rates of pancreatic fistula and length of hospitalization [49]. These data have been reproduced in a single-center trial comparing patients treated with minimally invasive surgery or an endoscopic step-up approach. In this trial of 66 patients, the endoscopic approach was associated with reduced complications, cost, and increased quality of life [50]. Taken together, these data suggest an evolving treatment paradigm for patients with pancreatic necrosis, and a key role for both percutaneous and endoscopic procedures.

Percutaneous Catheter Drainage

Percutaneous catheter drainage (PCD) can be performed either as a "step-up" toward endoscopic or surgical necrosectomy once WON has developed, or in some cases as definitive therapy [31]. PCD may be further considered when endoscopic drainage is unfeasible due to the anatomic distribution of the pancreatic necrosis. For example, in patients with necrotic extension into the pelvis or the paracolic gutters, PCD may be necessary to access these dependent collections, which are inaccessible from the gastric or duodenal lumen [7].

Catheters are placed using either a transperitoneal or retroperitoneal approach under CT or ultrasound guidance. Multiple catheters are often required, with follow-up procedures to place additional or larger catheters [51]. One significant advantage of PCD is the opportunity to address symptomatic or infected necrotic collections before WON has developed. This may be particularly useful for patients who are failing conservative management or who require rapid source control due to clinical signs of sepsis. PCD may be of additional benefit in patients deemed unfit for surgical intervention, or to address residual collections after surgical or endoscopic debridement [6]. Placement of large (24Fr or greater) percutaneous drains may also assist with later minimally invasive debridement methods, such as video-assisted retroperitoneal debridement (VARD) [7].

One potential risk of percutaneous drainage is the development of pancreatocutaneous fistulas. In a prospective study comparing endoscopic and percutaneous approaches, fistula formation was observed in 32% of the percutaneous group compared to 5% in the endoscopic group [49]. Simultaneous endoscopic drainage with percutaneous drain placement may help minimize this risk [52].

As noted, catheter drainage alone is often effective without necrosectomy. Success of PCD has been associated with necrosis <50% and absence of extrapancreatic infection [53]. In the PANTER trial, use of catheter drainage resulted in significantly decreased morbidity with equal mortality compared to surgical necrosectomy [31]. Other studies have shown an approximately 50% success rate in treating necrotizing pancreatitis, whether sterile or infected [54]. PCD is less likely to be successful as a definitive intervention in patients with duct disruption, who may require eventual surgical or endoscopic therapy [55].

Direct Endoscopic Necrosectomy

Initially described in 1996, endoscopic necrosectomy is a recognized alternative to surgical debridement, though its availability is limited to specialized centers. A series of 104 patients at six centers showed resolution of WON in 91% with endoscopic necrosectomy, with only 4% requiring surgical debridement [56]. Furthermore, data suggest that endoscopic necrosectomy is associated with fewer complications, less organ failure, and decreased periprocedural inflammation [36]. Another meta-analysis including 400 patients with infected pancreatic necrosis concluded that a step-up approach with endoscopic debridement should be preferred, followed by step-up with delayed surgical debridement [57].

Similar to PCD, multiple procedures may be required, and not all patients may be candidates for endoscopic therapy. Ideally, collections for endoscopic access are not only walled off but also are adjacent to the gastric or duodenal lumen. Some acute necrotic collections cannot be approached endoscopically due to lack of abutment of the stomach or duodenum. As mentioned above, while endoscopic approaches can be started less than 4 weeks from onset of pancreatitis, patients who can wait ≥4 weeks prior to endoscopic intervention have been shown to have decreased mortality. Furthermore, early collections are not ideally suited for endoscopic therapy due to the risk of intra-abdominal spread of an infected collection. Multifocal collections are also less easily approached in this manner.

Traditionally, double-pigtail plastic stents (DPPS) were placed from the gastric lumen into the pancreatic

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collection. EUS-guided transmural entry is generally preferred to reduce rates of bleeding, which have been reported in up to 20% of patients [56,58]. Given the narrow caliber of these stents, DPPS without subsequent endoscopic necrosectomy provides suboptimal treatment for most patients [59]. To address this limitation, there has been increased interest in use of larger caliber self-expanding metal stents (SEMS). In one series evaluating 94 patients who received SEMS vs. DPPS, treatment with SEMS decreased the need for repeat necrosectomy and risk of intervention-related hemorrhage [59]. The development of lumen-apposing metal stents (LAMS) has also demonstrated favorable results. Due to their shorter length and larger diameter, these stents facilitate endoscopic necrosectomy and are at lower risk for migration [60]. The placement of double-pigtail plastic stents through LAMS has also been proposed as a method to reduce the risk of stent occlusion and/or migration [7].

Direct endoscopic necrosectomy (DEN) may be performed via stents, with passage of forceps, polypectomy snares, and retrieval nets. In general, serial imaging after debridement is performed every 1–2 weeks to follow evolution of necrosis. Routinely, repeat debridement and irrigation is indicated for management of residual solid, necrotic material. The use of acid-suppressive medications is generally discouraged after drainage, with some data suggesting that discontinuation of proton-pump inhibitors reduces the number of endoscopic procedures required [61].

While DEN has been associated with reductions in morbidity and mortality, compared to more invasive techniques, mortality rates remain high at 7.5%. Similarly, complications include bleeding, perforation, sepsis, or organ failure, with an estimated morbidity rate of 14–26% [62]. As these high rates of morbidity have been mostly attributed to procedural and provider variability, standardized techniques for DEN have been proposed [62].

Surgical Debridement

Open surgical debridement for years was considered the gold standard of surgical intervention for pancreatic necrosis, by removing necrotic pancreatic and peripancreatic tissue and establishing a means of postoperative drainage while preserving viable pancreatic parenchyma. Methods have included debridement with closure over drains, debridement with open packing of the pancreatic bed, debridement with internal drainage and cyst gastrostomy or debridement with closure over irrigation drains [10,63–65]. Mortality and complication rates for published series utilizing these techniques vary widely, although comparisons between studies are confounded by the lack of standardization of disease severity or operative indications.

In the setting of minimally invasive options such as image-guided catheter drainage and direct endoscopic necrosectomy as described above, several important potential indications for surgery remain. Due to its invasiveness and associated perioperative complications, open surgery is typically reserved for patients in whom less invasive methods have failed. One advantage of open surgical necrosectomy is that it may offer the best chance to completely remove all necrotic tissue and address other associated complications in a single procedure. In some cases, collections may not be accessible via image-guided techniques, may be multifocal, or persistent after minimally invasive necrosectomy (Fig. 27.2). In other instances, a patient may not be deemed clinically stable for minimally invasive measures. Surgical therapy in these instances should be delayed as long as possible given the increased risk of early surgical intervention. Other indications for surgical debridement include the presence of bowel perforation, obstruction, fistula to a hollow viscus such as the colon, and abdominal compartment syndrome [66] (Fig. 27.3).

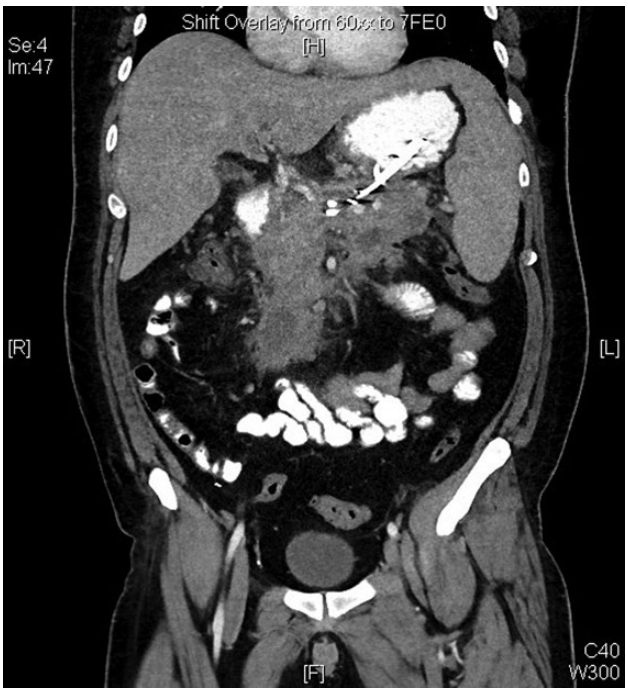


Figure 27.2 Undrained mesenteric abscess after endoscopic debridement. A 50-year-old man underwent uncomplicated endoscopic debridement for symptomatic walled-off pancreatic necrosis. He represented with fevers, pain, leukocytosis, and a phlegmonous abscess tracking down into the small bowel mesentery. Endoscopic debridement and CT-guided drainage were not felt to be possible. Surgical debridement was required.

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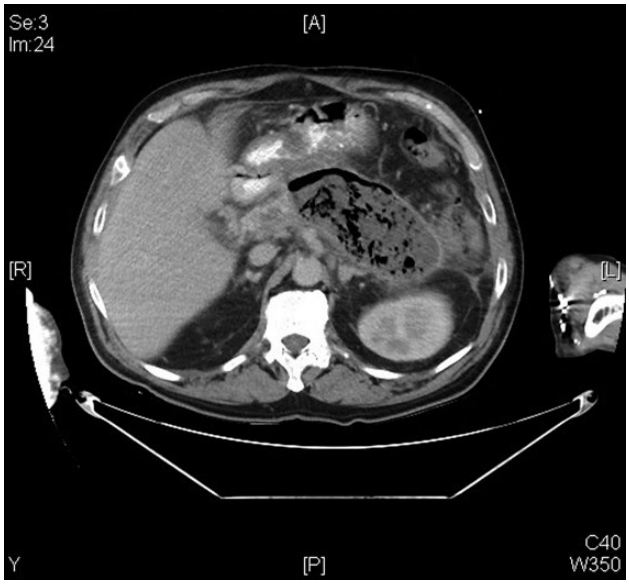


Figure 27.3 Infection of walled-off necrosis with fistula to colon. The patient in Fig. 27.1 presented 12 months after his original episode of pancreatitis with fever and bacteremia. Imaging demonstrated gas in the area of walled-off necrosis, consistent with infection. Endoscopic debridement was attempted, though contrast injection to the cavity demonstrated a fistula to the transverse colon. Open surgical debridement was pursued.

Of the available surgical approaches, open debridement with external drainage has been considered the gold standard, with operative morbidity of 72% and mortality of 4% [67]. Consideration of enteral access (i.e., jejunal feeding tube placement) during open debridement is reasonable to support postoperative nutritional optimization. Alternatively, internal drainage with cystgastrostomy may be performed in patients with WON. Other surgical techniques such as open packing with planned return to the operating room in 48–72 hours may be considered when early surgical intervention is required, or in cases when complete debridement cannot be obtained during the index procedure. Although this approach can effectively control intra-abdominal sepsis, it has inherently higher risk due to the need for multiple procedures and prolonged intubation time. Trans-gastric debridement is similar to endoscopic debridement and can be performed laparoscopically or open.

Of note, minimally invasive forms of surgical debridement have been used in addition to traditional "open" necrosectomy. Laparoscopic approaches are well described and may be more successful in completely removing all necrotic material compared to other minimally invasive methods [68]. Laparoscopic-assisted transperitoneal debridement has been described with placement of three ports for debridement, although this approach increases the chances of peritoneal contamination. Video-assisted retroperitoneal debridement (VARD) is a procedure by which the retroperitoneal collection is accessed via the tract of a large percutaneous catheter [51]. Patients with central necrosis may benefit from VARD, although this approach has limited efficacy for drainage of necrosis to the right of the mesenteric vessels [7]. Notably, VARD avoids pneumoperitoneum and peritoneal seeding possible with a laparoscopic procedure. This approach is not preferred for patients who may require simultaneous cholecystectomy or jejunostomy tube placement [6]. While open necrosectomy can be avoided in many patients, limited data are available comparing outcomes of these procedures [51].

Surgical debridement has several associated complications. Persistent or recurrent intra-abdominal fluid collections are a common postoperative complication, and often require intervention such as additional percutaneous drainage procedure. Bleeding is the most common postoperative complication requiring reoperation after debridement. Early bleeding is often due to injury of the peripancreatic vessels whereas late bleeding may be due to pseudoaneurysm rupture. Pancreatic fistulas and pancreatic insufficiency are also common side effects of the procedure.

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Management of Infected Necrosis: Step-Up Approach

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Introduction

In the majority of patients with acute pancreatitis, the disease course is mild and self-limiting requiring supportive care only. Approximately 20% of patients, however, develop necrotizing pancreatitis. This is characterized by necrosis of the pancreatic or peripancreatic tissue, as seen on contrast-enhanced computed tomography (CT) [1,2]. Necrosis of the pancreatic or peripancreatic tissue is sterile, therefore initial management remains supportive including fluid resuscitation, pain control, and nutritional support [2,3].

Secondary infection of pancreatic or extrapancreatic necrotic tissue occurs in one-third of patients with necrotizing pancreatitis [1]. Infected necrosis is associated with a prolonged hospital and intensive care stay, sepsis, multiple organ failure, and a 20–30% mortality rate [4–6]. Although infection can occur in the early phase of pancreatitis, it usually develops 3 to 4 weeks after onset of disease [7–9]. Infected necrosis is suspected when the patients show clinical deterioration, in the absence of an alternative source of infection, despite maximal conservative support [10] or when gas configurations are present in the necrotic collections or necrosis as demonstrated on abdominal imaging [3]. Fine-needle aspiration of peripancreatic or pancreatic collections is not indicated because of the considerable number of false negative (20–29%) and false positive (4–10%) results [10–12].

The History of Pancreatic Interventions

The benefit of surgical treatment in acute pancreatitis has been an ongoing debate since the late nineteenth century. It was in 1886 that Nicholas Senn considered surgery in the early phase of pancreatitis as ineffective and risky [13]. Despite a mortality rate of more than 50%, laparotomies with drainage of the lesser sac and placement of gauze to achieve optimal drainage and to prevent wound closure, were considered the best treatment for acute pancreatitis until the 1930s [14]. Around this time, it became possible to diagnose acute pancreatitis without needing laparotomy by determination of serum amylase levels. This contributed to the use of conservative treatment for acute pancreatitis, which was reinforced in 1948 by a publication highlighting the poor survival rates after early surgery [15]. However, since conservative treatment was not giving satisfactory results, in the 1960s surgical procedures were reconsidered and surgical treatment was again indicated in the initial stages of acute pancreatitis. It was in the 1980s that the therapeutic approach of acute pancreatitis changed again, when a series of prospective studies showed superior results of conservative treatment compared with surgical treatment in patients with sterile necrosis [16–18].

The value of abdominal abscess drainage under ultrasound or CT was discovered in 1979, while it was not until 1987 when the possibility of aspiration of pancreatic or peripancreatic fluid ultrasound or CT-guided

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aspiration was used for early diagnosis of infected necrosis [19,20]. At the beginning of the twenty-first century, the first study was published on laparoscopic necrosectomy followed by a study involving endoscopic necrosectomy in 2009 [21,22]. The necessity of surgical debridement for infected necrosis was subsequently questioned when Runzi et al. showed that initial conservative therapy, including antibiotic therapy, could be instituted [23]. Mortality in patients managed with surgery was identical to those managed conservatively [23]. Surgical therapy, when required, was often delayed to a later stage of disease, when the systemic inflammatory response has been stabilized and necrotic pancreas had become demarcated. In other patients, surgical therapy was avoided altogether. Subsequent studies have confirmed this strategy, Garg et al. describe a 10-year series of 80 patients with infected pancreatic necrosis in whom 47 were treated with antibiotics alone [24]. The urge for surgical debridement for all patients with infected pancreatic necrosis is therefore no longer considered valid [25]. Although laparoscopic direct necrosectomy was already described in the 1990s, it failed to gain popularity due to technical difficulty. Therefore, until publication of the PANTER trial in 2010, necrosectomy by laparotomy was the standard intervention [26]. In the PANTER trial, 88 patients were randomly assigned to the "step-up" approach or to immediate open necrosectomy. A step-up approach consisted of percutaneous catheter drainage, followed, if needed, by minimally invasive necrosectomy. Major short-term complications such as new onset multiorgan failure and long-term complications such as endocrine insufficiency, and costs, were decreased in the patients who were assigned to the "step-up" approach. The effect of the step-up approach was beneficial in patients with and without organ failure [26]. In addition, necrosectomy was avoided in 23–50% of the patients treated with percutaneous catheter drainage [26–29]. Since then, the step-up approach is considered to be the standard treatment. Several new minimally invasive strategies have been introduced and compared in randomized controlled trials with the goal of improving survival and decreasing complications and comorbidities. In the most recent study, 19 out of the 49 (39%) patients with infected necrosis did not require intervention at all and could be treated with antibiotics alone [30].

Step-Up Approach

Antimicrobial Management of Infected Necrosis

When infected necrosis is clinically or radiologically suspected, antibiotic therapy can be initiated without fine-needle aspiration or pancreatic culture [11,31]. Since it is hypothesized that translocation of bacteria from the gut is the major source for infection of necrosis, antibiotics that are effective on gut-derived bacteria with the potential to penetrate into the pancreas (carbapenems, quinolone, metronidazole, third-generation cephalosporins) should be considered as empirical treatment [7,32,33]. Antibiotic therapy should be adjusted accordingly once pancreatic culture results have been obtained. Since there are no data on the adequate duration of antibiotic therapy, it remains unknown when to stop antibiotic administration or when to proceed to pancreatic intervention. Current guidelines recommend that antibiotics are discontinued once the last percutaneous catheter drain has been removed for more than 48 hours and/or pancreatic cultures remain negative [11]. In addition, improvement of clinical, biochemical, and radiological signs aids in the decision to stop antibiotics. This is especially important in patients undergoing endoscopic treatment of the infected necrosis, as no drains are removed and no new pancreatic cultures are available.

Percutaneous or Endoscopic Drainage of Infected Necrosis

Pancreatic intervention is indicated in patients who fail to improve or who show clinical deterioration under antibiotic therapy [11]. Invasive intervention should preferably be delayed until collections have become walled-off, typically 3–4 weeks after the onset of disease [11]. In the recent multicenter randomized POINTER trial, no difference in the rate of complications or mortality was found between patients randomly assigned to immediate drainage (<24 hours after suspected or proven infected necrosis, 55 patients) or postponed drainage (when the collections were walled-off, 49 patients). The mean number of pancreatic interventions was higher in the group of patients who underwent immediate drainage [30].

Radiologically guided percutaneous catheter or endoscopic transluminal drainage is the first step in the step-up approach. The choice of one approach over another is based on multiple factors including characteristics of the collection (i.e., location, extent, integrity of the pancreatic duct) and clinical (i.e., hemodynamic) status of the patient. The randomized TENSION trial assigned 98 patients to either the endoscopic step-up approach (51 patients) or the surgical step-up approach (47 patients). No difference was found in major complications or death during a 6-month follow-up between the two groups. The rate of pancreatic fistulas and length of hospital stay were lower in the group assigned to the endoscopic step-up approach [34]. Therefore, the endoscopic approach is preferred.

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Endoscopy

There are several endoscopic techniques to treat (infected) walled-off necrosis. The similarity between these techniques is the transmural access route. Since the superiority of endoscopic ultrasound (EUS)-guided drainage in patients with pseudocysts using an echo-endoscope has been shown in two randomized trials, conventional transmural drainage using a standard endoscope (blind access) has nowadays been replaced by EUS-guided drainage [35,36].

During endoscope drainage a transmural drain is inserted into the cavity through either a single or several access sites (multiple transluminal gateway technique) [37]. The multiple transluminal gateway technique led to more frequently reported clinical success compared with single-access endoscopic drainage in two retrospective series [37,38]. In both methods, balloon dilatation is performed to create a fistula between the gastrointestinal tract and the collection after the collection is accessed [39]. This fistula must be maintained to allow the evacuation of pus, debris, and necrotic tissue. This can be done by inserting multiple plastic double-pigtail stents or a self-expandable metal stent (e.g., lumen-apposing metal stents [LAMS]). Due to the larger lumen of the LAMS, expectations were high and this was confirmed in one small retrospective study [40]. An interim analysis of an ongoing single-center randomized trial, however, has revealed an important rate of delayed stent-related adverse events, consisting of bleeding and embedded LAMS. This led to the need to perform imaging to exclude vascular complications and the retrieval of the LAMS within 4 weeks [41]. A recent prospective observational cohort study, conducted by the Dutch Pancreatitis Study Group, has shown no increased risk of complications, including bleeding, in patients treated with LAMS [42].

With regard to removal of the endoscopic drains, plastic double-pigtails stents can be left in situ indefinitely, unlike LAMS, which it is advised to remove within 6 weeks due to worrisome long-term adverse events [41,43]. Subsequently, in the presence of a disruption of the pancreatic duct, LAMS should be replaced by plastic double-pigtail stents. The use of LAMS did not reduce the need for endoscopic transluminal necrosectomy compared with plastic double-pigtails stents (34 [64%] patients vs. 27 [53%], respectively). In the TENSION trial, 57% of the patients who underwent endoscopic drainage required a necrosectomy [34].

Radiology

As shown in the PANTER trial, percutaneous catheter drainage is feasible in >95% of the patients [26]. According to the Seldinger or the tandem trocar technique regular silicone pigtail drains are used [29]. The percutaneous catheter drain is preferably inserted in the retroperitoneal cavity to facilitate minimally invasive retroperitoneal necrosectomy if necessary as the next step. During the initial percutaneous procedure (real-time) ultrasound guidance in combination with fluoroscopy is often preferred to prevent puncture of organs of the gastrointestinal tract. If the collection contains limited liquid content, visualization with ultrasound can be difficult. In these patients, CT-guided drainage can be performed. Drain diameter may vary and there is no comparative data regarding the influence of different sizes of the drain; however, large-bore catheters of more than 14 French seem to obstruct less frequently [29]. In half of the patients, drains are required to be replaced or upsized [26]. Successful percutaneous catheter drainage can be predicted when the collection shows a decrease in size of at least 75% after the first 10–14 days following percutaneous catheter drainage [28,44]. No data is available on the optimal timing of removal of percutaneous catheter drains. In about half of the patients surgical necrosectomy was required following primary percutaneous catheter drainage as the primary treatment [29,35].

Pancreatic Debridement of Infected Necrosis

If no further clinical improvement is seen or when patients show clinical deterioration after endoscopic drainage or percutaneous catheter drainage without options for further percutaneous drainage, debridement of pancreatic necrosis is indicated. The optimal timing for repeat intervention, however, remains unclear. If clinically possible, the collection should be walled-off before necrosectomy is performed since early necrosectomy is associated with poor outcomes [45]. As with the choice for the first step, the subsequent approach (either endoscopic or surgical) for necrosectomy should be based on patient characteristics and location of the peripancreatic or pancreatic necrosis and should be performed as minimally invasive as possible [11,26,34].

Especially in high-risk, critically ill patients minimally invasive surgery and endoscopic necrosectomy were associated with reduced death rates as compared to open necrosectomy [46]. Regardless of the benefits of minimally invasive intervention, patients with intra-abdominal hemorrhage, perforation and/or abdominal compartment syndrome may require immediate intervention using either a minimally invasive or more invasive method [11].

The TENSION trial did not show superiority of endoscopy necrosectomy in outcomes such as major complications and death. Length of hospital stay, rate of pancreatic fistulas, and costs were significantly reduced in the patients undergoing the endoscopic step-up approach [34].

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Endoscopy

Endoscopic transluminal necrosectomy is performed to remove solid necrotic debris by a combination of sucking debris through the working channel of the endoscope directly inserted into the necrotic collection (direct transluminal endoscopic necrosectomy), removing necrotic material with a removal device, and applying irrigation [37,47]. Although not well studied, the anatomical position of the initial puncture is also important for direct transluminal endoscopic necrosectomy [42]. Due to the lack of specifically designed endoscopic accessories, pre-existing tools are used during necrosectomy, such as different types of stone removal baskets (i.e., Dormia), polypectomy snares, balloons, nets, and different types of forceps [42]. These devices often lack sufficient grip, however, making the procedure time-consuming and often marginally effective requiring more than one procedure. Preliminary results suggests that the EndoRotor device (i.e., an automated mechanical endoscopic resection system designed for tissue dissection and resection with a single device) can safely, rapidly, and defectively remove necrotic tissue in patients with (infected) walled-off necrosis [48].

Surgery

There is a large variance in the used and personal favor of the various techniques. Surgical debridement can be performed with open or minimally invasive (laparoscopic) techniques [44,49]. Open debridement with external drainage is performed through a laparotomy followed by entry in the retroperitoneum to remove necrotic tissue. Subsequently, two to four large closed suction drains are left to facilitate drainage of the cavity. However, this procedure is only appropriate in patients with walled-off necrosis. There are various minimally invasive approaches described, including percutaneous necrosectomy (MIRP), video-assisted retroperitoneal debridement, laparoscopic transgastric necrosectomy, laparoscopic cystgastrostomy, and personal variations on the aforementioned techniques [50–54]. In general, minimally invasive surgery continues to be the preferred technique; however, open necrosectomy remains a possibility for some patient groups.

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Management of Infected Pancreatic Necroses: An Endoscopic Approach

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Pancreatic Necrosis

Pancreatic fluid collections (PFC) can occur as a complication of acute pancreatic injury (acute pancreatitis, trauma, surgical resection or injury to the pancreas during abdominal surgery) or chronic injury (chronic pancreatitis, autoimmune pancreatitis). At the basis of this pancreatic injury is disruption of the main pancreatic duct and/or side branches. Acute necrotizing pancreatitis (ANP) is at the severe end of a spectrum of inflammation associated with pancreatitis, resulting in cell death. Pancreatic necrosis is defined as nonviable pancreatic parenchyma usually with associated peripancreatic fat necrosis and occurs in 20–30% of all episodes of pancreatitis [1]. The resultant devitalized tissue becomes a potential bed for infection. Approximately 30% of patients with pancreatic necrosis develop infection of the necrotic tissue [2]. The amount of necrotic tissue is the strongest predictor of mortality necrotic pancreatitis. Fortunately, with early recognition and improvements in critical care most patients survive the early phase of systemic inflammatory response syndrome (SIRS) and many survive multisystem organ failure. Even with aggressive intravenous fluid replacement, nutritional support, and early intervention of pancreatic necrosis, the presence of pancreatic necrosis is associated with an overall increase in mortality as compared to interstitial or edematous pancreatitis. The mortality rate from sterile pancreatic necrosis is approximately 13% and rises to 35% when infected [2].

ANP is detected radiographically on contrast-enhanced CT (CECT) by the presence of non-enhancing pancreatic parenchyma. In the first few weeks after onset of ANP, pancreatic necrosis and/or peripancreatic fat necrosis can evolve into more organized processes that expand the initial area of necrosis. If this process occurs prior to 4 weeks after the onset of ANP it is termed an acute necrotic collection, which is potentially amenable to endoscopic drainage. After 4 weeks from onset of ANP such collections are termed walled-off pancreatic necrosis [3]. Both of these processes contain variable amounts of fluid (pancreatic juice) and solid debris (pancreatic and/or peripancreatic fat necrosis). Infected necrosis refers to bacterial invasion of necrotic pancreatic tissue and can lead to clinical infection, sepsis, and death. Infected necrosis is rare during the first week after onset of ANP [4,5]. Evidence suggests no absolute correlation between the extent of necrosis and the risk of infection and duration of symptoms. The mortality rate is substantially increased when infection occurs and most patients will require intervention and drainage.

Mechanical Intervention

Mechanical intervention for infected pancreatic necrosis can be surgical, percutaneous, and endoscopic. Open surgical therapy is not considered as first-line approach [6] and has largely been replaced by minimally invasive approaches [7,8] using flexible endoscopic, rigid endoscopic (via percutaneous catheter sites) [9], percutaneous drain placement, and laparoscopic approaches, alone or in combination [5]. It has been more than 25 years since the first report of endoscopic drainage for pancreatic necrosis [10]. Optimal management of necrotizing pancreatitis requires a multidisciplinary team including dedicated surgeons, interventional radiologists, and gastrointestinal endoscopists. Such a multidisciplinary team needs to be involved from the onset of the disease to decide if, when, and how an intervention needs to be performed.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Intervention in asymptomatic or minimally symptomatic patients with sterile necrosis is not indicated regardless of size, location, and extension [11,12]. For patients with sterile WOPN and persistent gastric outlet, intestinal, or biliary obstruction due to mass effect, intervention may be undertaken at least 4 weeks after onset of symptoms, the timing dependent on severity. In patients with persistent symptoms such as pain and "failure to thrive" the form and timing of intervention is debated and current intervention can be considered 8 weeks after onset [12].

In clinically stable patients with infected necrosis, it is advisable to continue supportive care with antibiotic therapy directed empirically or by culture data and delay surgical, radiologic, or endoscopic approaches for more than 4 weeks in order to facilitate the formation of WOPN with liquefaction of the contents. Indeed, in a recent landmark randomized trial of patients with infected necrosis, there was a significant improvement in outcome when endoscopic intervention was delayed until patients developed WOPN [1]. Prompt drainage is required for patients with infected necrosis and clinical instability. In these cases, minimally invasive methods of drainage are preferred. Distinguishing sterile from infected necrosis can be difficult but is important as the presence of infection alters prognosis and management. Percutaneous fine-needle aspiration (FNA) of pancreatic and peripancreatic collections for the detection of infection should not be routinely performed. It may postpone interventions, give false negative results or induce secondary infection [5]. Suspicion of infection is usually based on clinical deterioration despite medical support, high fever with rising inflammatory markers and/or positive blood cultures. The presence of gas on imaging studies is highly suggestive of infection, likely due to fistula, but it is only present in a minority of cases [13,14]. Infection can be confirmed by FNA or through cultures obtained at the time of drainage, and can be used to guide antibiotic therapy [11].

The goals of endoscopic therapy for infected WON are: (i) drainage of fluid and removal of solid components using a transmural approach (transgastric or transduodenal), and (ii) treatment of pancreatic ductal (PD) leaks and/or disruptions using a transpapillary approach, in selected patients. Theoretically, addressing pancreatic disruptions may lead to better long-term outcomes [15]. However, despite the relatively high incidence of ductal disruptions in patients with WOPN, subsequent disconnected duct syndrome following endoscopic therapy is uncommon [16]. Transpapillary endoscopic drainage as primary therapy of WOPN is not an adequate method to remove solid debris. Removal of solid debris is vital to any type of intervention during transmural drainage, which can be "mechanical," by irrigation, or a combination.

In case of proven or suspected infected necrotizing pancreatitis, intervention should be delayed when possible until ≥4 weeks after onset of ANP [17,18]. Endoscopic transmural access can be undertaken for acute necrotic collections as early as 2–3 weeks after the onset of acute pancreatitis in the setting of sepsis as long as they are deemed to be organized as determined by CT or MRI [19–21].

Transmural Drainage

The evolution of endoscopic therapy of WOPN began as with pseudocyst drainage using small diameter transmural tracts (8 mm) and placement of 10Fr plastic stents, in addition to a nasocystic irrigation tube [10]. Early in the endoscopic experience many patients required adjunctive percutaneous drains, especially to treat large paracolic gutter extensions [22]. Larger diameter transmural dilations were then added to the irrigation approach. Nasocystic irrigation tubes can be used for continuous flushing with sterile fluid per 24 hours or by bolus lavage every 3–4 hours for several days to weeks depending on the volume of debris and patient tolerance and may avoid the need for subsequent necrosectomy. However, they are uncomfortable, and with the advent of large-diameter transluminal metal stents, their use is decreasing.

Direct endoscopic necrosectomy (DEN) was introduced by Siefert [23], and subsequently Seewald [24] as a method to remove necrotic tissue by passing forward or side-viewing endoscopes transmurally into the collection; baskets, grasping forceps, and snares are used to remove solid debris [25]. Transmural placement of large diameter covered (esophageal) SEMS or large diameter (15–20 mm) self-expandable lumen-apposing metal stents (LAMS) can not only avoid the need for additional endoscopic intervention by allowing egress of fluid and debris, but also facilitate passage of endoscopes into the necrotic cavity to perform direct necrosectomy while preventing the need for repeated balloon dilation of the gastric or duodenal wall to enter the cavity. Indeed, in most Western countries a commercially available LAMS that has an electrocautery tip and which is specifically designed for use with endoscopic ultrasound (EUS) scopes has greatly simplified the technical aspects of the procedure [26]. Instillation of hydrogen peroxide into the necrotic cavity may facilitate removal of necrotic debris during DEN and reduce the likelihood of further necrosectomies [27].

In conjunction with percutaneous drain placement, hybrid approaches have also been described [28]. In some patients with peripheral collections that are not accessible from a transluminal approach, a percutaneous drain is placed. Subsequently, a large-bore self-expandable metal stent is placed through the

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percutaneous tract to allow for direct endoscopic necrosectomy with a flexible endoscope.

A dual-modality drainage technique using CT-guided percutaneous irrigation/drainage catheter placement is followed directly by endoscopic transmural drainage. The percutaneous catheter is used for irrigation, with egress internally through the transmural tracts. This allows avoidance of direct endoscopic necrosectomy. Using this approach with endoscopically placed plastic stents resulted in decreased length of hospitalization and number of radiological and endoscopic procedures compared with either modality alone [29]. This approach also hastened resolution, but also prevented development of external fistulae and bleeding related to percutaneous manipulations. Surprisingly, the introduction of LAMS did not appear to offer an advantage to plastic stents at the same institution [30].

For complex organized necrosis, a multi-gateway approach [31] has been described, which utilizes two or more transmural entry approaches to permit irrigation and improved drainage. Nasocystic irrigation enters one site and egresses from another.

Transmural Entry Devices

Devices used to perform transmural puncture of WOPN can be divided into cautery and non-cautery devices. Cautery devices include standard diathermy wires (needle knives), specialized fistulotomy devices (Cystotome CST-10; Cook Endoscopy, Winston-Salem, NC, USA) and specialized stent delivery systems with cautery incorporated (AXIOS-EC; Boston Scientific, Marlborough, MA, USA). Non-cautery devices include 19-gauge EUS-FNA needles.

The collection is punctured transmurally using EUS guidance to be certain of the puncture site and to avoid vessels using Doppler. Fluid is aspirated during the procedure and sent for microbial analysis including Gram stain and culture. The procedure can be performed with or without fluoroscopy.

Stent Placement

Antithrombotic agents should be discontinued whenever possible prior to transmural drainage, and certainly prior to direct endoscopic necrosectomy. In case of severe bleeding during the procedure which cannot be treated endoscopically, immediate assistance of an interventional radiologist should be requested. Endoscopic drainage and necrosectomy are preferably performed with patients under deep sedation or general anesthesia. Plastic stents are not ideally suited to drain WOPN because of their small diameter. The use of large-diameter fully covered self-expandable metal stents are used instead. Specially designed biflanged short length (10 or 15 mm) LAMS (AXIOS; Boston Scientific) with luminal diameters of 15–20 mm and electrocautery incorporated delivery systems are now commonly used due to ease of placement [32]. With commercially available electrocautery-equipped LAMS delivery systems the stent is placed in a single-step (puncture and stent deployment). One needs to be particularly careful of proper device deployment, particularly the final, crucial step involving proximal flange release. Some endoscopists prefer to place a plastic double-pigtail stent through the LAMS to prevent occlusion due to impaction of necrotic material and contact of the stent edge against the inner wall of the cavity.

Direct endoscopic necrosectomy (DEN) can be performed using a standard forward-viewing endoscope during the initial endoscopic procedure after balloon dilation of the tract (12–20 mm) or the LAMS lumen (Fig. 29.1) to its maximal diameter although placement of the LAMS alone may be adequate to resolve WOPN (Fig. 29.2). In one study, LAMS alone allowed complete resolution of WOPN without necrosectomy in approximately half of 136 patients [33]. Patients with collections ≥10 cm in size, paracolic extension, or ≥30% solid debris within the collection were more likely to require additional intervention. Some authors advocate scheduled endoscopic debridements at intervals ranging from days to weeks depending upon inpatient or outpatient status, severity of illness, anticipated volume of residual necrosis, and findings on follow-up CT or MRI. Internal drains are endoscopically removed several weeks after complete resolution of the collection and after removal of external drains (if placed) to prevent persistent pancreatico-cutaneous fistula. Patients



Figure 29.1 Image after direct endoscopic necrosectomy through a LAMS. The LAMS was removed at the end of the procedure as seen alongside a portion of the necrotic debris removed during the procedure.

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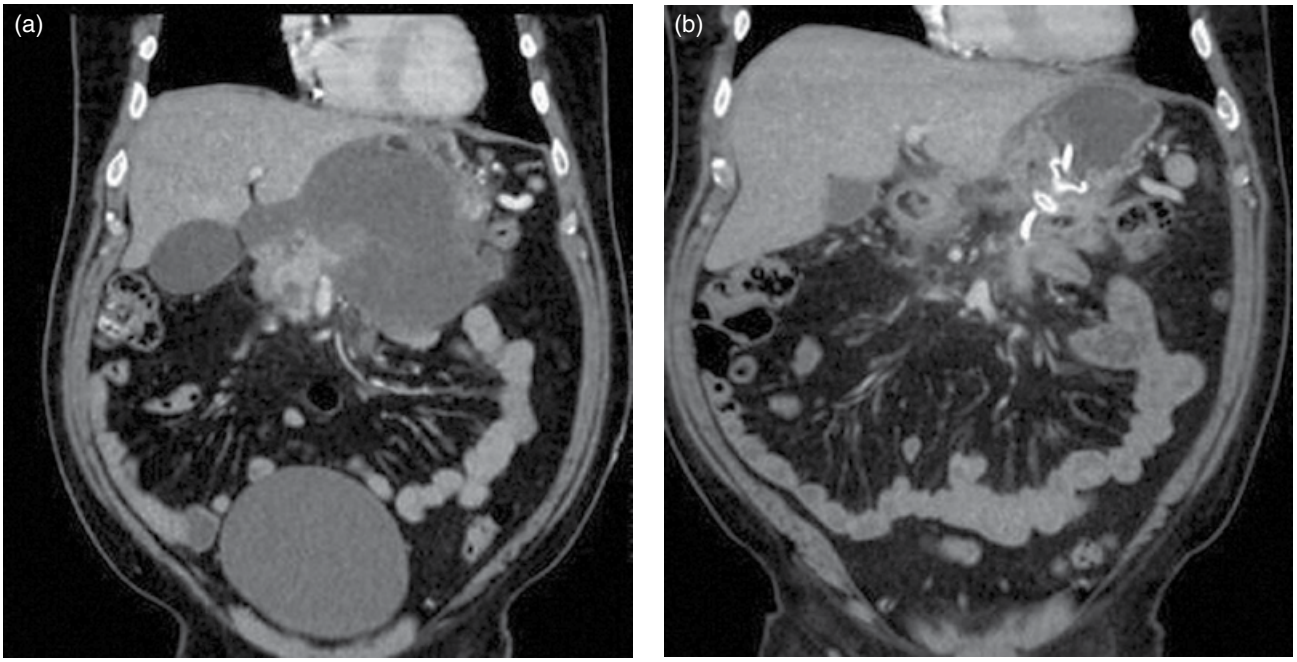


Figure 29.2 Endoscopic resolution of WOPN using a 20 mm luminal apposing metal stent. (a) Coronal CT image showing classic WOPN; (b) coronal CT after resolution with LAMS in place and plastic double-pigtail stent within it.

with infected necrosis continue antibiotic therapy, either empirically or based upon culture data obtained during drainage and/or debridement. All procedures should be performed with carbon dioxide (CO_2) insufflation since fatal gas embolism has been described.

Tools for performing DEN include standard snares, baskets, large caliber grasping forceps, and retrieval nets. Recently, an endoscopic morcellator has become available to enhance removal of necrotic tissue [34].

Results of Endoscopic Therapy of Pancreatic Necrosis

There are many series showing that endoscopic treatment of WOPN is successful in achieving nonsurgical resolution in the majority of patients with central pancreatic necrosis [18,35]. The outcomes appear to be improving with the use of large-diameter metal stents with clinical resolution of WOPN occurring in 90% [26,36,37].

Adverse Events of Endoscopic Therapy of Pancreatic Necrosis

Life-threatening adverse events may arise following attempted endoscopic drainage of pancreatic necrosis. It is recommended that endoscopic drainage be performed with the availability of surgical and interventional radiology support. The most feared adverse events of transmural drainage are bleeding and perforation. Bleeding after transmural drainage may be managed supportively, endoscopically, surgically, or with angiographic embolization. If perforation occurs during attempted transgastric drainage and is limited to the gastric wall (does not involve the collection), it may be successfully managed nonsurgically if a stent is not mistakenly placed through the perforation and outside the gastric wall. If egress of gastric contents is prevented, the gastric wall rapidly closes with conservative treatment consisting of nasogastric suction and antibiotics. If plastic stents were used during initial placement, large-diameter covered SEMS can be used to close perforation at the transmural site and tamponade bleeding. Infectious adverse events usually occur from inadequate drainage of fluid and/or solid debris. Stent migration into the collection through the gastric or duodenal wall may occur during or after endoscopic stent placement. Endoscopic retrieval is possible if the collection has not completely collapsed and the transmural tract is still patent. Fatal air embolism has been reported following DEN [38]. This has prompted the use of CO_2 rather than air insufflation during drainage and necrosectomy.

Endoscopic therapy may be associated with adverse events and/or failures that require surgical management. It is possible that the outcome of surgical therapy may be adversely altered when compared to those patients undergoing primary surgical therapy.

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What is clear is that if endoscopic therapy is undertaken, commitment is required by the endoscopist, clinical care team, and most importantly the patient. Endoscopic debridement is a time-consuming, labor-intensive process not for the uncommitted [39] or the faint of heart since adverse events occur more commonly than in any other pancreaticobiliary intervention and have the potential to be fatal. Therefore, even more importantly, perhaps, is the need for support from intensivists, endoscopists, surgeons, and interventional radiologists to manage these complicated patients.

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Minimally Invasive Debridement and Lavage of Necrotizing Pancreatitis

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Introduction

The prevalence of acute pancreatitis has increased over the decades according to the Global Burden of Disease Study in 2017. Prevalence has increased from 3,038,787 in 1990 to 6,115,833 in 2017 with an age standardized prevalence rate of 67.2 in 1990 to 76.2 per 100,000 in 2017 [1]. This is an increase of 13.3% and given that approximately 20–30% of patients develop moderate to severe pancreatitis, there is a significant impact on survival and burden on health resources [2]. The revised Atlanta criteria classifies acute pancreatitis into stages based on organ failure and local complications. If organ failure exists for more than 48 hours then the patient has severe pancreatitis. It is this set of patients that will need intervention as acute necrotic and peripancreatic fluid collections develop into walled-off necrosis or pseudocysts [3]. Necrotizing pancreatitis consists of necrosis of peripancreatic tissue and of the pancreatic parenchyma and comprises 5–10% of all cases [4]. The pathological process leads to maturing collections that afford the opportunity of specifically targeted intervention in a minimally invasive manner. This chapter will focus on three minimally invasive techniques: minimal access retroperitoneal pancreatic necrosectomy (MARPN), single port retroperitoneal pancreatic necrosectomy (SPRPN), and laparoscopic approaches to necrosectomy.

Minimal Access Retroperitoneal Pancreatic Necrosectomy

The original technique published from Liverpool in 2003 gained access to the necrotic cavity using a percutaneous drain placed under CT guidance [5,6]. The optimal retroperitoneal path is on the patient's left flank, inferior to the spleen, superior to the kidney and posterior to the splenic flexure, Figs 30.1 and 30.2. This drain can be used alone to evacuate liquefied necrosis and can be used as a single strategy in 9% of patients, in modern step-up approach strategies, and even higher in other reported cohort studies [7,8]. The first ever attempt to perform a MARPN was under sedation, in the operating room in a patient who was unable to tolerate a general anesthetic. This strategy is still possible but it is preferred to give the patient anesthesia and muscle relaxant. Patients are placed on the operating table in a supine position with the patient tilted allowing the drain tract to be as horizontal as possible. They are placed at the edge of the table with a sandbag placed under the left-hand side of the patient for additional positioning. The surgeon can either sit at the patient's left or stand and vary the table height. Under fluoroscopic guidance a guidewire is placed through the pigtail drain, ensuring it passes through into the cavity with enough length to allow the drain to be removed. After making a 1 cm skin incision, a renal dilator set is used to dilate the track following the guidewire, ensuring not to pass further than necessary. Once the dilatation is complete, a 24Fr Amplatz sheath is inserted over the guidewire and fixes the position of the track, and frequently a significant amount of pus and liquid debris drains. A nephroscope with a wide-bore operating channel is then passed through the sheath and warm saline irrigation commences. This allows direct visualization of the necrotic cavity and piecemeal evacuation using laparoscopic grasping forceps, Fig. 30.3. The initial procedure does not afford significant necrosectomy as the debris is adherent to granulating cavity walls, and removal can lead to significant bleeding. At the end of the procedure the wire is replaced through the sheath and then an irrigation device is placed into the cavity, over the wire at a pre-measured distance to ensure it is not placed too

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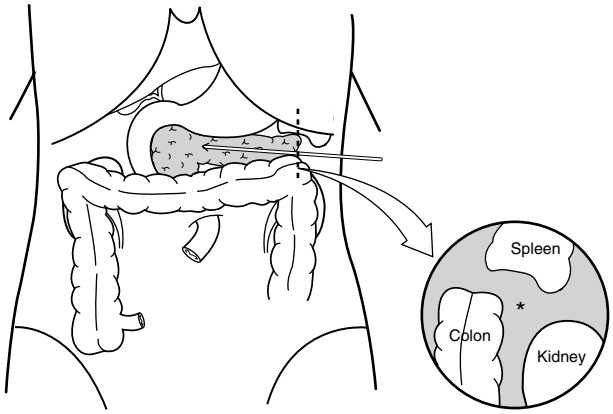


Figure 30.1 Preferred retroperitoneal approach to infected pancreatic necrosis, avoiding the spleen, left kidney, and colon. *Source:* Raraty et al. Trattamento miniinvasivo della pancreatite acuta necrotizzante. In: Pedrazzoli S, ed. Neuro Trattato di Tecnica Chirurgica Pancreas: Peritoneo, Retroperitoneo, Surrene, Milza. Milan: UTET, 2006.

medially. The irrigation device consists of a 28Fr chest drain with a 10/12Fr irrigation nasogastric tube sutured to it, Fig. 30.4. The cavity is irrigated with 0.9% saline at 125 ml/h and after 1–2 weeks, the necrosis is easier to remove with clearly demarcated cavity walls, allowing a larger necrosectomy. Once the cavity appears clear and granulating, the MARPN procedure can cease and a CT scan is performed to check for cavity resolution. The irrigation rate can slowly be reduced and eventually the drain replaced with a single NG, sutured in place, which can be flushed if required. The patient can then be discharged and the cavity will slowly granulate and close over the next few weeks whilst the NG tube is slowly pulled back. A median of three procedures has been reported to completely clear the necrotic cavity [5].

A similar technique using video-assisted debridement was described in 2001 where the patient is placed in a similar position to MARPN [9]. A 4–5 cm incision is made below the costal margin at the mid-axillary line close to the percutaneous drain. Blunt dissection is performed through the muscle layers of the abdomen to locate the percutaneous drain and enter the cavity. A laparoscope is inserted into this cavity and a parallel laparoscopic grasper or suction device to perform the necrosectomy under direct vision. Once the necrosectomy is performed two large-bore drains are placed, deep and superficial with an irrigation catheter. The fascia is closed to perform closed irrigation and the skin can be closed or left open. This technique has been part of regular practice in many centers and employed in step-up trials for the management of necrotizing pancreatitis [10].

Acute Complications

Intervention for necrotizing pancreatitis brings with it a further set of complications adding to an already significant pancreatitis burden. There is commonly a physiological systemic inflammatory response as a contained infected collection is released systemically and patients can become septic. In MARPN patients, this has been reported at 12% with multiorgan failure and with 41% of patients requiring an ITU admission. MARPN remains

(a) (b)

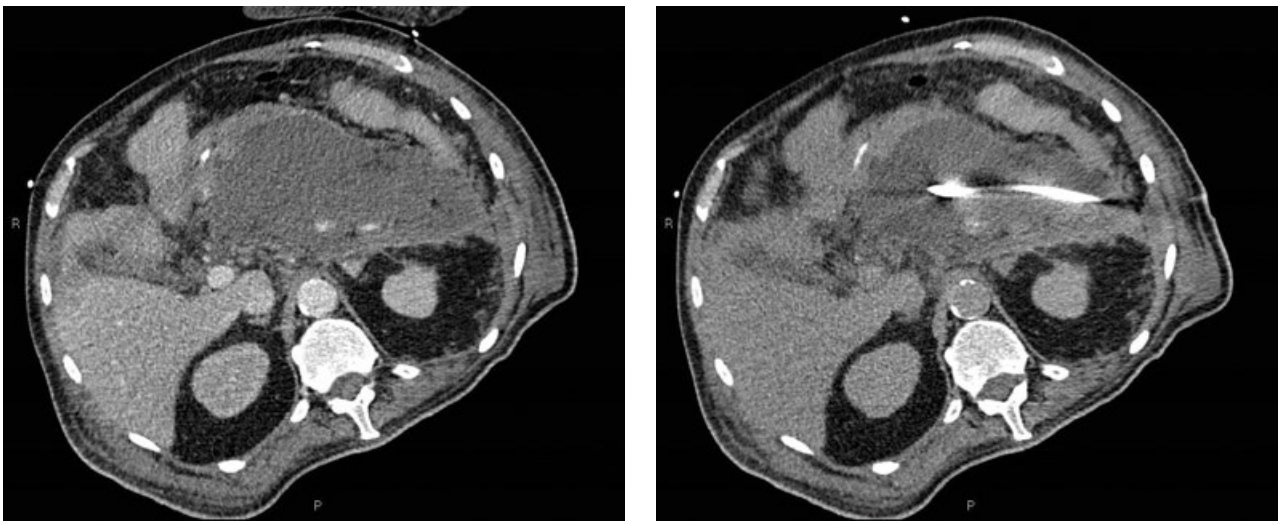


Figure 30.2 (a, b) Radiological access to the necrotic cavity via the left flank. Tilting the patient with left side up facilitates access to the necrotic cavity.

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Figure 30.3 Debridement of necrotic pancreatic tissue under direct vision using an operating nephroscope.

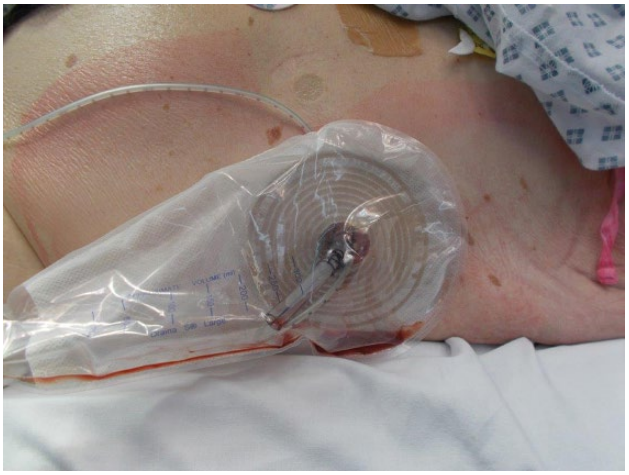


Figure 30.4 A 12F Ryles nasogastric tube and 28F chest drain are placed into the cavity at the end of the procedure and used as an irrigating drainage system to continuously flush the necrotic cavity with 0.9% saline solution at a rate of 125 mL/h.

the commonest minimal access technique, though endoscopic approaches have become first line in many institutions as part of a step-up approach strategy. Most data published in the form of comparative studies and trials compare open surgery with minimally invasive strategies. Hence why the largest cohort study of MARPN remains of 274 patients published from the pancreatic unit in Liverpool in 2016 [11]. They describe a procedure-specific complication rate of 20.4% with a conversion rate to open necrosectomy of 13.1% due to technical difficulties in maintaining a tract, bleeding during the procedure, and inaccessible collections.

One of the most important complications is that of bleeding during or after the procedure; the incidence of this is 11–21% [8,10,11]. Primary bleeding during the procedure is from contact with granulating tissue or avulsion of a vessel, with the rare possibility of injury to the splenic artery. If cessation of the procedure and irrigation fails to stem the bleeding then the cavity requires closing by a pack, suture, or drain clamp in order to facilitate tamponade. Secondary bleeding can occur at any time in the postoperative period from an erosion into a vessel or a pseudoaneurysm rupture. If clamping the drain does not prevent cardiovascular instability then an urgent CT angiography investigation needs to be performed with a view to a mesenteric angiogram and embolization of a bleeding vessel.

Subsequent procedures may prove difficult and a period of conservative management is advocated to ensure there is no further bleeding.

Fistulation to the GI tract has been reported but the incidence remains very low. Approximately 1% can occur from erosion of necrosis into the lumen of the bowel or the development of focal ischemia as tributaries of mesenteric vessels become occluded [12]. It may also become apparent from the medial border of the duodenum as necrosectomy of the head of the pancreas reveals the defect. Management of this is on a case by case basis and may require cessation of intervention, keeping the patient starved and commencing total parenteral nutrition. Fistulation from the pancreas duct occurs in 5–28% of patients from the remnant healthy pancreas and is managed conservatively providing flow proximally is not obstructed [8,11]. An endoscopic retrograde cholangiopancreatography (ERCP) and pancreatic duct stent may treat an established fistula.

Compared to open surgery, MARPN has significantly lower complications (35.4% vs. 51.7%), less incidence of multiorgan failure (12–20% vs. 35–40%) but mortality rates remain similar (23.1% vs. 22.9%), respectively [8,11,13,14]. The difficulty in comparing techniques in the management of necrotizing pancreatitis is that the development of novel drainage strategies has provided multiple options. In previous cohort studies, it has been reported that the use of MARPN is not suitable in 30% of cases in some studies and one quarter of all patients will require additional percutaneous drains [8,11]. This implies that as good as MARPN is as a technique, there will be areas of walled-off necrosis that may not be accessible.

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Thus is the nature of necrotizing pancreatitis and why the development of different drainage techniques has improved management.

Single Port Pancreatic Necrosectomy

There has been a single report published reviewing the use of a single port for necrosectomy in seven patients [15]. It is important to state that this technique is used for extrapancreatic walled-off collections, predominantly those that are accessible using a three-channel SILS port. A percutaneous drain is inserted radiologically into the collection under local anesthetic and then the patient is given a general anesthetic where a 3 cm cut-down incision is made over the drain site to afford the SILS port. A zero-degree nephroscope is then inserted through one channel and an articulating grasper through the other, with a 0.9% saline irrigation channel. A necrosectomy is performed under direct vision and an irrigation nasogastric tube is then placed for further lavage and drainage. The case series is small, a morbidity rate is not possible to accurately calculate and the post-procedural median length of stay was 47 days [15]. Though this is a technically feasible technique, it is for a specific, difficult to access, area of necrosis of critically unwell patients. It should become part of an array of minimal access techniques for patients with complex necrotizing pancreatitis.

Laparoscopic Approaches to Pancreatic Necrosectomy

Many small volume case series have been reported over the past couple of decades but the technique remains low in popularity and there are no large volume studies published [16]. The peritoneal approach has been commonly reported and the pancreatic cavity is approached from either the mesocolon or through the greater omentum into the lesser sac. It is also possible to enter transgastrically once the collection/necrosis is walled-off and ready to drain through a cystgastrostomy [17]. The major benefit is that only single operation is needed for necrosectomy, though it has been reported that 20% of patients require a further procedure [16]. Other reported benefits include a morbidity rate of 21% and the simultaneous ability to perform a cholecystectomy [16,18]. The only comparative study between laparoscopic and open techniques of necrosectomy was published in 2012, which stated that there was a lower complication rate, less blood loss, and a shorter length of stay [19]. The operation duration was longer, which leads to specific respiratory complications from prolonged abdominal insufflation. There is a further risk of introducing a contained collection into a previously sterile peritoneal compartment. Many units prefer to approach necrosectomy through the retroperitoneum. There has been a retroperitoneal laparoscopic approach described where two ports are placed into the necrotic cavity over percutaneous drains. This allows insufflation of carbon dioxide and necrosectomy can be performed using laparoscopic instruments and clips and diathermy can be used to control bleeding [20]. The major advantage of this technique is that it requires only two procedures, compared to other retroperitoneal techniques, with a lower median time to discharge of 44 days. There remains a complication rate of 38% and the series was of only 13 patients [20]. The retroperitoneal is still an important aspect of pancreatic necrosectomy, though the MARPN technique remains the most commonly used minimally invasive strategy.

Modern Management of Necrotizing Pancreatitis

In 2016 a Cochrane review was published comparing interventions in necrotizing pancreatitis and summarized that there was low to very low quality evidence to compare minimally invasive step approaches to open necrosectomy [21]. This highlights the difficulties in comparing techniques and establishing the role of MARPN with a solid evidence base. More recent studies have established that minimally invasive step-up approaches have significantly fewer deaths than open surgery (2% vs. 10%), respectively and a risk ratio of 0.7 [22]. Two randomized control trials have been reported from the Dutch Pancreatitis Group. The Panter trial, which compared open necrosectomy with a minimally invasive step-up approach and found the latter to be superior in terms of mortality, postoperative complications, and pancreatitis insufficiency [23]. Van Brunschot et al. published a randomized trial reviewing surgical step-up and endoscopic step-up approaches and determined that there was no difference in mortality or major complications. The only differences reported was a short length of stay and few pancreatic fistulae in the endoscopic step-up group. It was concluded that there should be a shift toward endoscopic approaches [10].

As the evidence bases slowly improves, the primary use of open necrosectomy becomes less recommended and minimally invasive strategies have become first line. The advent of endoscopic therapies has further shifted management from surgically minimally invasive techniques, especially MARPN. Given these advances a modern pancreas unit should be able to provide multiple strategies and afford a multidisciplinary decision-making process, where patient factors, collection distribution and timing can be discussed in order to tailor personalized management.

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31

Open Surgical Debridement of Necrotizing Pancreatitis: Late Postoperative Morbidity and Outcome

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Introduction

Open surgical debridement, once considered as the first-line treatment for necrotizing pancreatitis, is now reserved as the final step in contemporary treatment algorithms with the "step-up" approach and is needed in fewer than 20% of cases [1]. However, an open approach may have advantages over minimally invasive debridement techniques in the following conditions: (i) infeasible for minimally invasive approaches, due to solid material constituting majority of the necrosis, or unfavorable anatomic location of the necrosis; (ii) complications including abdominal compartment syndrome, enteric fistula, ileus, and massive intra-abdominal hemorrhage; (iii) additional surgical procedures are needed (e.g., cholecystectomy for biliary etiology); (iv) efficient removal of necrotic tissue and rapid control of systemic infection are warranted, particularly in critically ill patients with severe sepsis. In selected cases, a "step-jump" open surgery first approach, by skipping the precedent treatments in the "step-up" approach including percutaneous catheter drainage and minimally invasive debridement, may be beneficial [2].

Historically, open surgical debridement with large incision and extensive necrosectomy resulted in a high incidence of complications and mortality after surgery [3,4]. A better understanding of the natural course of disease, advances in medical treatment especially in critical care, incorporating a "step-up" strategy, and accumulation of expertise in high-volume centers significantly improved clinical outcomes after open surgical debridement for necrotizing pancreatitis [5–11]. Improvement of surgical techniques also played an important role in continuous optimization of patients' prognosis in this clinical setting. Traditional open surgical procedures for necrotizing pancreatitis included debridement and continuous closed lavage [12], debridement and open packing/staged laparotomy [13], debridement and closed packing [14]. Nowadays, the tendency of minimalization in open surgery for necrotizing pancreatitis is remarkable, and reported techniques included open transgastric necrosectomy [5,8] and small incision retroperitoneal debridement [15].

Late complications in necrotizing pancreatitis are common and have a significant impact on patients' long-term wellness (Table 31.1). In a recent report involving 578 consecutive cases of necrotizing pancreatitis with a median follow-up time of 46 months, 85% of the patients developed ≥1 long-term complication, and 59% of them required invasive interventional treatment [16]. In an earlier cohort of patients with necrotizing pancreatitis after surgical debridement with a median follow-up time of 28.9 months, 62% of the patients developed a long-term complication and 26% of them required intervention [17].

The following paragraphs will focus on individual long-term complications closely related to the procedure of open debridement.

Pancreatocutaneous Fistula

Pancreatic leakage develops in necrotizing pancreatitis when the main pancreatic duct or its branches are destructed and subsequent pancreatic juice extravasates to the peripancreatic space. Any transcutaneous interventions including open surgery with postoperative drainage may cause pancreatocutaneous fistula [18]. Another form of pancreatic fistula in necrotizing pancreatitis is internal fistula, which is less associated with necrosectomy, thus is not discussed in this chapter.

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Table 31.1 Clinical results and long-term complications after open surgical debridement for necrotizing pancreatitis.

First author	Surgery period	Surgical technique	Patient *N*[a]	Short-term mortality rate %	Follow-up time	Hemorrhage %	Pancreatic fistula %	Enteric fistula %	Incisional hernia %	Endocrine insufficiency %	Exocrine insufficiency %	Supplementary enzyme use %
Tsiotos [21,41]	1983–1995	OD & SL	44/72	25	mean: 60 mo	18.1	19.4	23.6	27.3	36.4	25	25
Tzovaras [22]	1987–1999	mixed	21/44	18.3	median: 48 mo	NA	9.1	13.6	47.6	47.6	9.5	NA
Rodriguez [10]	1990–2005	OD & CP	167	12	NA	4	41	15	NA	16	20	NA
Cinquepalmi [42]	1990–2005	OD & CL	32/35	22	median: 85 mo	NA	NA	NA	91	29	NA	NA
Busse [49]	2003–2012	TGOD	50	20	NA	NA	NA	NA	NA	35	NA	20
Hollemans [19,34]	2005–2008	OD & CL	38/45	16	mean: 86 mo	27	38	22	53	56	56	42
Luckhurst [6]	2006–2019	OD & CL	88	10[b]	12 mo	9	73	NA	NA	26	NA	14
Chandrasekaran [48]	2009–2010	OD & SL	21	NA	>12 mo	NA	NA	NA	NA	61.9	57.1	80.9
Jones [35]	2010–2015	mixed	33	21.9[b]	12 mo	9.1	30.3		9.1	9.1	NA	48.5
Zhang [15]	2010–2019	SIOD	31	16	6 mo	6	16	6	6	13	NA	10

[a] Patient number included in long-term follow-up/patient number after necrosectomy; [b] 90-day mortality rate.
mo: months; NA: not applicable; OD & CL: open debridement & continuous closed lavage; OD & CP: open debridement & closed packing; OD & SL: open debridement & open packing/staged laparotomy; SIOD: small incision open debridement; TGOD: transgastric open debridement.

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Pancreatic fistula rate after surgical debridement in necrotizing pancreatitis was 8–73% from different studies [6,7,9–11,15,19–26]. Transgastric necrosectomy has the innate advantage of minimizing risk of external fistula by creating durable internal drainage for potential gland leaks, and the reported pancreatic fistula rate after open transgastric necrosectomy was 2.0–4.7% [5,8]. When postoperative pancreatic fistula persists, underlying anatomical deformity of the pancreatic duct secondary to parenchymal necrosis should be suspected. When duct stricture or disconnected pancreatic duct syndrome (DPDS) presented, persistent pancreatic fistula after pancreatic debridement increased from 27% in cases with normal duct to 54% and 85%, respectively [27]. Disconnected left pancreatic remnant on preoperative CT scan was also found to be a risk factor for the development of pancreatic fistula after necrosectomy [7].

Around two-thirds of the post-necrosectomy pancreatic fistula will close spontaneously after noninterventional treatments at around 4 months after surgery [18,28]. Conservative treatments included optimized drainage, somatostatin analogues, antibiotics, and nutritional support. If the fistula is refractory to medical treatment, the choice between different interventional modalities currently lacks strong evidence support. Endoscopic transpapillary duct drainage [29], surgical interventions including fistulojejunostomy, pancreaticojejunostomy, and left pancreatectomy [30] are among the physician's arsenal and were reported with a satisfactory safety and efficacy profile. Changes in ductal morphology may provide helpful information in clinical decision-making to choose the appropriate treatment [31]. Simultaneous left pancreatectomy resection with the index debridement for cases with DPDS were also recommended [7].

Hemorrhage

Hemorrhage is one of the most fatal complications and contributes to a substantial mortality rate in necrotizing pancreatitis. Late hemorrhage in necrotizing pancreatitis is related to the presence of residual peripancreatic or pancreatic necrosis, long-standing pseudocyst, and gastrointestinal varicosis following thrombosis and obstruction of the portosplenomesenteric vein. Too aggressive or expectant timing for debridement and traumatic manipulation during necrosectomy may also increase the risk of postoperative bleeding. The common sites of hemorrhage in necrotizing pancreatitis include splenic artery, gastroduodenal or pancreaticoduodenal artery, portal vein, spleen, and unspecified peripancreatic vessels [32,33]. Isolated vessels or even vascular stumps in the necrotic cavity are frequently found during necrosectomy; proper ligation or transfixation of the vessel or its stump is required, and surgical debridement holds technical advantages in this respect (Fig. 31.1).

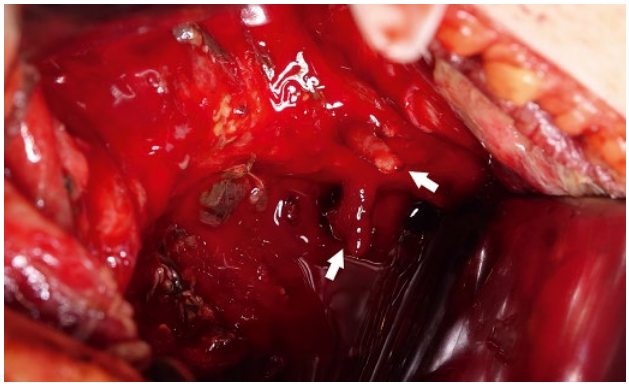


Figure 31.1 Isolated vascular stumps (arrows) in necrotic cavity during open debridement, which require proper management with ligation or transfixation.

Various studies have reported a rate of postoperative hemorrhage of 2.7–10.1% after open pancreatic necrosectomy [6–10,15,19–21,23–26,34–36]. In the extended observational study of a randomized controlled trial, two more patients (5%) had intra-abdominal bleeding requiring intervention during the long-term follow-up period, making an overall hemorrhage rate of 27% in the open surgery arm [34]. As regards a different but closely related disease entity, the visceral artery pseudoaneurysm was reported to be 4.3% in all patients with necrotizing pancreatitis with a median incidence timing of 63.5 days after disease onset and 21% of the patients were diagnosed based on incidental CT findings [37]. Age >50 years, presence of any organ failure, and previous endoscopic transluminal necrosectomy with lumen-opposing metal stent were reported to be risk factors for visceral pseudoaneurysm in necrotizing pancreatitis [37,38].

Recognition of early signs of hemorrhage and/or pseudoaneurysm is critical for prompt intervention and successful treatment; these include blood in drainage, acute onset of abdominal pain, gastrointestinal bleeding, and early presentations of hemorrhagic shock. Visceral angiography is considered as the first step in management of bleeding after necrosectomy if the patient is hemodynamically stable, which could provide detailed information on bleeding sites. And further intravascular embolization with a coil or covered stent would provide definite treatment or a bridging measure for surgery [33,37]. Emergent open laparotomy for hemostasis is a lifesaving procedure for patients with catastrophic intra-abdominal bleeding or failed percutaneous vascular embolization, and has the advantage of eliminating underlying causes of bleeding including residual infected necrosis and direct compression from the drainage tube,

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and so on. Extensive blood oozing into the necrotic cavity represents another challenging scenario, in which gauze packing may be the only choice of treatment. Postoperative hemorrhage would have a profoundly detrimental impact on a patient's outcome with a mortality rate of 34.1% [32].

Enteric Fistula

Multiple factors were involved in the pathogenesis of enteric fistula in necrotizing pancreatitis, which include organ ischemia secondary to vascular thrombosis due to enzyme-rich and inflammatory exudates involvement, colonic ischemia in hypoperfusion status in splanchnic blood supply, direct autodigestion from extravasated pancreatic juice, and iatrogenic causes during interventions [28]. Enteric fistula was reported with an incidence rate of 6–23.6% after surgical debridement from various studies [7,9,10,15,19–23,25]. The incidence of enteric fistula in necrotizing pancreatitis was associated with organ failure, presence of extensive necrosis, and operative intervention [16,39].

Once the diagnosis of enteric fistula is established, timely interventional management is essential to stabilize the patients. Percutaneous catheter drainage, endoscopic stenting, enterostomy, enteric resection, enteric fixation, or proximal diversion of the gastrointestinal tract is indicated for different clinical settings. Although surgery is still the mainstay treatment for enteric fistula, nonsurgical interventions have been increasingly applied in recent years. In one report focused on colonic fistula after necrosectomy for infected pancreatic necrosis, 34.8% of the cases with colonic fistula closed spontaneously [40]. Once colonic ischemia is suspected during surgical debridement, it is recommended that a prophylactic loop ileostomy be constructed [20]. Necrotizing pancreatitis complicated with gastrointestinal fistula represents a treatment challenge, as studies have found out that the disease course is significantly prolonged, and mortality is substantially high in this group of patients [16,40].

Incisional Hernia

Risk factors for the development of incisional hernia including wound infection, repeated laparotomies, obesity, diabetes mellitus, malnutrition are commonly seen in patients after open debridement. Various incidence rates of incisional hernia after traditional transperitoneal surgical debridement were reported with a wide range of 9.1% to 91% [22,25,34–36,41,42]. Patients with incisional hernia increased from 24% to 53% if the follow-up time was extended from 6 months to an average of over 7 years after open necrosectomy [19,34]. In a retrospective study specifically focused on long-term hernia development after laparotomy for necrotizing pancreatitis, elder age was found to be the only risk factor for hernia development [43].

Hernias are more common when marsupialization of the lesser sac is used as a controlled laparostomy [44,45]. Transverse incision resulted in less incisional hernia when compared with midline incision [46,47]. However, a retrospective case-control study in necrotizing pancreatitis did not find a difference in hernia development between various types of incision [43]. Minimalization of the incision in open necrosectomy may help to avoid the risk of incisional hernia [15]. In the authors' institution, we now use uni-/bilateral flank incision (retroperitoneal) and/or mini transverse incision (transperitoneal) instead of a midline incision for open debridement. The choice of incision is flexible and depends on the location and extension of necrosis (Fig. 31.2). A minimally invasive "step-up" approach could significantly reduce the chance of hernia development by avoiding laparotomy in some patients [19,34].

Incisional hernia is a condition that frequently requires surgical reintervention and 52–86.5% of the patients who developed incisional hernia subsequently received hernia repair [16,22,41,43].

New-Onset Endocrine Insufficiency

Acute necrosis of the pancreatic parenchyma, extensive debridement, and subsequent chronic inflammation after acute onset will cause permanent loss of functional unit both in the endocrine and exocrine compartment of the pancreata. Pancreatic functional loss in necrotizing pancreatitis seems to be progressive and irreversible in long-term follow-up [16,34].

Endocrine insufficiency after open necrosectomy was reported with an incidence rate of 9.1–61.9% after various follow-up times [6,10,15,22,34,35,41,42,48,49]. Endocrine insufficiency occurs early in necrotizing pancreatitis, as serum glucose greater than 200 mg/dL was included in Ranson's score. Worth noting, over one-third of euglycemic patients at the time of acute attack resolution further developed endocrine insufficiency, after follow-up time was extended from 6 months to 86 months in the PANTER trial [19,34]. And this finding was supported by other observations [16,41].

Studies have suggested that functional loss of the pancreas was more dependent on the severity of the attack rather than on the action of debridement [16,50]. Development of organ failure, infection other than sterile necrosis, higher computed tomography (CT) severity index, and more extensive necrosis during acute onset of necrotizing pancreatitis were associated with the development of endocrine insufficiency afterward [16,41,48].

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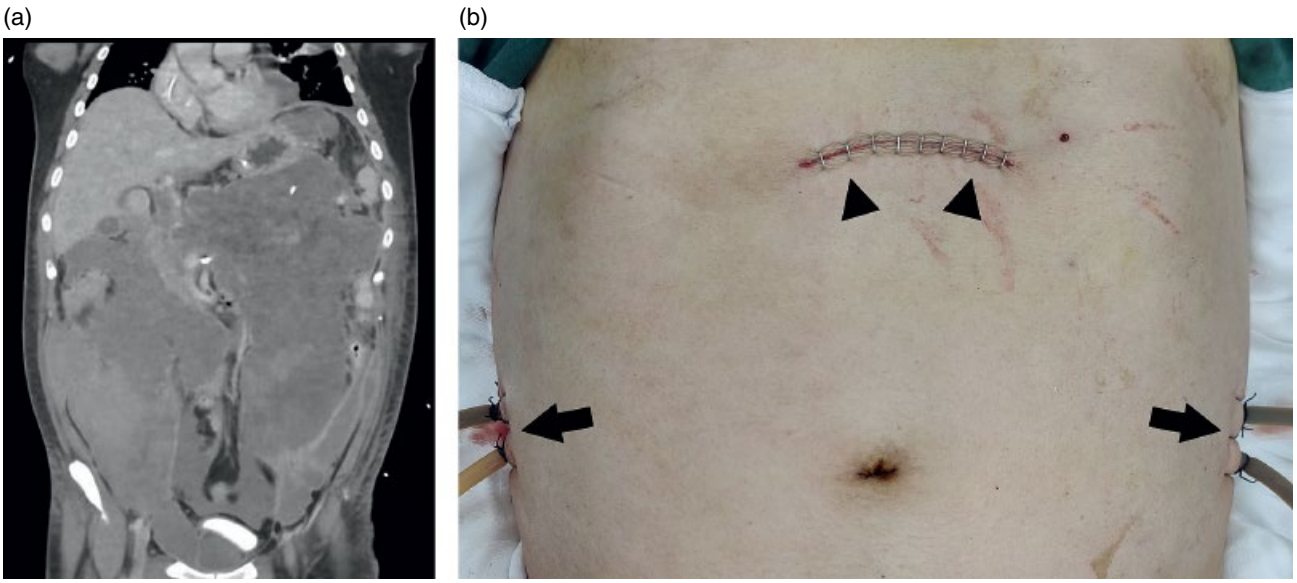


Figure 31.2 Minimalization of incision in open debridement. (a) Extensive pancreatic necrosis was found in a preoperative computed tomography (CT) exam of a patient with infected necrotizing pancreatitis. (b) Epigastric 7-cm transverse incision (arrow heads) with bilateral flank incisions (arrows) in open necrosectomy for this patient (drainage tubes were introduced via the flank incisions).

New-Onset Pancreatic Exocrine Insufficiency (PEI)

The incidence of PEI after open debridement for necrotizing pancreatitis varied from 9.5% to 57.1% [10,22,34,41,48], and the percentage of patients who relied on enzyme supplementation was reported to be 10–80.9% [6,15,19,34,35, 41,48,49]. Different diagnostic criteria will lead to different estimations of the burden of exocrine insufficiency. One study used fecal elastase-1 <200 μg/g and found the incidence rate of long-term PEI after open necrosectomy to be 56% [34], while exocrine insufficiency was diagnosed in 25–57.1% of patients when fecal fat excretion >7 g/24 h was used [41,48].

Direct open debridement was reported to increase the risk of long-term exocrine insufficiency when compared with the minimally invasive step-up approach both in functional test and supplementary enzyme dependence [34]. The extent and infection status of the necrosis, and no or incomplete visualization of the main pancreatic duct are associated with the incidence of exocrine insufficiency [41,48]. In another study, renal failure and cardiovascular failure during the acute phase were found to be independent risk factors for long-term PEI development in patients with necrotizing pancreatitis [16].

Summary

Late complications are common in patients with necrotizing pancreatitis and after open surgical debridement. Long-term follow-up in these patients is essential and warranted to identify potential complications and initiate treatment promptly. In a contemporary treatment algorithm, the role of open surgery for necrotizing pancreatitis has fundamentally changed but remains indispensably important, as it seems to be decisive for the fate in a subset of patients with necrotizing pancreatitis, not only as a bail-out procedure after failed minimally invasive interventions but maybe also as a first choice in selected patients. In future, novel treatment strategy and surgical techniques for necrotizing pancreatitis should be tested in well-designed clinical trials focusing on both short-term outcomes and long-term morbidities.

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Endoscopic Treatment of Acute Biliary Pancreatitis

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Pathogenesis of Acute Biliary Pancreatitis

Acute biliary pancreatitis (ABP) is caused by pancreatic duct obstruction mainly due to bile duct stones. Once a bile duct stone is impacted at the common channel or distal end of the bile duct, pancreatic duct outflow is obstructed directly or by the compression of the pancreatobiliary septum. Previous reports showed that bile duct stone impaction was found in 26–72% of patients who had ABP when surgery was performed soon after the attack [1]. Spontaneous passage of bile duct stones into the duodenum has been described in up to 50% of ABP cases [2,3]. Sphincter of Oddi spasm might be another cause of ABP. Therefore, the diagnosis of ABP is not always easy at the time of diagnosis of pancreatitis.

Biliary pancreatitis, as well as alcoholic pancreatitis, is a major etiology of acute pancreatitis. ABP accounts for 20–71.4% of cases of acute pancreatitis, but the rate varies across countries. Biliary pancreatitis is more common than alcoholic pancreatitis in Greece, Italy, the United Kingdom, Sweden, and the United States of America, whereas alcoholic pancreatitis is the most major cause in Hungary, France, Taiwan, Korea, and Japan [4–9].

Diagnosis

In addition to the increased levels of serum pancreatic enzymes, such as amylase and lipase, increased levels of hepatobiliary enzymes and bilirubin suggest the possibility of ABP. In such cases, imaging tests are strongly recommended for diagnosis. Although transabdominal ultrasound is the most convenient imaging modality, the extrahepatic bile duct is often difficult to visualize clearly due to the retention of gastrointestinal gas, especially in patients with acute pancreatitis. Abdominal computed tomography (CT) is also relatively convenient and has high sensitivity in detecting calcified stones (Fig. 32.1), but its sensitivity to detect small stones lacking calcification is limited. Endoscopic retrograde cholangiopancreatography (ERCP) may be indicated in highly suspected cases such as those with bile duct dilation and/or cholangitis. However, magnetic resonance imaging (MRI) or endoscopic ultrasonography (EUS) is recommended to be performed before ERCP in such cases because they are safer and more convenient. Magnetic resonance cholangiopancreatography (MRCP) can provide an image similar to ERCP. It has high sensitivity and specificity in detecting common bile duct stones (more than 90%) [10], but its sensitivity decreases in cases with dilated bile duct and small stones [11]. EUS is recognized as the most reliable imaging modality in detecting bile duct stones [12], has fewer complications, and shows higher sensitivity in detecting small bile duct stones than ERCP [13].

Indication of Endoscopic Treatment

Endoscopic treatments are indicated for patients with a bile duct stone confirmed on imaging tests or highly suspected from clinical or laboratory findings. In addition, patients with persistent or repeated increasing levels of biliary and pancreatic enzymes are also indicated even if the presence of biliary stone was unclear. In such cases, a dysfunction in the sphincter of Oddi might be a cause of biliary pancreatitis.

The timing of endoscopic treatments is discussed later, but urgent ERCP should be considered when there is evidence of cholangitis and/or ongoing biliary

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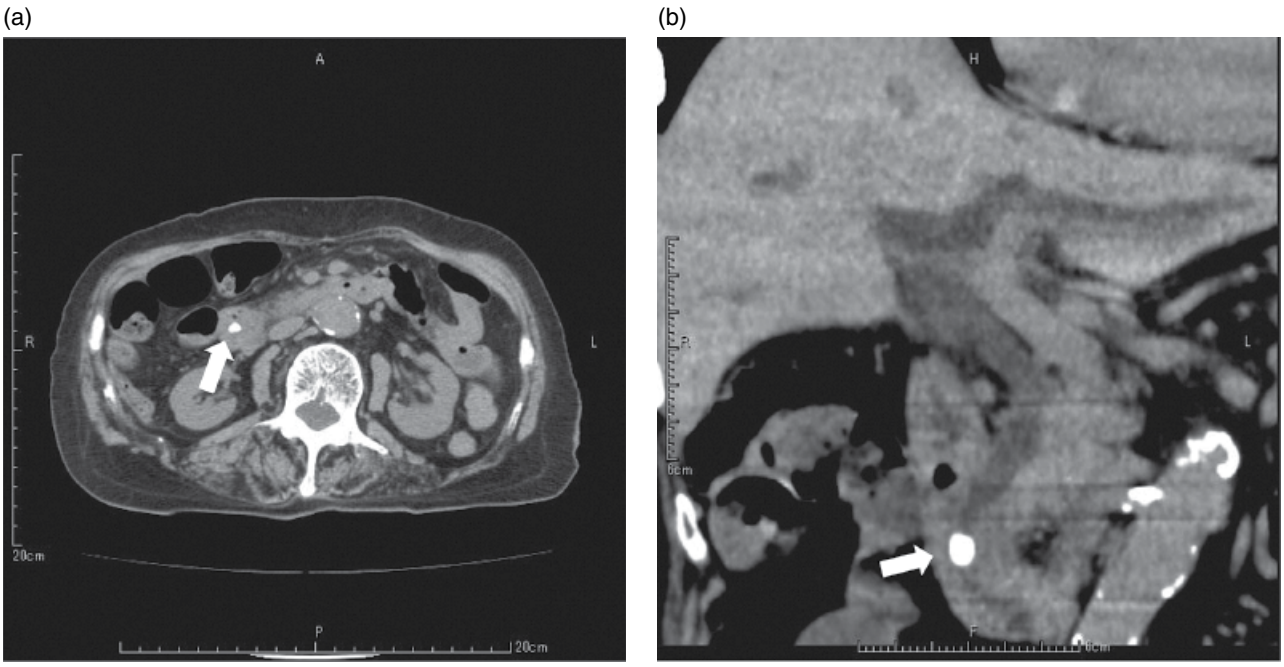


Figure 32.1 Computed tomography image of an impacted stone at the duodenal papilla. White arrow indicates an impacted stone. Axial image (a) and multiplaner reconstruction image (b).

obstruction. However, conservative treatments such as fasting, rehydration, and administration of antibiotics should be attempted first in patients with mild clinical symptoms and with mild abnormal laboratory data.

Several previous studies have suggested the utility of EUS in narrowing down eligible patients by showing that a preceding EUS avoided unnecessary ERCP in 71.2–75.4% of patients without increasing the risk of adverse events [13–16].

Techniques

The best way to treat biliary pancreatitis is the removal of the bile duct stone. Endoscopic sphincterotomy is generally performed for this. ERCP is initially attempted to confirm the stone in the bile duct, and endoscopic sphincterotomy is then performed using a sphincterotome if a stone is detected on cholangiogram. Subsequently, endoscopic stone extraction is performed using a retrieval basket or balloon. If the stone is impacted at the papilla, precut papillotomy using a needle knife would be preferred to conventional endoscopic sphincterotomy owing to the difficulty in cannulation into the bile duct in such cases (Fig. 32.2).

Endoscopic sphincterotomy with subsequent stone extraction is currently a well-established technique with a high success rate (approximately 90%) [17]. However, procedure-related adverse events, including pancreatitis, hemorrhage, perforation, and cholangitis, can occur in approximately 10% of the cases [18]. Aggravation of pancreatitis is a particularly considerable concern in patients with pancreatitis. Therefore, cannulation and contrast medium injection into the pancreatic duct should be avoided as much as possible; however, there is no evidence that accidental cannulation into the pancreatic duct affects the clinical course or outcome adversely. Recently, the efficacy of pancreatic duct stenting was suggested in ABP following endoscopic sphincterotomy. In a nonrandomized study, complications were less frequent in the pancreatic duct stent group than in the control group without pancreatic duct stent (9.86% vs. 31.43%, $P < 0.002$) [19]. However, so far, there is no significant evidence to recommend pancreatic duct stenting after endoscopic treatment for ABP.

Outcomes and Timing of Endoscopic Interventions

Endoscopic treatments for ABP were initially described in 1981 [20,21]. Since then, a number of prospective randomized controlled trials (RCTs) have compared early endoscopic treatments with conservative therapy for ABP. However, as several clinical trials and meta-analyses have provided conflicting evidence, the role and timing of endoscopic intervention in ABP remain controversial.

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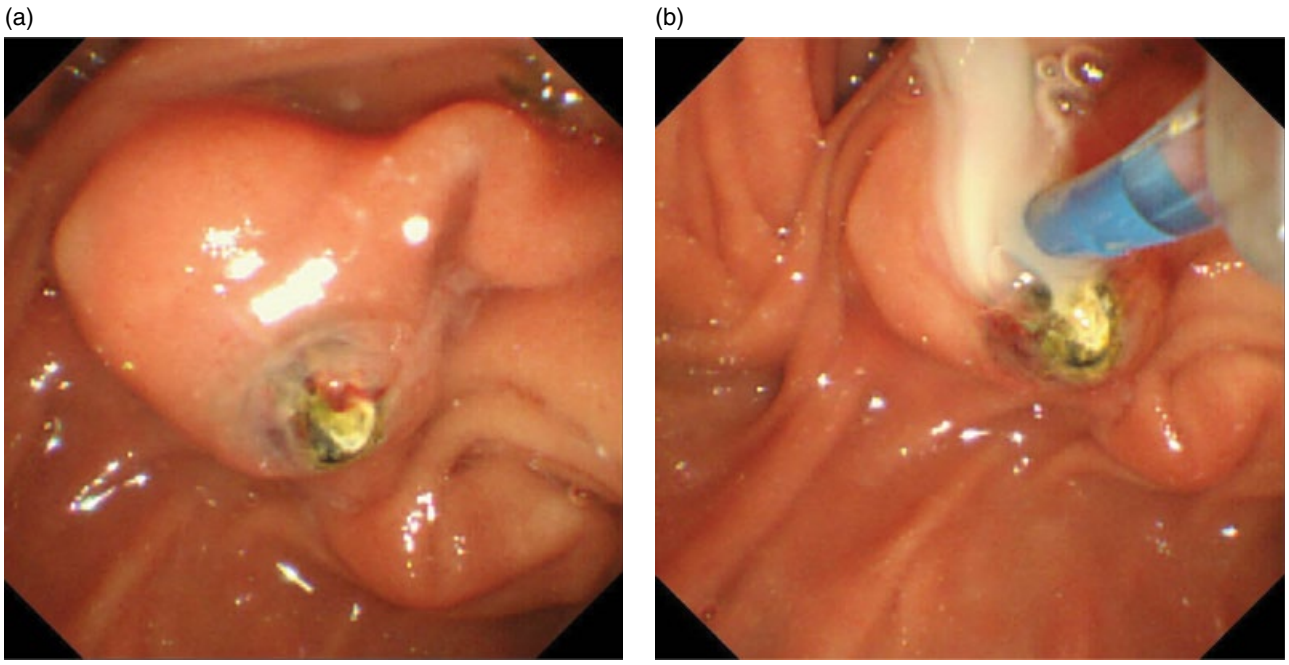


Figure 32.2 Endoscopic view of an impacted stone at the duodenal papilla. A stone is impacting at the biliary orifice (a). Needle knife papillotomy is preferably performed in such a case. Whitish pus is discharged after cutting up the papilla from the orifice using a needle knife (b).

Two early RCTs showed lower complication rates, shorter hospital stays, and lower mortality rate in the urgent ERCP group than in the conservative group [22,23]. However, another RCT showed that the overall rate of complications was similar in the two groups, and patients in the early ERCP group had more severe complications [24]. The first meta-analysis published in 1999 showed a high success rate of ERCP (92%) and concluded that early ERCP significantly reduced morbidity (25.0% vs. 38.2%, $P < 0.001$) and mortality (5.2% vs. 9.1%, $P < 0.05$) in ABP [25]. However, later studies suggested that early endoscopic intervention was beneficial in further limited patients.

Several studies have concluded that urgent endoscopic intervention should be considered only in patients with severe biliary pancreatitis [26–28]. In a meta-analysis by Ayub et al. [27], early endoscopic intervention was associated with significant reduction in complications only in predicted severe biliary pancreatitis (odds ratio [OR] 0.27, 95% confidence interval [CI] 0.14 to 0.53), whereas reduction of mortality was not significant in both predicted mild and severe biliary pancreatitis. Later, a meta-analysis by Moretti et al. [28] also reported that a significant difference in the pooled rate for complications was found only in predicted severe pancreatitis (38.5%, 95% CI −53% to −23.9%, $P < 0.0001$).

Meanwhile, several other studies have suggested that the benefit of urgent endoscopic intervention was expected only in cases with cholangitis or cholestasis [29–34]. Petrov et al. [29] reviewed RCTs on early endoscopic intervention versus conservative management in patients with ABP without acute cholangitis. They found that early endoscopic intervention in patients with predicted mild and predicted severe biliary pancreatitis did not lead to a significant reduction in the risk of overall complications and mortality. Later, Van Santvoort et al. [35] conducted a prospective, observational multicenter study including patients with predicted severe ABP without cholangitis. They analyzed the outcomes in patients without and with cholestasis separately and noted that endoscopic intervention was associated with fewer complications as compared with conservative treatment in patients with cholestasis (25% vs. 54%, $P = 0.020$), whereas it was not associated with reduced complications (45% vs. 41%, $P = 0.814$) in patients without cholestasis. A Cochrane review by Tse and Yuan [32] in 2012 showed no evidence that early routine ERCP significantly affected mortality or local/systemic complications of pancreatitis, regardless of predicted severity. However, among trials that included patients with cholangitis, the early routine ERCP strategy significantly reduced mortality and local and systemic complications. In addition, among trials that included patients with biliary obstruction, early routine ERCP strategy was associated with a significant reduction in local and systemic complications. Finally, they concluded that early

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ERCP should be considered only in patients with coexisting cholangitis or biliary obstruction. A systematic review [36] including 8 meta-analyses and 12 guidelines documents a consensus among them regarding indication for early endoscopic intervention is indicated only in ABP patients with coexisting cholangitis and/or persistent cholestasis. In addition, most recently, Schepers et al. [37] assessed urgent ERCP with sphincterotomy versus conservative treatment in predicted severe acute biliary pancreatitis without cholangitis in a multicenter RCT. They recorded no relevant differences in a composite of mortality or major complications (new-onset persistent organ failure, cholangitis, bacteremia, pneumonia, pancreatic necrosis, or pancreatic insufficiency) within 6 months between the groups (38% vs. 44%, $P = 0.37$).

In summary, urgent ERCP is not necessary in mild acute biliary pancreatitis. Moreover, it can also be avoided even in severe acute biliary pancreatitis when cholangitis or persistent cholestasis is not coexistent.

Cholecystectomy After Endoscopic Treatment

Recurrence rates of ABP of up to 61% have been reported in the absence of definitive treatment [38,39]. Therefore, subsequent cholecystectomy after endoscopic treatment of bile duct stones has been recommended to prevent recurrent attacks of ABP [40,41], although 25–50% of patients do not undergo cholecystectomy for various reasons [42–44]. The Dutch Pancreatitis Study Group assessed the timing of cholecystectomy after mild biliary pancreatitis in a systematic review including 8 cohort studies and 1 RCT (998 patients). In this cohort, cholecystectomy was performed during index admission in 48% of the cases and interval cholecystectomy was performed in 52% of the cases after a median duration of 40 days (interquartile range: 19–58 days). Before interval cholecystectomy, 18% of the patients were readmitted for recurrent biliary events such as pancreatitis, cholecystitis, and biliary colics. Therefore, cholecystectomy during index admission for mild biliary pancreatitis appeared safe [45]. Conversely, in cases of severe ABP, the current consensus is to postpone cholecystectomy until after resolution of local or systemic complications [39–41,46]. Most recently, the Dutch Pancreatitis Study Group assessed the optiomal timing of cholecystectomy after severe ABP (necrotizing biliary pancreatitis) in a post hoc analysis of a multicenter prospective cohort. It was found that the risk of overall recurrent biliary events prior to cholecystectomy was significantly lower up to 10 weeks after discharge (risk ratio [RR] 0.49, 95% CI 0.27 to 0.90, $P = 0.02$). The risk of recurrent pancreatitis before cholecystectomy was significantly lower up to 8 weeks after discharge. Therefore, they concluded that the optimal timing of cholecystectomy was within 8 weeks after discharge (RR 0.14, 95% CI 0.02 to 1.0, $P = 0.02$).[47]

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Strategies for the Treatment of Pancreatic Pseudocysts and Walled-Off Necrosis After Acute Pancreatitis: Interventional Endoscopic Approaches

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Introduction

A series of trials following improvements in intensive care medicine and endoscopic techniques has led to a paradigm shift in the management of fluid collections developing after an attack of acute pancreatitis: if undertaken at all, interventions should be delayed as much as possible and the least-invasive method should be considered first, before escalating treatment (step-up approach) [1–3]. Intervening a post-acute pancreatic fluid collection (PFC) endoscopically is considered safe once a well-defined wall, then called WOPN (walled-off pancreatic necrosis) has developed, roughly 4 weeks into the disease course [4]. Immediate drainage of infected fluid collections is not superior to a delayed approach and with adequate antibiotic treatment, invasive procedures can often be avoided, as demonstrated by a Dutch multicenter trial (POINTER) [5]. Post-acute pancreatic pseudocysts are considered a rare complication arising from a disruption of the main pancreatic duct or major duct branches without considerable necrosis and by definition contain only fluid rich in pancreatic enzymes. In contrast, collections with a fibrous wall originating from pancreatic and/or peripancreatic necrosis are called walled-off pancreatic necrosis (WOPN), which will contain variable amounts of solid debris and may reach into areas distant from the gland [6].

Indications for Endoscopic Treatment

In general, only collections that cause symptoms or are at a high risk for severe complications require intervention. Indications for endoscopic intervention are features of infection on imaging or a high suspicion for infection with persistent signs of sepsis that do not improve under adequate antimicrobial treatment. Less common indications are pain, persistent unwellness, and failure to thrive, jaundice caused by the collection compressing the bile duct, bleeding and arterial pseudoaneurysms, disconnected duct syndrome, gastric outlet obstruction, or pancreatic fistulas.

Endoscopic Drainage vs. Necrosectomy: Choosing the Right Patient

It is currently unclear which collections will improve spontaneously or with conservative management, which require drainage, which need irrigation, and for which collections should a patient undergo advanced endoscopic necrosectomy, as reflected by discordant results of a recent international expert survey [4]. In many cases, patients will initially improve after a drainage procedure and optional nasocystic lavage with few plastic pigtail stents in place to ensure the patency of the tract. A systematic review and meta-analysis comparing 324 patients who underwent conservative management of infected pancreatic necrosis with 157 who underwent necrosectomy concluded that conservative management was successful in 64% and that mortality was lower than in patients who underwent percutaneous treatment [7] although this result is fraught by significant selection bias. Multiple early case series that included pancreatic necrosis and pancreatic abscesses even reported full resolution of these collections without further necrosectomy in over 80% of cases [8–10]. Unfortunately, a nonuniform nomenclature impairs the comparability of these observations. These findings are supported by a recently published Dutch multicentre trial [5]. Between 2015 and 2019, 104 patients with infected pancreatic necrosis occurring within 35 days from onset of symptoms were

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randomized to either receive immediate percutaneous or endoscopic drainage with optional necrosectomy or a delayed approach with antibiotic treatment first and escalation to drainage and necrosectomy only if clinical deterioration occured. The median time difference to first invasive procedure between the treatment arms was 10 days and there was no difference with regard to complications, organ failure, or death. Patients in the delayed treatment arm had considerably fewer invasive procedures and were less often taken to necrosectomy. Notably, 39 % of patients in the delayed treatment arm did not require any invasive procedures at all, suggesting that immediate drainage, especially before encapsulation of a necritc collection, is not generally beneficial.

However, in patients who do not improve on conservative treatment alone or whose recovery stalls at a certain level, the question remains, how soon should one move from drainage to necrosectomy. A Swedish trial comparing drainage of pseudocysts to pancreatic abscesses with variable amounts of debris showed that the rate of successful drainage was lower in abscesses (94% vs. 80%; $P = 0.04$) and the risk for complications five times higher ($P = 0.02$). Of note, all abscesses underwent necrosectomy and lavage later [11]. This suggests that in patients with a higher burden of necrotic material and/or infected collections a more invasive approach may be warranted. The amount of solid debris is best assessed by EUS or MRI.

Transmural endoscopic necrosectomy has been shown to be a safe and efficient way to deal with necrotic collections accessible to endoscopy. It is equally safe and effective when compared to minimally invasive surgical approaches, but appears to be more cost-effective and leads less often to pancreatic fistulas [3,12]. It remains burdened, however, with serious complications even in the hands of experienced investigators [13–16]. In a retrospective comparison of conventional transmural drainage versus necrosectomy in patients with evidence of WOPN on contrast-enhanced computed tomography (CT), Gardner et al. showed superiority of direct necrosectomy in terms of treatment success, need for surgery or additional percutaneous drainage, and recurrence [17]. Another registry-based, matched cohort study comparing direct necrosectomy to initial percutaneous access as suggested by the original "step-up approach" in 12 patients showed favorable outcomes for the direct endoscopic approach [18]. Taken together, the current data suggest that mere endoscopic drainage is reasonable and often sufficient in defined collections with minimal amounts of solid material, whereas patients with WOPN and more extensive necrotic material will most likely profit from sometimes repeated sessions of endoscopic removal of necrotic tissue [19]. In unstable patients who develop sepsis due to infected WOPN requiring ventilator support and vasopressors, an initial endoscopic or even percutaneous drainage to achieve sepsis control and delayed more advanced endoscopic necrosectomy may be more appropriate. Endoscopic drainage is generally preferred over percutaneous drainage for infected fluid collections, but if drainage is required before a fibrous wall has formed (generally 4 weeks) percutaneous drainage is still a valid and frequently used alternative.

The introduction of through the scope, electrocautery-enhanced deployment devices for fully covered self-expandable lumen-apposing metal stents (LAMS), which allow efficient endoscopic drainage as well as necrosectomy through the same access route, have replaced the use of conventional double-pigtail stents for treatment of WOPN in many centers. Placement of LAMS is faster and comes at lower risk for stent dislocation and rupture of the wall of the collection. However, they bear a considerable risk for stent migration and delayed bleeding if left in place for more then 3 weeks (32.3% vs. 6.9%, $P = 0.01$) [20] and despite the larger diameter, they are not more effective with regard to resolution of WOPN when compared to conventional pigtails [21].

Due to shorter procedure duration for the initial placement and the option of through-the stent necrosectomy, many centers now use a dual approach: LAMS are used initially to allow for effective large-bore drainage and if needed endoscopic necrosectomy, but will be replaced by multiple pigtail stents later, when collections can be managed in an outpatient setting.

Preventing Recurrence by Treating Disconnected Duct Syndrome

A disconnected pancreatic duct with pancreatic juice leaking into the connected PFC is a major complication of acute pancreatitis and a well-known risk factor for persistence or recurrence of PFC. This includes pseudocysts and WOPN, even after initially successful endoscopic treatment [22,23]. The integrity of the pancreatic duct should therefore be confirmed whenever pancreatic necrosis requiring an intervention is present and preferably by noninvasive methods such as magnetic resonance cholangiopancreatography (MRCP). Although found in up to 50% of patients with acute necrotizing pancreatitis, studies on the optimal management of PFC associated with disconnected pancreatic duct syndrome are scarce. A small randomized controlled trial ($n = 28$) recruiting patients with and without disconnected pancreatic duct showed a significant reduction of recurrence (0 vs. 5, $P = 0.013$) when transmural stents were not removed [24]. The approach of long-term indwelling plastic stents has been adopted for the treatment of WOPN with disconnected pancreatic duct syndrome as reported in two

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retrospective series including 26 and 33 patients, respectively, in which it appears to have led to a satisfactory outcome with regard to resolution of the collection [25,26]. Another approach involves stenting the pancreatic duct after transmural access and cavity stenting is established. This allows transpapillary drainage of both the content of the connected collection and, more importantly, pancreatic juice away from vital pancreatic tissue distal to the duct disruption [27]. ERCP should be performed with caution in these patients as it is associated with considerable rates of adverse events [28]. A small preliminary study by a group from Mumbai, India described a promising strategy in 42 patients with symptomatic post-acute pancreatic pseudocysts. Three weeks after initially successful drainage using an expandable covered nitinol stent, the patients underwent MRCP. A pancreatic duct leak was detected in three patients and treated successfully by stenting the pancreatic duct with consecutive retrieval of the transmural stent [29]. A larger retrospective study including 375 patients from the USA with different types of PFC compared the treatment success after transmural treatment alone with combined transmural and transpapillary access with no difference in long-term resolution (69% vs. 62%; $P = 0.61$). The presence of duct disruption was not routinely investigated [30]. It is due to these shortcomings in study design and the lack of prospective data that the optimal treatment of disconnected duct syndrome is still unknown, as highlighted by two recent meta-analyses [31,32]. Subject to the significant heterogeneity of the studies included, transpapillary drainage has so far not been shown to be superior to transmural approaches, but combination strategies or step-up management as suggested by Dhir et al. have not been studied. Of note, also surgical treatment such as cystgastrostomy or distal pancreatectomy are a viable option in selected cases.

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Pseudocysts and Walled-Off Necrosis After Acute Pancreatitis: Surgical Approach

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Introduction

The strategy for surgical intervention in patients with pancreatic pseudocysts (PPC) and walled-off necrosis (WON) has dramatically changed in recent decades. In the early 1980s, open drainage and closed lavage were the most common surgical procedures performed for "pancreatic abscess." A more aggressive approach resulting in earlier surgical intervention, with more extensive drainage and debridement of associated necrotic tissue has been recommended [1]. However, early intervention including open necrosectomy is associated with poor outcomes and the latest guidelines suggest that surgical intervention should be delayed as long as possible, until at least 4 weeks after the onset of the illness [2,3].

Peripancreatic fluid collections are frequently seen in the management of patients with acute pancreatitis. Acute pancreatitis is divided into interstitial edematous pancreatitis and necrotizing pancreatitis [4]. In interstitial edematous pancreatitis, fluid collections are usually resorbed spontaneously and clinical symptoms are improved after a week. However, remnant localized fluid collections sometimes require intervention in patients with necrotizing pancreatitis. The terminology for these remnant localized fluid collections was changed completely in 2012, by the revised Atlanta classification [4]. This chapter will focus on surgical strategies for the treatment of patients with PPC and WON after episodes of acute pancreatitis.

Definition of Pancreatic Pseudocyst and Walled-Off Necrosis

In the Atlanta classification, advocated at the International Symposium on Acute Pancreatitis in Atlanta in 1992, acute fluid collections and pancreatic necrosis/infected necrosis were defined as local complications in the early stage of acute pancreatitis [5]. Additionally, PPC and pancreatic abscess are also defined as local complications in the late stage. The term "pancreatic pseudocyst" had been used to describe a wide spectrum of fluid collections derived from necrotizing pancreatitis, interstitial edematous pancreatitis, and acute exacerbations of chronic pancreatitis. Capsulized liquefied necrotic pancreatic and/or peripancreatic tissue after necrotizing pancreatitis should be considered to be different from a capsulized collection of pure pancreatic exocrine secretions. If the same treatment had been performed, the outcome would be different [6,7]. In fact, pancreatic abscess was seldom encountered in either Western countries or East Asia. Based on this background, the concept of "walled-off pancreatic necrosis" was proposed for an encapsulated fluid collection derived from necrotic pancreatic and/or peripancreatic tissue in patients with necrotizing pancreatitis [8]. The term was changed to "walled-off necrosis" (WON), and the concept of this condition was then established by the revised Atlanta classification in 2012 [4] (Fig. 34.1). WON is defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall and usually occurs more than 4 weeks after the onset of necrotizing pancreatitis [4]. Fluid collections originating from necrosis less than 4 weeks after the onset of necrotizing pancreatitis is referred to as an acute necrotic collection (ANC). The concept of a pancreatic pseudocyst (PPC) was proposed to be limited to an encapsulated collection of fluid with a well-defined inflammatory wall, usually outside the pancreas, with minimal or no necrosis that occurs more than four weeks after the onset of interstitial edematous pancreatitis [4,9]. As the concept of PPC changed and the new concept of WON was developed in

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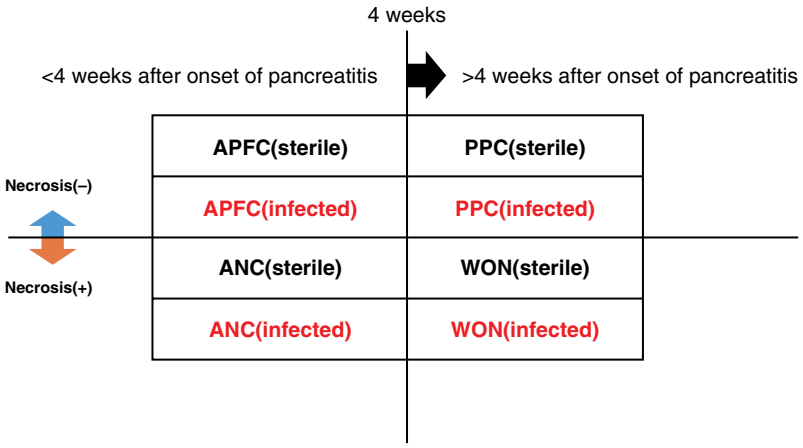


Figure 34.1 Eight categories of local complications of acute pancreatitis defined by the revised Atlanta classification of 2012. APFC: acute peri-pancreatic fluid collection; ANC: acute necrotic collection; PPC: pancreatic pseudocyst; WON: walled-off necrosis.

2012, care must be taken to avoid confusion regarding the terms PPC and WON, especially when reviewing clinical studies reported before 2012.

The International Association of Pancreatology and the American Pancreatic Association (IAP/APA) guidelines were revised according to the revised Atlanta classification of 2012, and the IAP/APA evidence-based guidelines for the management of acute pancreatitis were published in 2013 (IAP/APA guideline 2013) [2]. At the same time, Japanese guidelines for the management of acute pancreatitis were revised and the fourth and the fifth editions were published in 2015, 2021 (JPN guidelines 2015, 2021) [3]. The diagnosis and treatment of acute pancreatitis should be based on these guidelines.

Indications for Surgical Intervention

Previously, surgical intervention with drainage and necrosectomy, was the gold standard for treatment of the infectious complications of acute pancreatitis. In the early 2000s, minimally invasive interventions were developed and have been replacing highly invasive surgical procedures such as open drainage. Minimally invasive interventions include procedures such as endoscopic and laparoscopic drainage and necrosectomy. Both the IAP/APA guideline 2013 and the JPN guidelines 2015, 2021 recommend that interventions should be performed in patients with infections or other persistent symptoms, such as ongoing gastric outlet, intestinal, or biliary obstruction, pain, or complications due to a mass effect secondary to WON or PPC. Most patients with infected localized fluid collections that cannot be managed by the administration of wide-spectrum antibiotics will require some therapeutic intervention.

The terminology for drainage and necrosectomy should be appropriately used. Drainage is a procedure to drain fluid by percutaneous, transgastric, enteral, or transpapillary routes, or by open surgery. Necrosectomy is a procedure to remove necrotic tissue aggressively, using percutaneous, transgastric, or enteral approaches, or by open surgery. Confusion regarding the terminology for drainage and necrosectomy procedures must be considered when evaluating clinical studies reported before 2012.

Timing of Interventions and Optimal Interventional Strategy for WON

In the past, outcomes following early invasive surgical interventions were very poor [10–12]. In a prospective study of 629 patients, late intervention significantly decreased mortality and morbidity [13]. Both the IAP/APA guideline 2013 and the JPN guidelines 2015, 2021 refute the beneficial therapeutic effect of early intervention and recommend that intervention should be delayed as long as possible, until at least 4 weeks after the onset of pancreatitis [2,3]. Interventions should be performed when fluid collections are encapsulated, and the capsule wall is thickened.

The optimal interventional strategy is still controversial. Open surgery was the only choice for intervention before 2000. Minimally invasive interventions, including endoscopic drainage and necrosectomy, and laparoscopic necrosectomy, were introduced in the late 1990s and early 2000s. Though the use of these novel interventions has been increasing, they require advanced technical skills and should be done only in high-volume centers. Some centers reported good results, although there is a large variation in expertise in performing these novel interventions among centers. Further assessment is necessary for these interventions to become standard approaches.

The Dutch Pancreatitis Study Group proposed a step-up approach for the treatment of patients with suspected

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or confirmed infected necrotizing pancreatitis [14]. The step-up approach is composed of two parts, including initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage followed by endoscopic or surgical necrosectomy. Percutaneous catheter drainage alone is reported to reduce the necessity for necrosectomy in 23–50% of patients with infected necrotizing pancreatitis [2,14–19]. Additionally, the step-up approach is reported to decrease major short-term and long-term complications and reduce overall costs compared to conventional surgical necrosectomy [14]. At present, the step-up approach is thought to be the most effective approach and both the IAP/APA guideline 2013 and the JPN guidelines 2015, 2021 clearly recommend it as the optimal interventional strategy [2,3]. The IAP/APA guideline 2013 also states that no subgroup of patients requiring a different strategy can be defined, and the optimal method of necrosectomy (i.e., surgical or endoscopic necrosectomy) is unclear if catheter drainage fails [2].

Catheter drainage is always the first step for intervention in patients with local infectious complications of necrotizing pancreatitis. Less-invasive procedures, such as percutaneous drainage guided by ultrasonography or computed tomography, and endoscopic transluminal drainage are the initial recommendations [13–16] (Fig. 34.2). Surgical drainage with a small incision is indicated in patients for whom percutaneous or endoscopic approaches are contraindicated or fail. Multi-loculated cysts, multiple cysts, presence of significant necrotic debris, cysts in the pancreatic tail and uncontrolled hemorrhage are also indications for surgical drainage. If catheter drainage fails to control infection, minimally invasive or open surgery or endoscopic transluminal necrosectomy are the next steps [20,21].

Laparoscopic and video-assisted retroperitoneal debridement (VARD) have become new choices for a second-step intervention [14]. The results from 14 recent series of percutaneous drainage for necrotizing pancreatitis indicate a 19.4–26.4% conversion rate from percutaneous drainage to surgical drainage, with a 15.2–21% mortality rate [14,22–34]. The results from 18 recent series of surgical necrosectomy indicate the need for additional necrosectomy in 10–16.5%, additional drainage in 13–13.8%, and an overall 1.7–25.8% mortality rate [35–52]. However, the step-up approach has better outcomes. The results from 10 recent series report a 17.4% conversion rate to the surgical approach with a 9.1–14.9% mortality rate [14,36,43–59]. Recently, robot-assisted transgastric cyst-gastrostomy, robot-assisted transgastric drainage and debridement of WON were reported as new minimally invasive surgical treatment [60–62]. Bleeding, pancreatic fistula and gastrointestinal fistula are frequent complications of these interventions.

Surgical Intervention for PPC

Since acute exacerbations of chronic pancreatitis are a leading cause of PPC, the strategy for the treatment of PPC should be different from that used for WON. Most small PPC spontaneously regress without specific interventions. Evidence of infection or persistent symptoms are a common indication for intervention in patients with PPC (Fig. 34.3). External or internal drainage is the first choice for infected PPC, and other novel interventions have been developed



Figure 34.2 Computed tomography scan findings of infected walled off necrosis on the 170th day after the onset of necrotizing pancreatitis. Air bubbles were observed in the area of walled-off necrosis located in the lesser omentum, which strongly suggests the presence of infection.



Figure 34.3 Computed tomography scan findings of a pancreatic pseudocyst. The pancreatic pseudocyst resulted from an acute exacerbation of chronic pancreatitis and is located in the left subphrenic space.

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and evaluated clinically. Open cyst-enterostomy (i.e., cyst-gastrostomy or cyst-jejunostomy) is often used with a reported 15.9–25.4% morbidity and 0.2–0.4% of mortality in six recent retrospective series [63–68]. Laparoscopic cyst-enterostomy, a minimally invasive approach, is becoming more common and performed by various methods, including a Roux-en-Y anastomosis and intra-gastric procedures [69–76]. The laparoscopic procedure has good outcomes, with 9.5–26.9% morbidity, 3.6% PPC recurrence, and 0% mortality in eight recent series [69–77]. Percutaneous cyst-gastrostomy, draining the PPC via both percutaneous and transgastric routes with a gastroscopic procedure, is feasible with 11.3% morbidity and 9.4% requiring an additional surgical cyst-gastrostomy [14,78–80]. Robot-assisted cyst-enterostomy for PPC has not been reported. Bleeding, abdominal abscess including cyst infection, pancreatic fistulae, and surgical site infections are common complications of surgical procedures for PPC [63–77]. Pancreatectomy, distal pancreatectomy, pancreaticoduodenectomy, or duodenum-preserving pancreas head resection, are indicated in some patients with a PPC and persistent chronic pain [67].

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35

Management of Fluid Collection in Acute Pancreatitis

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Introduction

Acute pancreatitis is the most common cause for hospitalization in gastroenterology and has an incidence of 13–45/100,000 with regional variations [1,2]. Alcohol and gallstones are the main risk factors (30–50%) with alcohol as an etiology being more common in men [3].

Considering the variety of different courses of pancreatitis, ranging from mild abdominal pain to death, it is important to predict the likely severity of the disease early in the clinical course.

The current definition of acute pancreatitis, the grades of severity (mild, moderately severe, and severe), and the detailed description of the systemic and local complications based on the revised Atlanta classification from 2012 [4] are discussed in Chapter 20.

Definitions

The way acute fluid collections are classified depends on the time frame of their development as well as some morphological imaging features. The acute (peri-)pancreatic fluid collection (APFC) is a typical complication of the interstitial and edematous subtype and often develops during the first 7 days of pancreatitis. It has no wall and a homogenous internal structure. The spread of an APFC is orientated along the fascial anatomy. Occasionally, APFC are found in multiple locations and they tend to regress spontaneously. If an APFC persists for longer than 4 weeks there is a high probability that a pseudocyst or walled-off pancreatic necrosis (WOPN) will develop.

A pseudocyst is defined as a fluid-filled space, similar to a neoplastic cyst, with a fibrotic wall. In contrast to neoplastic cysts, pseudocysts have no internal epithelial cell lining. Pseudocysts are considered merely complications of chronic pancreatitis and occasionally of acute pancreatitis. Following the latter they evolve from APFC usually later than 4 weeks after the onset of symptoms. The treatment strategies of pancreatic pseudocysts are described in Chapter 3.23.

Regions of nonvital tissue damaged by hemorrhage extravasated pancreatic juice or immune cells are defined as necrosis. It represents a form of tissue injury resulting in premature nonapoptotic cell death. The morphological characteristics of necrosis caused by acute pancreatitis are highly variable. The necrotic tissue may appear as a (semi)solid or fluid structure on imaging, although the sensitivity for detecting the solid component varies greatly between computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) [5].

An acute necrotic collection (ANC) arises within the first 4 weeks of the disease in the pancreatic parenchyma as well as the extrapancreatic tissue. It contains varying amounts of fluid or solid material. The solid parts are the crucial feature to distinguish an ANC from an APFC or a pseudocyst [4] as illustrated in Fig. 35.1.

If a necrotic area is enclosed by a radiologically distinguishable capsule it is called walled-off pancreatic necrosis (WOPN). The difference between WOPN and a pseudocyst is the presence of variable amounts of solid content in the cystic cavity. Usually it arises from an ANC later than 4 weeks from the onset of pancreatitis. Contrast-enhanced MRI and EUS are best suited to distinguish solid from liquid contents, but in most cases contrast-enhanced multiphase CT or even contrast-enhanced ultrasound will enable the diagnosis to be made [3,5].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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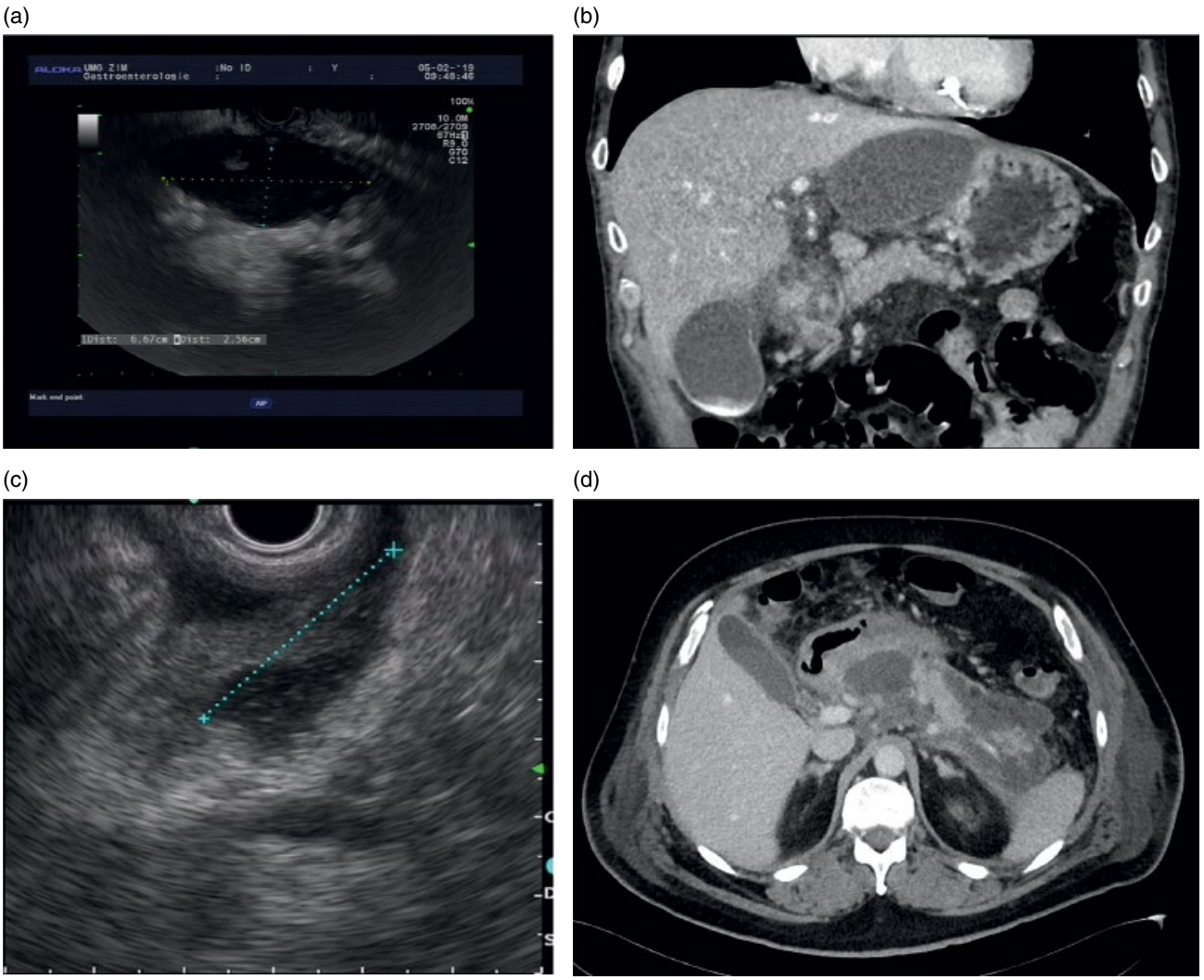


Figure 35.1 Examples for the occurrence of acute pancreatic fluid collections (APFC), post-acute pancreatic pseudocysts (PP), acute necrotic collection (ANC), and walled-off pancreatic necrosis (WOPN) on imaging. The upper panels depict an APFC on EUS (a), which later developed into a large, but oligo-symptomatic pseudocyst (b), demonstrated on a CT scan. The reader will appreciate the absence of solid debris within the collection. In contrast, the lower panel shows an ANC on EUS (c), which matured to a WOPN. On both images, the solid content is clearly visible. The CT scan (d) was obtained prior to percutaneous drainage of the collection, which was necessary due to infection.

An originally sterile necrosis can maintain its status or become infected over the course of the disease. The diagnosis of infected necrosis is based on the patient's clinical presentation and the presence of gas in the necrotic cavity on radiological imaging. It is of note that an asymptomatic fistula from the necrotic cavern to the gastrointestinal tract also leads to the presence of gas within the necrosis but can be without any signs of infection. Fine-needle aspiration followed by microbiological analysis of the content can confirm the presence of infected necrosis but is not needed in most cases and has a high false negative rate. Moreover, microorganisms isolated from the blood of patients with the clinical presentation of an infection or signs of an infected necrosis on imaging are of greater relevance for choosing appropriate antibiosis than those isolated from cultured content of the necrotic cavity. Other than the extent, there are currently no features by which to predict whether necrosis will persist or regress over weeks and months.

Imaging of Acute Fluid Collections

Transabdominal Ultrasound

Transabdominal ultrasound is an inexpensive, immediately available technique to allow a first imaging impression of a patient with an acute abdomen. The imaging of the pancreatic gland is often impaired by abdominal pain and an atonic gut. Edematous pancreas is characterized

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by an inhomogeneous, hypoechoic structure with poorly defined boundaries [6]. The pancreatic main duct is often not visualized inside the edema. Necrotic and hemorrhagic tissue appears more hypoechoic than the inflamed parenchyma. The echo contrast gain or use of ultrasound contrast agent permits a somewhat better distinction between vital or nonperfused tissue. For the detection of small amounts of free fluids in the abdominal or pleural cavity ultrasound remains the undisputed gold standard. The presence of ascites or the mostly left-sided pleural effusions are predictors for a more severe course of acute pancreatitis. Another domain of sonography is the fast and reliable imaging of the gallbladder and, if present, gallstones, which can confirm or rule out a biliary pathogenesis and detection of pleural effusions, which indicate poor prognosis [7]. In expert hands, transabdominal ultrasound with optional contrast enhancement is equally accurate as CT in detecting necrosis, vascular involvement, and severity grading [8–12].

Computed Tomography Endoscopic Ultrasound, and Magnetic Resonance Imaging

Contrast-enhanced CT scan is the fastest and most accurate method for the differential diagnosis of an acute abdomen. At hospital admission CT scan is not recommended for patients with clinical confirmed acute pancreatitis unless other differential diagnosis cannot be ruled out. Imaging via CT should not be performed to assess the severity of pancreatitis on admission [13], because the extent of necrosis can still evolve until up to 72 hours after the disease onset. Therefore, a CT scan should be delayed, if required at all, for 4 days after symptom onset [3,14].

Contrast-enhanced CT can confirm the size, shape, and volume of fluid collections or necrosis and is a valuable tool to identify extrapancreatic complications including hemorrhage or pseudoaneurysms.

Two alternative methods are EUS and MRI. Despite having cost and procedural disadvantages, both methods are more sensitive in detecting solid content within a fluid collection and thus in distinguishing between plain fluid collections and pseudocysts on the one hand and areas of necrosis and WOPN on the other [5]. For more details Chapters 25 and 3.23 are recommended.

Conservative Treatment of Pancreatitis and Pancreatic Fluid Collections

Basic Support

All patients with acute pancreatitis should be monitored regularly within the first 48 hours after admission [3,15]. Important parameters include:

- heart frequency, 6-lead ECG, blood pressure, respiratory rate and oxygen saturation (to detect circulatory respiratory failure and shock);
- blood gas analysis (in case of oxygenation <90%) (to detect respiratory failure) and lactic acidosis;
- hourly urinary excretion measurements for the management of fluid resuscitation (for fluid management and to detect renal failure);
- abdominal pressure measurement via bladder pressure measurement (to detect compartment syndrome) if clinically suspected;
- blood electrolytes;
- blood glucose levels (to detect endocrine failure).

Fluid and Electrolyte Management

Due to retroperitoneal edema and increased vessel permeability a massive fluid shift is typical for acute pancreatitis leading to APFC. Fluid resuscitation is currently the most important intervention for reducing incidence of necrosis and patient mortality [16]. Mortality can increase to 61% if less than 3.5 L of fluid are transfused in the first day. An increase of blood urea nitrogen (BUN) of 5 mg/dL within 48 hours is a sign of prerenal kidney failure and increases mortality by a factor of 2.2 [17,18]. The recommended amount of fluid is 5–10 mL/kg body weight/h or 200–250 ml/h for the first day of treatment [16], or even less, as shown by a recent randomized trial comparing aggressive to moderate fluid resuscitation, which was stopped due to increased rate of fluid overload in the aggressive treatment arm (20.5% vs. 6.3%, p=.004) [33]. Greater therapeutic fluid volumes lead to a mortality increase partially due to abdominal compartment syndrome (intra-abdominal pressure >20 mmHg), sepsis, or a prolonged stay in the intensive care unit [19]. The monitoring of fluid resuscitation should use either invasive thermodilution techniques or, if unavailable, the following parameters:

- heart frequency <120 bpm;
- mean arterial pressure between 65 and 85 mmHg;
- urinary excretion >0.5–1 mL/kg per hour;
- hematocrit between 35 and 45%.

Another important point is the composition of administered fluid. Crystalline solutions are superior to colloids. Colloidal infusions are suspected of being associated with a higher incidence of renal insufficiency and should be avoided. The advantage of Ringer's solution is its similar composition to blood as well as the nonimpairment of electroneutrality by compensating the anion gap with lactate or acetate. Moreover, the incidence of systemic inflammatory response syndrome (SIRS) is reduced within the first 24 hours if Ringer's solution is used rather than saline [20].

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Nutrition

Complete fasting has no positive influence on the outcome and course of pancreatitis [21]. In fact, fasting leads to atrophy of gut villi resulting in a more rapid translocation of intraluminal bacteria, facilitating the infection of necrotic areas. Starting enteral nutrition early is recommended [22]. If the patients are not able to take oral food, feeding by tube is the most effective method. Nasogastric and nasojejunal tubes have been shown to be equally effective and safe [23], although nasojejunal feeding tubes tend to dislocate more often. The best and most natural form of nutrition remains eating by mouth. Once patients are pain-free (with pain medication if required) and can tolerate food they should take oral food. If not enteral nutrition is less expensive and more physiologic than parenteral nutrition. Starting enteral nutrition immediately after admission was not found to lead to better outcomes than withholding food for 72 hours [24]. The current approach to nutrition has become much more pragmatic than in the past when all patients were put on nil-by-mouth for long periods. There is no role for a specific pancreatitis diet.

Antibiotics

Prophylactic application of antibiotics is not necessary for patients with acute pancreatitis, regardless of its predicted severity, and could contribute to the rise of multiresistant bacteria. Neither the mortality nor the rate of infected necrosis is positively influenced by prophylactic antibiotics [17]. Conversely, if infected necrosis is suspected, antibiotic therapy must be initialized immediately. Antibiotics with appropriate pancreatic tissue levels are carbapenems, fluorochinolones, or metronidazole. If the response to the administered antibiotics is insufficient, fine-needle aspiration followed by microbiological testing allows switching to antibiotics based on resistograms. In patients with sepsis other infectious foci must be considered, such as peritonitis, cholangitis, or pneumonia. In general, microbes sampled from blood cultures of pancreatitis are often more informative than those from necrotic fluid collection because of the high rate of false negatives among the latter.

Management of Edematous Fluid Collections

An APFC tends to regress spontaneously. If it persists longer than 4 weeks under conservative treatment it may develop into a pseudocyst or WOPN. Simple intra- or extrapancreatic fluid collections, the focus of this chapter, generally do not require interventional treatment unless they give rise to compartment syndrome as characterized by fluid overload and elevated urinary bladder pressure. An abdominal compartment syndrome is defined as an increased abdominal pressure (>20 mmHg) for longer than 12 hours and simultaneous organ failure [25].

Minimally Invasive Treatment of Acute Fluid Collections in Acute Pancreatitis

When conservative management is unsuccessful, minimally invasive treatment is recommended. The following sections give an overview about the different modalities.

Imaging-Guided Percutaneous Drainage

This is a technically easy and well-established method to treat pseudocysts or fluid collections. Ultrasound, CT, or MRI can be used for imaging. Although single-step needle aspiration is associated with a high relapse rate, continuous catheter-drainage systems are recommended based on their high success rate (70–100%) and a low recurrence rate[26,27]. The risk of fistula formation must be considered.

Endoscopic Drainage

This method provides a minimally invasive access for draining a pseudocyst. Transpapillary and transmural approaches from the stomach or duodenum are available. The aim is to create an artificial connection between the cyst cavity and the gastrointestinal tract. For pseudocysts communicating with the pancreatic main or branch duct transpapillary techniques are to be considered [28]. However, the superiority of transpapillary vs. transmural drainage in these cases has not been established. A larger retrospective study including 375 patients from the USA with different types of PFC compared the treatment success after transmural treatment alone with combined transmural and transpapillary access with no difference in long-term resolution (69% vs. 62%; $P = 0.61$). The presence of duct disruption was not routinely investigated [29]. Therefore, a step-wise diagnostic approach with duct assessment via MRI for cases with suspected duct disruption might be more promising [30].

In the authors' view endoscopic transmural drainage is recommended for cysts that do not communicate with the pancreatic ductal system. Based on a better visualization of vessels EUS-guided drainage is associated with a lower complication rate than the endoscopic technique without EUS visualization and the latter should be abandoned [3,14,31].

For the treatment of pseudocysts with a location distant to gastric lumen and with a thick fibrotic capsule a laparoscopic approach should be favored. In Chapter 3.23 the strategies for surgical and endoscopic interventions for pancreatic pseudocysts, infected necrosis, and WOPN are outlined and discussed in detail.

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Conclusion

Fluid collections that arise in the context of acute pancreatitis generally regress under conservative treatment and do not require interventional treatment in most cases. They may require endoscopic or surgical treatment when they fulfil the morphological criteria of infected (walled-off) necrosis, when they represent complication-causing or complication-prone pseudocysts, or when they precipitate abdominal compartment syndrome. As supported by the results of the Dutch POINTER trial, an initial conservative approach is justifiable: 104 patients with infected pancreatic necrosis occurring within 35 days from onset of symptoms were randomized to either receive immediate percutaneous or endoscopic drainage or a delayed approach with antibiotic treatment first and escalation to drainage and necrosectomy if clinically needed. There was no difference with regard to complications, organ failure, or death. Patients in the delayed treatment arm had considerably fewer invasive procedures and were less often taken to necrosectomy. Notably, 39% of patients in the delayed treatment arm did not require any invasive procedures at all [32].

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Management of Pancreatic Fistula in Acute Pancreatitis

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Introduction

A pancreatic fistula is defined as a leakage of pancreatic juice as a result of disruption of pancreatic ducts or parenchyma. During severe acute necrotizing pancreatitis—besides the systemic SIRS, or sepsis associated consequences—the management of local complications plays a major role. Local complications include infected necrosis, and pancreatic absesses which cause destruction of the pancreatic parenchyma and eventually small or larger ducts, leading to a leakage of pancreatic enzyme-rich fluid. This can either provoke the formation of pseudocysts, or—in case of arrosion of surrounding structures—the onset of a fistula. In most cases parenchyma or duct leakages are self-limiting and can be covered by the surrounding organs, reabsorbed by the serosa, or encapsuled by a fibrous pseudowall with the sequela of a pseudocyst [1]. In case of acute fistula-associated complications, including arrosional bleeding or bowel perforation, immediate interventional and surgical treatment is required, including angiographic bleeding localization and management (i.e., stent placement in the arroded vessel) or emergency surgery. However, if pancreatic fistula does not cause acute complications, a continous leakage may occur and require therapy that needs to be adapted to the site and clinical symptomatology of the fistula. In this context, internal fistulas to the gastrointestinal tract, bronchi, pleural, mediastinal space, pericardium, and other organs [2–4] have to be differentiated from external—cutaneous—fistulas. As internal fistulas are often clinically asymptomatic, they are more difficult to diagnose and may not immediately be detected [5]. By contrast, external fistulas are more often observed, and can be easily diagnosed through the analysis of pancreatic enzyme content in the fluid [5,6].

Pathogenesis and Classification

Pathogenesis

The pathogenesis of pancreatic fistulas is multifactorial and seems to differ according to the site of origin of the fistula and to the time-point when it occurs. On the basis of the necrotizing process in the pancreas, the peripancreatic fat and soft tissue as well as the retroperitoneal space during severe acute pancreatitis, a widespread induction of autodigestion, with interaction between pancreatic exocrine enzymes and inflammatory mediators [7]. Pancreatic parenchyma necrosis is understood as a consequence of oxidative stress and potential calcium overload, leading to a combination of necrosis, apoptosis, pyroptosis and autophagy, in which damage-associated molecular pattern molecules (DAMP) play a central role. Microvascular perfusion failure, as a consequence of local thrombosis and inflammation, contributes to formation of necrosis. Following parenchyma necrosis, proteases and the entire spectrum of all other activated pancreatic enzymes are released into the retroperitoneum and an autodigestive process is initiated. Local leukocyte recruitment and further activation of inflammation favor the necrotizing process throughout the peripancreatic region and the retroperitoneum, toward the mesocolon, small bowel mesentery, and paracolic retroperitonal gutters. The autodigestive process may extend to the skin, bowel, or any other organs. In addition, the development of colonic fistulas during acute pancreatitis can be a consequence of colonic wall necrosis due to venous ischemia (e.g., following mesenteric thrombosis) or arterial infarction as a consequence of systemic hemodynamic instability in

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the hyperacute phase. In the end, iatrogenic fistula can be produced during intraoperative manipulation or endoscopic treatment.

Classification

Pancreatitis-associated fistula can be defined as an abnormal communication between the ductal pancreatic systems, and other spaces or organs due to the leakage of pancreatic secretions from damaged pancreatic ducts [8]. In contrast to postoperative pancreatic fistulas, there is no grading system for fistulas associated to acute pancreatitis [9]. Pancreatitis-associated fistulas can be classified into internal and external fistulas. If their orifice is located intracorporally—regardless of the organ or structure affected—they are classified as internal fistulas; in case of a connection to the skin, the fistula is defined as external. External fistulas can be classified as low- or high-output fistulas, according to the daily cutoff of 200 mL [10]. Further characterization of fistulas includes description as simple (straight channel from the pancreas toward the skin or another organ) or complex (multiple channels and tracts to different organs or structures). Moreover, the fluid can be characterized as clear pure pancreatic juice (due to external drainage of a pseudocyst communicating with the pancreatic duct) or as mixed (consisting of pancreatic juice in combination with gastrointestinal secretions or bile). In the latter case, the pancreatic juice might be activated by enterokinase, leading to proteolytic effects of the fluid and a more severe injury. Finally, the unfortunate event of disruption of the main duct can give rise to a persistent pancreatic fistula, in the so-called "disconnected pancreatic duct syndrome" [11].

Diagnosis

External Fistulas

The vast majority of external fistulas form along the tract of interventional or surgically placed drainages that are inserted to treat the complications of pancreatic necrosis. They can easily be recognized by their typical rich content of amylase and lipase. As mentioned earlier, there is no standard defined cutoff for the increase in pancreatic enzyme, amount of fluid, or duration of secretion. To differentiate between simple and complex fistulas radiological imaging should be performed. Conventional fistulography, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) are the most described [12–15]. CT scan is the gold standard in the diagnosis and classification of acute pancreatitis and its complications, namely abscesses, pseudocysts, and walled-off infected necrosis [8]. However, CT scan shows a lower accuracy in fistula detection compared with MRI/MRCP imaging. Conventional fistulography is useful to determine potential connections to other organs (i.e., colon), and ERCP has the advantage of providing simultaneous diagnostic and therapeutic possibility, namely the placement of a pancreatic stent in cases of pancreatic duct disruption (Fig. 36.1).

Internal Fistulas

Internal pancreatic fistulas are mostly asymptomatic, and may be difficult to recognize. In case of persisting ascites and/or a pleural effusion an internal fistula should be ruled out. In rare cases also acute mediastinitis arising from a pancreato-mediastinal fistula can be observed [16]. Unfortunately, unrecognized internal fistulas can lead to life-threatening conditions, if the activation of pancreatic enzymes leads to arrosional bleeding or bowel perforation [17]. Once an internal fistula is suspected, further imaging work-up needs to be tempestively done. CT scan remains the gold standard for diagnosis and treatment, and the biochemical analysis of collected fluid can confirm the suspected diagnosis [18,19]. For internal fistulas, MRCP or ERCP can be useful for the diagnosis and as well as ERCP for ultimate treatment [20].

Surgical Treatment

The treatment of pancreatits associated fistulas refers mainly to the international guidelines for the management of severe acute pancreatitis [8,21–24]. Supportive care management, namely adequate fluid resuscitation, pain control, nutritional support, and antibiotic treatment in cases of infected necrosis are the recommended strategies. In cases of failure of the conservative treatment, either due to organ compression from a fluid collection, or to persistent systemic infection, the so-called "step-up approach" is recommended, involving first of all an endoscopic attempt, followed by radiologic effort and, in case of failure of the first two, leading to a surgical minimally invasive or open intervention [25].

Open surgery in acute pancreatitis is no longer a gold standard in acute pancreatitis and should be cautiously evaluated just for those patients in whom all other options were not successful. However, a short overview on classical surgical approaches is mandatory [26]. The historically used open surgical techniques are the necrosectomy combined with open packing [27], the planned staged relaparotomies with repeated lavage [28], the placement of "kissing-drains" in the lesser sac and closed continuous lavage [29,30], and the closed packing [31], with mortality rates of up to 15% in referral centers [27,32–34]. In the first two techniques several consequent re-laparotomies are mandatory in order to achieve a satisfactory debridement of necrotic tissues.

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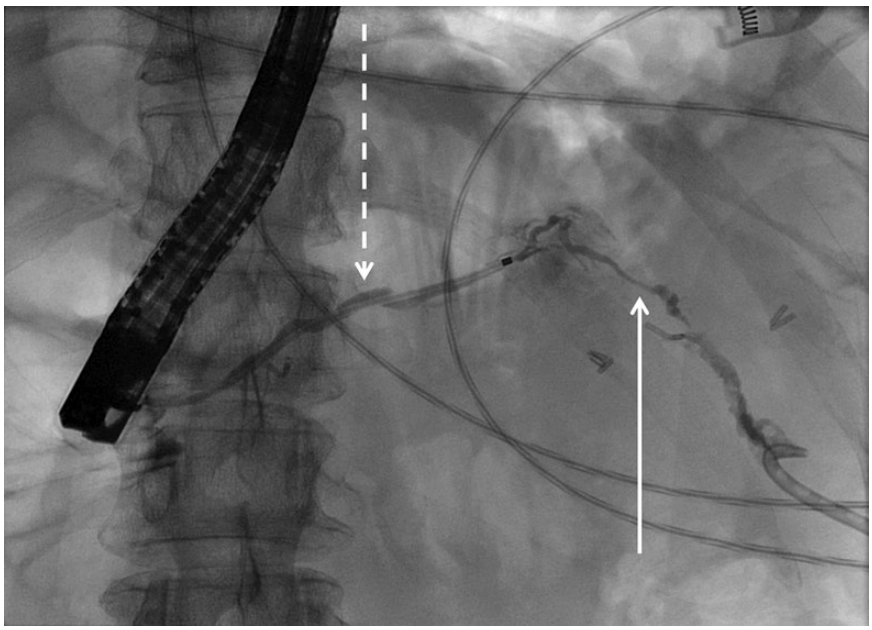


Figure 36.1 Internal pancreatic fistula to the retroperitoneal space after severe necrotizing pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) showing the pancreatic duct (broken white arrow) and the leakage with contrast medium extravasation (white arrow).

The last two, conversely, allow a progressive and continuous lavage of the necrotic region, without the need of subsequent surgeries. As the mortality rate and the risk of following injuries increases with the number of relaparotomies, the last two techniques should be preferred.

Drain Management

Once a pancreatitis-associated fistula is diagnosed, the amount and duration of drain in place are related to the size of the involved duct (main duct or branches of first, second, or third order), the localization of duct rupture (head, body, or tail of the pancreas), and the functionality of the sphincter of Oddi. In the acute phase of the disease, edema or spasm of the sphincter of the papilla may impair outflow, leading to increased pressure within the ductal system and subsequent rupture of the duct or maintenance of the outlet via the fistula. Once outflow via the papilla is restored, secondary to resolution of either the edema or spasm, spontaneous healing of the fistula can be observed in most cases.

Management of Internal Fistulas

Most fistulas (80–100%) close spontaneously within 2–3 months [35]. Failure to heal is mainly due to larger defects of the pancreatic duct system, resulting in high-volume output. Endoscopic trangastric drainage, or surgical treatments should be considered. The surgical approach to internal fistulas focuses mainly on treatment of the underlying disease, as once infected necrosis is treated adequately, internal fistulas will close rapidly [36,37]. As suggested in international guidelines, the surgical approach is indicated only after failure of all conservative strategies and should be deferred at least for 4 weeks after the onset of acute pancreatitis.

The choice of treatment depends on the characteristics of the patient and the fistula, and comprises several drainage techniques. Endoscopic transmural drainage and percutaneous drainage (Fig. 36.2) have become the procedures of choice in cases of internal fistula with symptomatic pseudocyst formation [38]. Furthermore, endoscopic sphincterotomy with or without transpapillary stent placement facilitates the drainage of pancreatic juice into the duodenum and can consequently release pressure from the disruption site. This accelerates the healing and may even allow the closure of partially disrupted pancreatic ducts within a median interval of 10 days [39-41]. In case of severe damage and disconnected pancreatic duct syndrome endoscopic treatment cannot be sufficient. An early surgical treatment may be considered after initial drainage of a fluid collection by endoscopic therapy. Surgical treatment (i.e., central pancreatectomy or distal pancreatectomy) has a long-term success rate of approximately 90%; however, atrophy of the pancreatic gland is a frequent and early complication after disrupted duct syndrome, leading to chronic pancreatits and diabetes in up to 30% of cases [42].

Management of External Fistulas

Simple fistulas do not necessarily lead to complications; therefore, a conservative management should be pursued. Complex fistulas are more likely to develop

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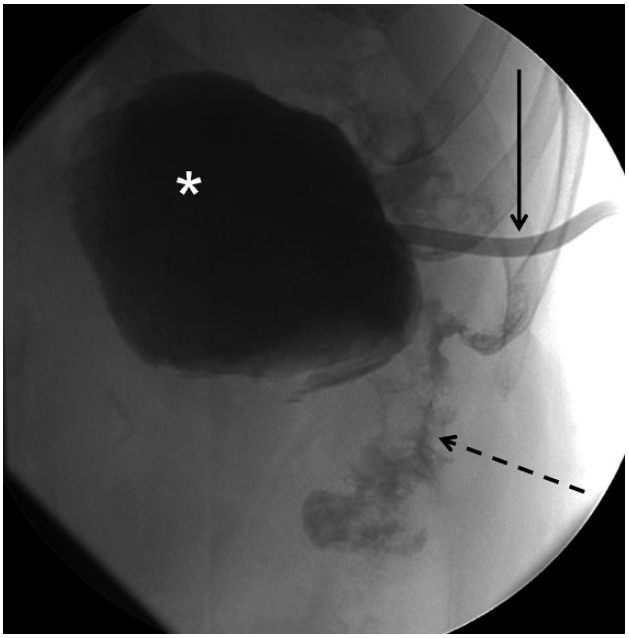


Figure 36.2 Internal pancreatic fistula during severe necrotizing pancreatitis. X-ray after percutaneous catheter drainage (black arrow) of a large fluid collection (white star). Transition of contrast medium to the descending colon (broken black arrow).

dangerous complications because of high risk of free activation of pancreatic enzymes in the abdominal cavity and digest surrounding structures. The aim of surgical therapy of external pancreatic fistulas is to redirect the drainage into the intestinal tract [43]. The surgical procedure chosen is based on the site of the fistula, the thickness and nature of the fistula tract, as well as the texture of the pancreatic tissue. If the fistula tract is located on the right side of the body of the pancreas or even in the head, resection should be avoided and internal drainage into a Roux-en-Y jejunal loop is preferred [6,43]. For persisting fistulas located in the body or tail of the pancreas, central or distal pancreatectomies are suitable procedures to remove the fistula-bearing part of the pancreas [24]. Crucial for surgical treatment of external pancreatic fistula is the timing of the procedure. Formal pancreatic resections should be avoided in the early phase of fistula occurrence, as fistulas may spontaneously close even 6 months after an acute episode.

Nutritional Support

Nutritional support care can be added to improve not only healing of a fistula but also patients' general performance status, which is often reduced after acute pancreatitis. If chosen, the enteral route should be preferred in all phases of the disease. A total parenteral nutrition regimen should only be considered if the enteral route is not tolerated or if the enteral feeding alone cannot achieve the expected nutritional daily requirements. When parenteral nutrition is indicated, a glutamine supplement should be administered, at 0.20 g/kg per day of L-glutamine. Otherwise, there is no role for immunonutrition in pancreatitis-associated fistula [44].

According to international nutritional guidelines, pancreatic enzymes should not be generally supplemented, except in patients with obvious pancreatic exocrine insufficiency. A debatable aspect in the management of internal fistula is the role of somatostatin analogs. No clear benefit of octreotide has been demonstrated [45], with the exception of the pancreaticopleural fistula, where it has been shown to reduce the output and decrease the time to fistula closure [46].

Conclusions

Pancreatic fistulas are common sequelae following acute pancreatitis and, in most cases, self-limiting processes. Pancreatic fistulas can occur spontaneously or be the consequence of interventions required to manage infected walled-off necrosis in severe acute pancreatitis. The majority of fistulas present with low output and tend to close spontaneously within a few months. For this reason, a conservative approach is recommended. After failure of the conservative treatment, a step-up approach is the gold standard, including a wide range of minimally invasive therapeutic options. Endoscopic and percutaneous interventions should be preferred, as surgery-related mortality remains high even at referral centers. The surgical option remains the ultimate treatment when the endoscopic and percutaneous intervention are not successful. The type and extent of resection must be considered and tailored for each case. Surgery should be delayed by at least 4–6 weeks following the onset of an acute episode.

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Long-Term Outcome After Acute Pancreatitis

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Introduction

Most patients with acute pancreatitis recover completely without any further symptoms or morphological alterations within days or weeks after discharge. This observation was described in the original definition of acute pancreatitis by the Consensus Symposium 1963 in Marseille [1]. However, recent reports on long-term outcome after acute pancreatitis show growing evidence that there is a certain risk for late pancreatitis-associated complications even after mild clinical courses [2–5].

Functional impairments can occur immediately or even years after sustaining acute pancreatitis [2,3,5–8], specifically loss of endocrine function resulting in diabetes mellitus type 3 or exocrine insufficiency with the need for pancreatic enzymes substitution, have been described in numerous studies [2,9–11]. Etiology or severity of the index episode are not clearly associated with the overall risk for an impairment of pancreatic function. In addition, episodes of pain with a considerable impact on quality of life can occur at any point of time after the initial event of acute pancreatitis. These possibly recurrent pain sensations bear a high risk for chronification and may be associated with recurrent pancreatitis; there is also a certain overlap with clinical courses of chronic pancreatitis [2,5,12,13]. This latter correlation has been examined in several recent publications [2–5,14–20]. It is sometimes difficult to distinguish between the primary episode of acute pancreatitis as a symptom of a chronic disease and chronic pancreatitis developing as a long-term consequence of pancreatitis. Morphological characteristics (i.e., those found in cross-sectional imaging at the initial episode of pancreatitis) can be useful for this differentiation as preexisting signs of subclinical chronic pancreatitis may be found in terms of fibrosis or calcifications and can be clearly distinguished from typical signs of new-onset acute pancreatitis.

In contrast to chronic pancreatitis, little is known about histomorphologic pathways and alterations of recurrent acute pancreatitis. One hypothesis is the so-called necrosis–fibrosis sequence [21], which suggests that acute inflammatory changes after an initial and acute damage of the pancreas result in mesenchymal cell activation with various patterns of subsequent fibrosis development and obstruction of pancreatic ducts. Another model is based on a "sentinel acute pancreatitis event (SAPE)," postulating a long-lasting intrapancreatic activation of immunomodulatory and stellate cells during the index episode. These alterations lead to hypersensitivity of the pancreas when responding to potential stimuli, resulting in recurrent attacks of acute and eventually chronic pancreatitis [22]. Despite these hypotheses, the possible pathophysiologic link between acute and chronic pancreatitis remains controversial and is not well understood [23].

Because there are no follow-up guidelines for clinical examinations and imaging after acute pancreatitis and histopathologic findings for such patients are rare due to the infrequent need for operations with respective tissue harvesting, the frequency of such alterations is unknown. In available cross-sectional imaging, alterations of the pancreatic duct, parenchyma, or surrounding areas (i.e., formation of pseudocysts or fluid collections) can be observed during both short- and long-term courses. These morphological findings may be correlated with the severity of the first attack and the type of treatment, in particular interventional or surgical necrosectomy.

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Their extent and the underlying initial etiology of the primary acute pancreatitis episode determine clinical outcome patterns. In alcohol-related acute pancreatitis a recurrent and eventually chronic course is observed more often than it is in a biliary genesis of the disease [13,15,19,20]. This fact underlines the importance of avoiding further exposure to risk factors such as alcohol and nicotine as a basic precaution following a first pancreatitis episode [14,24,25]. Furthermore, patient education can be regarded as a simple method to reduce the lifelong risk of recurrence and associated healthcare costs [20,24]. Follow-up examinations should therefore address the above-mentioned topics and should include clinical and laboratory as well as imaging examinations, when necessary. This chapter gives an overview of the long-term sequelae of acute pancreatitis with regard to risk factors, diagnosis, and management.

Risk Factors

Risk factors for long-term complications of acute pancreatitis have been examined in several cohort studies in recent years [4,5,7,14]. With regard to recurrent episodes of acute pancreatitis, a recent meta-analysis including nearly 8500 patients showed an overall risk of 22% with a nearly twofold increase in alcoholic etiology (38%) and a lower risk for biliary etiology (17%) [4]. With regard to biliary etiology, early removal of the gallbladder after the index episode of pancreatitis reduces the risk of recurrence [5,14]. In nonbiliary etiology, persistence of smoking and alcohol consumption are well-documented risk factors for both recurrent acute episodes as well as progression of primary acute to chronic pancreatitis in the long term [5,7,14]. Nevertheless, some authors report experience with patients who show a progression to chronic pancreatitis despite stopping consumption of alcohol and nicotine [14,15]. In addition, male patients seem to have a higher risk of progression to chronic pancreatitis, even when lifestyle-associated risk factors are excluded [4]. Risk factors for functional failure after acute pancreatitis include preceding necrosectomy, which leads to both exocrine and endocrine insufficiency due to the procedure-associated loss of tissue itself and the disease-specific damage to the remaining tissue [5,26,27]. Again, the risk for developing progressive pancreatic dysfunction and diabetes mellitus or exocrine dysfunction is increased in men [4,6]. Moreover, a subset of patients may also have unrecognized genetic risk alterations leading to increased risk of progressive pancreatic failure and chronic pancreatitis through an effect on trypsinogen activation [28]. Tables 37.1 and 37.2 summarize studies on patterns and risk factors for long-term sequelae after acute pancreatitis.

Endocrine Pancreatic Dysfunction

Hyperglycemia, impaired glucose tolerance, and diabetes mellitus occur frequently as a consequence of acute pancreatitis and have therefore been investigated as primary or secondary endpoints of several large studies on the loss of pancreatic function on long-term follow-up. A recent review analysed 34 studies focusing on diabetes mellitus after acute pancreatitis [3]. The authors concluded that especially pancreatic diabetes mellitus (type III) and impaired glucose metabolism after acute pancreatitis are increasingly recognized clinical findings requiring more detailed research on it as the published data are inconsistent. Of interest, one of two included meta-analyses had examined 24 prospective studies published between 1968 and 2009, and revealed that nearly 40% of patients showed a prediabetic metabolic situation or a full clinical manifestation of diabetes mellitus [2]. Within 12 months after the index episode of acute pancreatitis the prevalences of hyperglycemia and diabetes mellitus were 19% and 15%, respectively. After a 5-year observation period, the risk for diabetes mellitus showed a twofold increase compared with the prevalence after 12 months. A Dutch cohort study on 669 patients described a new onset of diabetes mellitus in 20% of the patients during a median follow-up time of 57 months [7]. These data are consistent with findings of a Taiwanese study, which showed a comparable twofold increase of diabetes risk after 10 years in nearly 3000 acute pancreatitis patients, regardless of the severity of the initial course of the disease [6].

In severe courses characterized by extensive parenchyma necrosis and the need for necrosectomy, the correlation between loss of tissue and function seems to provide an explanation for these observations, especially when the body and tail of the pancreas are affected. Decay of a considerable amount of islets predisposes for functional deterioration and 15–30% of patients undergoing extensive necrosectomy show insulin-dependency soon after recovery [5]. This is comparable to outcomes following distal pancreatectomy for other indications, with a rate of postoperative diabetes mellitus of approximately 10% [30–32], and underlines the relevance of the pancreatic body and tail for the endocrine function of the gland due to the pronounced location of islet cells in these segments of the pancreas. In contrast, the pathophysiologic explanation for mild episodes of acute pancreatitis resulting in endocrine insufficiency and an increased risk of diabetes mellitus remains unclear.

Exocrine Dysfunction

In the early phase after acute pancreatitis, exocrine function is often compromised and is easily diagnosed

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Table 37.1 Patterns of long-term sequelae after acute pancreatitis.

Author, year, country, observation period	Patients (*n*) etiology	Diabetes mellitus *n* (%)	Exocrine dysfunction *n* (%)	Recurrent pancreatitis *n* (%)	Chronic pancreatitis *n* (%)	Median follow-up
Pelli [15], 2000, Finland, 1972–1991	562 alcoholic	nm	nm	260 (46%)	nm	38 months
Lund [19], 2006, Sweden, 1995–1998	138 alcoholic: 61 biliary: 48	nm	nm	41% nonbiliary vs. 10% biliary	nm	6 years
Yasuda [29], 2008, Japan, 1990–2006	45 alcoholic: 23 biliary: 10	16 (36%)	18 (40%)	8 (18%)	8 (18%)	56 months
Nøjgaard [18], 2011, Denmark, 1977–1982	352 alcoholic: 129 biliary: 44	nm	nm	Nm	85 (24%) alcoholic: 41 (48%)	nm
Castoldi [16], 2013, Italy, 2001–2003	631 alcoholic: 36 biliary: 439	22 (3.5%)	16 (2.5%)	80 (13%)	nm	52 months
Yadav [20], 2014, USA, 1996–2005	6010 alcoholic: 1223 biliary: 1647	nm	nm	1950 (32%) with at least 1 readmission due to pancreatitis		39 months
Ahmed Ali [7], 2016, Netherlands, 12/2003–03/2007	669 alcoholic: 153 biliary: 384	136 (20%)	34 (5%)	117 (17%)	51 (8%)	57 months
Tu [17], 2017, China, 1995–2016	113 alcoholic: 3 biliary: 65	34 (30%) +impaired glucose tolerance 33 (29%)	40 (35%)	nm	nm	30 months
Karjula [25], 2019, Finland, 1995–2012	1644 alcoholic:1173 biliary: 217	nm	nm	510/1173 alcoholic (44%) 104/471 nonalcoholic (22%)	nm	114 months
Maatman [27], 2020, USA, 2005–2017	647 necrotizing alcoholic: 133 biliary: 317	195/549 (35%)	108/571 (19%)	nm	93/571 (16%)	46 months

nm, not mentioned.

by clinical symptoms of diarrhea, steatorrhea, and maldigestion. In the long term, the reported prevalence rates of exocrine dysfunction differ considerably in the available studies [5,7,26,33]. A study by Sand and Nordback reports 25% of patients having exocrine failure after necrosectomy in a follow-up period of 2–5 years [5], whereas other studies with comparable observation times reported much higher rates of 55% after mild and up to 83% after severe courses, independent of the etiology of acute pancreatitis [33–35].

Symptoms of exocrine failure can be controlled very well in most patients by oral enzyme replacement to prevent maldigestion, malabsorption, and consecutive malnutrition. Supplementation of the diet with fat-soluble vitamins in the follow-up period should also be considered [36]. A discontinuation of enzyme supplementation may be possible as several studies have reported a potential for long-term recovery of exocrine function within 12–24 months after acute pancreatitis [5,34], which is comparable to the functional recovery often observed after pancreatic resections for other indications.

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Table 37.2 Risk factors for long-term complications of acute pancreatitis.

Author, publication year, country, number of patients Long-term complications	Lankisch [14], 2009, Germany, 532	Ahmed Ali [7], 2016, Netherlands, 669	Yasuda [29], 2008, Japan, 45	Nøjgaard [18], 2011, Denmark, 352	Sankaran [4], 2015, meta-analysis, 8492	Shen [6], 2015, Taiwan, 2966	Karjula [25], 2019, Finland, 1644	Tu [17], 2017, China, 113	Nikkola, [8], 2017, Finland, 77
Recurrent acute pancreatitis	Age >40 years, male, biliary etiology without subsequent cholecystectomy	Younger age, nonbiliary etiology, smoking, pancreatic necrosis	Severity of initial attack	Smoking	nm	nm	alcohol	nm	nm
Progression to chronic pancreatitis	Alcohol consumption, heavy smoking, recurrent acute pancreatitis	Nonbiliary etiology, smoking, pancreatic necrosis	Severity of initial attack	nm	Alcohol, smoking, men > women	nm	nm	nm	nm
Death related to acute pancreatitis	nm	nm	nm	nm	nm	nm	alcohol	nm	Recurrent acute pancreatitis
Diabetes mellitus	nm	nm	nm	nm	nm	Men > women (HR 3.21 vs. 1.58)	nm	Pancreatic necrosis >50%	Recurrent acute pancreatitis

OR: odds ratio; HR: hazard ratio; nm: not mentioned.

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Recurrent Pancreatitis and Chronic Pancreatitis

Regarding the frequency and timeline of progressive pancreatic disease after acute pancreatitis, about 20% of all patients and 50% of patients with an alcoholic etiology show recurrent episodes within 10–20 years, but most recurrences occur during the first years after the initial attack [4,5,7]. Overall, 1 out of 10 patients will suffer from a progression to chronic pancreatitis [4], which may be associated with few symptoms for a long period but may finally result in end-stage findings of chronic pancreatitis despite a subclinical course (Fig. 37.1). In the case of recurrent acute episodes, the risk of progression to chronic pancreatitis shows a three- to fourfold increase, which is, again, pronounced in patients with an underlying alcoholic etiology [7].

Quality of Life and Pain

Several outcome studies report on the occurrence of pain and the quality of life after acute pancreatitis [5,7,12,13]. An observational study on 145 patients from Finland showed no impairment of quality of life, regardless of pancreatitis etiology, compared to the general population [12]. Similar results are shown in several smaller observational studies, even after necrosectomy [5]. In contrast, in a Polish study patients suffering from severe alcohol-induced acute pancreatitis showed a reduced quality of life in comparison to those with a biliary origin of the disease with regard to social and family life as well as emotional well-being [13]. How far persisting alcohol consumption after the index episode of pancreatitis contributes to these findings, however, remains unclear from the study data. With regard to chronic pain, a large Dutch cohort study including 669 patients found that 13% had recurrent episodes of pain related to acute pancreatitis [7]. A recent large US analysis observed 647 patients with necrotizing pancreatitis, who were treated and followed up in a single center [27]. The authors describe less commonly reported long-term complications such as chronic pain in 8%, strictures of the bile duct (16%), the pancreatic duct (5%), or the duodenum (5%) as well as splanchnic vein thrombosis (45%). Of interest, 340 (59%) patients developed complications that needed invasive intervention after completely recovering from necrotizing pancreatitis [27].

Incisional Hernia

With the implementation of minimally invasive management of infected pancreatic necrosis during the initial episode of acute pancreatitis, open surgical interventions have considerably decreased and are regarded as the last resort in modern treatment concepts [37,38]. Less than 5% of patients with acute pancreatitis need to

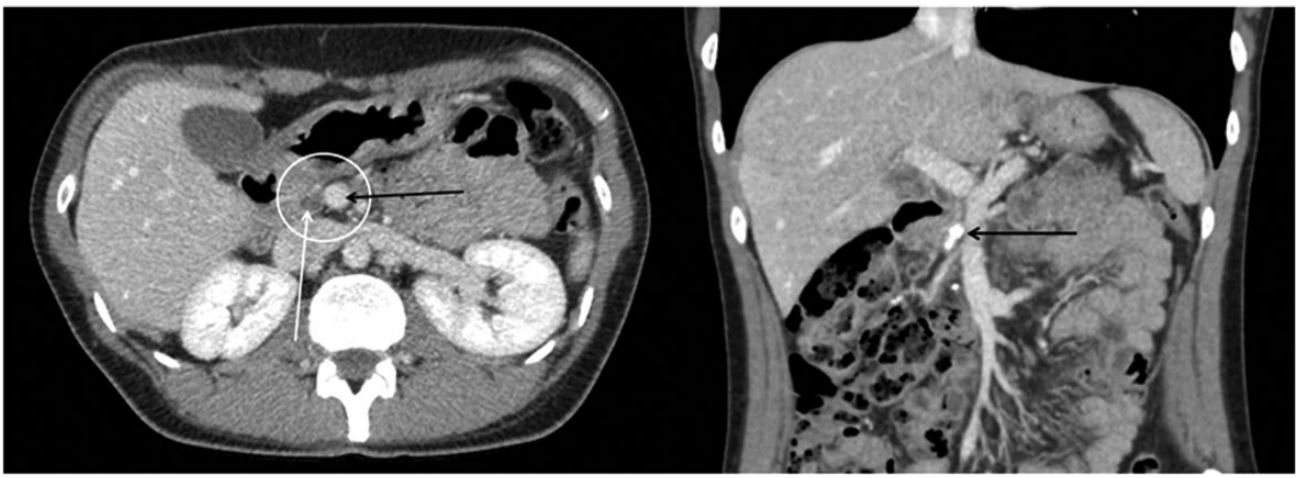


Figure 37.1 A 39-year-old female patient 9 years after a solitary episode of severe acute pancreatitis following hemorrhagic shock and acute respiratory distress syndrome (ARDS) due to atonic bleeding after cesarean section. This was followed by complete recovery and primary discharge from hospital after 5 weeks and complete remission of residual pseudocysts over a 6-month period. Afterwards, the patient had no clinical symptoms for 8 years before recurrent abdominal pain attacks irradiating to the back occurred. CT scan revealed nearly complete atrophy of the pancreatic parenchyma (left side, white circle; black arrow: portal vein, white arrow: bile duct) and a calcification in the pancreatic head (right side, black arrow). As no signs of inflammation, tumor suspicion, or endocrine insufficiency were present, symptomatic treatment was successful (oral enzyme replacement and analgesia).

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be treated by open surgery (e.g., in case of unsuccessful minimally invasive necrosectomy, for bleeding control, or due to organ perforation). These patients show a high rate of surgical site infections (80%) [34] and a correlating high risk of developing an incisional hernia (21–40%) [27, 40]; surgical reintervention is often required for symptomatic, functional, and cosmetic aspects of these, often large, hernias.

Pancreatic Cancer and Pancreas-Related Death

In general, death related to acute pancreatitis, besides short-term mortality during a severe necrotizing course, seems to be rare and not related to progression to chronic pancreatitis and finally pancreatic cancer. A German study reported on four deaths of pancreatic cancer in 532 patients (0.8%) observed after acute pancreatitis during an average follow-up of 7.8 years, which occurred 9–56 months after acute pancreatitis, none of them with a diagnosis of chronic pancreatitis [14]. In an Italian study, 3 of 631 patients (0.5%) died of pancreatic cancer 5, 6, and 19.9 months after acute pancreatitis with unknown etiology in the first case and biliary etiology in the others [16]. These data support the conclusion that the initial pancreatitis event may be a symptom of an already existing tumor rather than pancreatic cancer and the related mortality is a long-term consequence of acute pancreatitis. A recent study on 1644 patients from Finland showed, that after an acute episode of alcohol-induced pancreatitis with the need for hospitalization, long-term mortality was four times higher than that in an age- and sex-matched control population [25]. The most common cause of death was pancreatic cancer in patients with nonalcoholic acute pancreatitis, while patients with alcoholic pancreatitis died mostly by alcohol-related diseases.

Imaging Findings

Most episodes of mild acute pancreatitis do not result in any morphologic changes and, after restitution, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) scans show a normal pancreas without any damage to the gland or the duct system. Even when functional impairment occurs, this is not necessarily associated with any pathological imaging findings. This is also observed in most cases of diabetes mellitus of other genesis and in many patients with endocrine dysfunction without underlying chronic pancreatitis. In contrast, severe episodes of acute pancreatitis with or without the need for interventional or surgical treatment often result in morphologic pancreatic alterations of varying extent.

Common reversible or irreversible findings on CT or MRI imaging include:

- inhomogeneity of the parenchyma;
- atrophy of the parenchyma;
- duct alteration (strictures/dilation);
- residual peripancreatic fluid collections;
- pseudocysts.

Diagnosis of the abovementioned alterations alone does not require any measures, unless accompanying symptoms are present. Further follow-up examinations should be performed to evaluate a potential dynamic of these changes and recognize potential need for any interventional or surgical therapy early to prevent ongoing destruction of the pancreatic parenchyma in the case of recurrent pancreatitis episodes or development of chronic pancreatitis or chronic pain. The management of pseudocysts and persisting postpancreatitis fistulas is described in Chapters 34 and 35.

Another important aspect is the recognition of cystic lesions as the cause of acute pancreatitis and their differentiation from residual pseudocysts. It has been reported that 13–67% of all patients with intraductal papillary mucinous neoplasia (IPMN) show an episode of acute pancreatitis as their initial symptom [41–43]. However, this is frequently misdiagnosed and studies in the past report on a delay in diagnosis of a cystic neoplasm as the trigger of acute pancreatitis of several years or even more than two decades [41–43]. With growing awareness of cystic neoplasms in recent years this may be avoided in the future as distinguishing postinflammatory duct dilatation and pseudocysts from IPMN is of high importance because of the malignant potential of IPMN.

Postpancreatitis Care and Follow-Up Visits

Six to eight weeks after hospital discharge due to an episode of acute pancreatitis, a clinical control examination can be recommended to document the status, including symptoms and nutritional status with regard to pancreatic function, blood tests, and imaging in cases of severe acute pancreatitis. In case of biliary acute pancreatitis, cholecystectomy (preferably by a laparoscopic approach) must be scheduled if it has not been performed during the initial hospital stay. There is good evidence concerning the indication and timing of cholecystectomy which shows that a delay of this operation results in an increased

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risk of recurrent biliary pancreatitis [4,5,44]. For mild biliary pancreatitis cholecystectomy should be performed during index admission. In contrast, in patients with severe pancreatitis, cholecystectomy can safely be performed after resolution of symptoms (4–6 weeks). A similar time frame should be chosen for patients who undergo sphincterotomy during biliary pancreatitis [44]. Besides biliary pancreatitis, a Finnish study suggested that recurrence of idiopathic acute pancreatitis can also be prevented effectively by laparoscopic cholecystectomy, which should be evaluated for the respective patients [45].

No general guideline or consensus recommendations for long-term follow-up visits after acute pancreatitis exist to date. From the clinical point of view, follow-up at 6-monthly intervals during the first 2 years seems to be reasonable, followed by yearly examinations thereafter [46]. A possible scheme for follow-up could include:

- documentation of abdominal and unspecific symptoms;
- clinical examination;
- blood samples for the determination of routine parameters (including HbA_{1c}, electrolytes, creatinine, urea, liver enzymes, amylase, lipase, white and red blood cell counts, and C-reactive protein) as well as the serum tumor markers CEA and CA19–9;
- analyses of genetic factors (*PRSS1*, *SPINK1*, *CFTR*) in the case of unclear etiology of the underlying acute pancreatitis [4,28];
- cross-sectional imaging with abdominal CT or MRI scan.

Conclusions

Overall, the majority of patients show a good long-term outcome after acute pancreatitis. However, one out of four patients will develop some kind of problem in the long run, including endocrine or exocrine dysfunction, recurrent acute pancreatitis, or transition to chronic pancreatitis even many years after the initial event. Risk factors for clinical deterioration are incompletely examined and understood at present. Lifestyle habits, such as ongoing consumption of alcohol and nicotine, have been shown to increase this risk, especially for patients with alcohol-induced first attack of acute pancreatitis. Following biliary pancreatitis, removal of the gallbladder is an essential measure for prevention of future relapses and should preferably be performed during the initial hospital stay in mild pancreatitis and 6–8 weeks after recovery from a severe episode. To detect long-term loss of function before progression to an irreversible stage, regular follow-up is recommended, including clinical examination and blood tests at 6- to 12-month intervals to check for new onset of diabetes mellitus as well as maldigestion due to pancreatic exocrine dysfunction even when patients are asymptomatic. In the case of abdominal complaints, cross-sectional imaging should be considered. Pathologic findings alone (i.e., atrophy of the pancreatic parenchyma) do not require immediate intervention but should be further monitored during regular follow-up. In the case of transition to chronic pancreatitis with fibrosis and calcifications of the pancreas or dilatation of the pancreatic duct in combination with episodes of pain, a tailored approach including timely surgery should be considered to prevent ongoing deterioration of function and symptoms.

Recommendations for follow-up schemes after acute pancreatitis have not yet been standardized by international guidelines. The number of recent studies shows that heterogeneous protocols are being used in clinical practice and underlines the need for better and evidence-based recommendations to examine the long-term outcome of patients after acute pancreatitis as it is one of the most frequent gastrointestinal indications for inpatient treatment. The rising interest in this area and the results themselves underline the need for implementation of regular follow-up. This would allow a systematic evaluation of the risk of diabetes mellitus, pancreatitis relapse, and development of chronic pancreatitis, all of which exert an immense impact on healthcare costs. The possibility of earlier recognition and prevention of these complications on a risk-stratified basis could offer significant benefits.

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Section 4

Chronic Pancreatitis

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Definition and Classification of Chronic Pancreatitis

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Introduction

The term *chronic pancreatitis* describes a clinical syndrome of variable pancreatic inflammation, fibrosis, sclerosis, calcifications, pain, and loss of function of the exocrine gland (exocrine pancreas insufficiency, EPI) or endocrine dysfunction (e.g., diabetes mellitus, DM). This chapter provides an update on evolving definitions and classifications of chronic pancreatitis based on new concepts and techniques available to the clinician. It also notes the importance of standardized coding for pancreatic conditions and complications that must be appropriately defined and used.

The definition and diagnostic criteria associated with chronic pancreatitis have evolved over the past century as diagnostic tools and abdominal imaging techniques have improved. The "classic triad" required to diagnose chronic pancreatitis in the past included: (i) dense calcifications in the region of the pancreas on abdominal X-ray, (ii) diabetes mellitus, and (iii) steatorrhea—a triad that could only diagnose chronic pancreatitis at the final stages of disease. In contrast, autopsy studies suggest that pancreatic fibrosis was common in adults (especially alcoholics) and that the incidence increased with age. These historic observations indicated a large gap between various pathologic abnormalities and clinical detection of these features that could not be bridged with pancreatic biopsies because of the danger of triggering acute pancreatitis.

Advances in abdominal imaging technologies and introduction of genetics into the clinic have revolutionized our understanding of the essence of chronic pancreatitis, leading to a mechanistic definition, a progressive model, and etiology-based subtyping.

The importance of these new concepts is the belief that earlier detection, diagnosis, and targeted treatment will markedly improve outcomes, including reduction in suffering, avoidance of complications such as chronic pain, EPI with maldigestion and malnutrition, DM and pancreatic ductal adenocarcinoma (PDAC) plus minimize the health-cost burden. Implementation of these concepts requires more exact definitions of the elements of the chronic pancreatitis syndrome linked with better risk models and better biomarkers of disease state and activity. This chapter focuses on and extends the specific features and mechanisms linked to CP though a review of definitions and mechanism of chronic pancreatitis [1].

Disease Frameworks

Traditional Western Medicine

This framework for medicine was originally based on the germ theory of disease and the premise that one predominant or strong agent causes disease in people who are otherwise normal [2,3]. Evidence of disease etiology utilizes null hypothesis significance testing of one or more possible etiological factors. Evidence for the effectiveness of treatments utilizes case-control trials. Disease diagnosis and treatment relies on traditional clinicopathological definition and classification of disease, and standard clinical biomarkers. Thus, the diagnosis is delayed, complex etiologies cannot be resolved, and therapies are limited to controlling pain and replacing lost function.

Precision Medicine

Precision medicine, also called personalized or individualized medicine, is an alternative framework to modern Western medicine with a bottom-up approach for

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managing human diseases based on the premise that multiple weak agents cause disease in a person because one or more of their specialized cells are abnormal [2]. Precision medicine seeks to decipher the molecular, mechanistic *dysfunction* causing a *disorder* before it progresses to a clinicopathologically defined *disease*. Knowing the mechanism early should allow the use of targeted therapies to minimize dysfunction and maximize health. Under optimal situations the top-down and bottom-up approaches meet in the middle for the benefit of all the individual patients in a population. Precision medicine for pancreatic disorders in clinical practice is technically feasible, but numerous barriers slow implementation and widespread utilization [4,5].

Definition of Dysfunction

Dysfunction describes a variation in the action of a thing that deviates from normal, typically in a negative way. Dysfunction is typically applied to a system. The dysfunction may be essential (causing permanent system dysfunction under all conditions) such as an altered or missing component, or conditional, typically caused by external factors such as regulators or inputs that overwhelming the capacity of the system.

Definition of a Disorder

A medical disorder indicates disruption of the normal functions of specialized cells or systems resulting in abnormal signs, symptoms, biomarkers, or responses. Thus, they represent a failure of the body to compensate for molecular, cellular, or system dysfunction. Disorders can also be the result of external agents causing injury or overwhelming stress. In some cases the disorder has pathogenic consequences that eventually result in development of a disease [1]. An example is a cystic fibrosis transmembrane conductance regulator (CFTR)-related disorder [6,7] where CFTR is marginally functional and the patient develops clinical signs of pancreatic *dysfunction*, for example reduced bicarbonate secretion from duct cells, but has not caused diseases such as RAP nor met the criteria for CP [8,9] .

Definition of a Disease

A *disease* is a condition of the living animal or one of its parts that impairs normal function and is typically manifest by distinguishing signs and symptoms [1]. Thus, chronic pancreatitis is a disease the involves the pancreas, impairs normal function as an exocrine and endocrine gland, and has *distinguishing signs and symptoms*. However, the dysfunctions of the endocrine and exocrine pancreas are somewhat independent of each other, with endocrine dysfunction associated with DM that may or may not be associated with CP. Furthermore, the criteria for distinguishing signs and symptoms of CP versus other diseases with overlapping signs and symptoms such as maldigestion, fibrosis, and abdominal pain have been vague and nonspecific, resulting in agreement that only later-stage chronic pancreatitis can be diagnosed accurately, well past the stage when therapeutic interventions are likely to be most effective [10].

Mechanistic Definition of Chronic Pancreatitis

To overcome the limitations of classic criteria to diagnose chronic pancreatitis a new *mechanistic definition* of chronic pancreatitis was proposed in 2016, and subsequently adapted by the major national and international pancreas societies [10,11]. The mechanistic definition contains two components: the *essence* of the disease and the *characteristics* of advanced disease.

The essence of chronic pancreatitis. "Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" [11].

The characteristics of chronic pancreatitis. "Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, exocrine pancreatic dysfunction, pancreatic endocrine dysfunction, and dysplasia" [11].

Together the complementary aspects of the mechanistic definition of chronic pancreatitis provides two critical advantages over clinicopathologic definitions. First, defining the pathogenic mechanism of chronic pancreatitis helps differentiate it from other disorders and diseases that have overlapping features such as pancreatic atrophy, pain, strictures, exocrine pancreatic insufficiency, diabetes, and dysplasia or cancers. Second, it allows for the pathogenic mechanisms of chronic pancreatitis to be determined in individual patients very early in the process prior to development of irreversible features and for early management with targeted therapies. These concepts will be further developed in the progressive model.

Progressive Model of Chronic Pancreatitis

A progressive model of chronic pancreatitis development was proposed that included five stages (Fig. 38.1). This model is important in that the signs, symptoms, and

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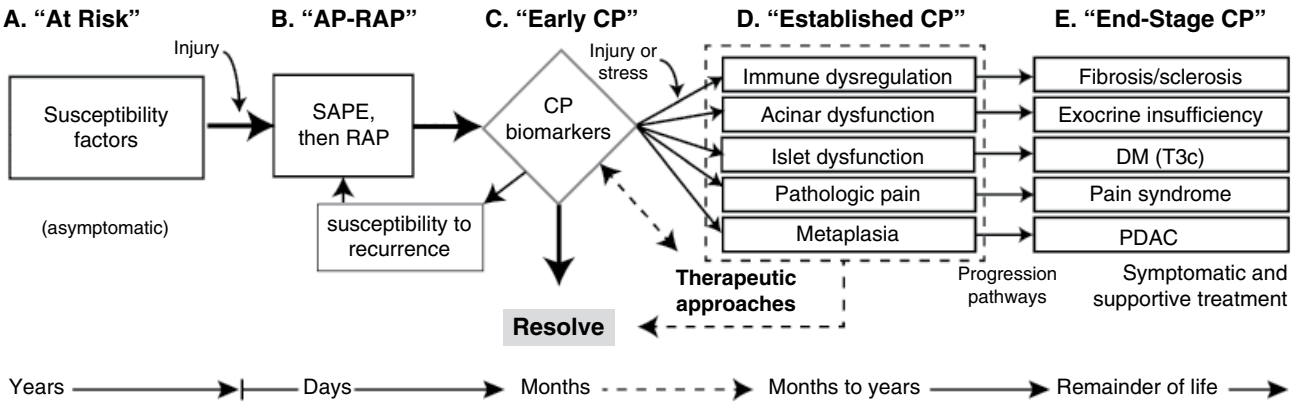


Figure 38.1 Progressive model of chronic pancreatitis development. This model is based on the sentinel acute pancreatitis event (SAPE) hypotheses where progression to CP begins with AP (stage B). Genetic and environmental risk/protective factors are present at all stages. Stage A is asymptomatic, with the effects of underlying disorders being adequately compensated. Stage B represents acute pancreatitis, which can be the first event (SAPE) or RAP, with SAPE sensitizing the pancreas to RAP. Stage C follows AP events where there is resolution or progression, depending on ongoing injury or stress. Stage D defines "irreversible" damage, as currently required for diagnosing CP as a disease. Note that risk/protective factors in different cell types are not surrogates of each other so the immune response (e.g., fibrosis) is not a strict surrogate of acinar cell function, islet cell function, nervous system response, or oncogenesis (e.g., failed DNA injury repair). This stage is hypothetically reversible with new therapies. Stage D is end-stage where cell function fails requiring replacement therapy or more radical surgical treatments. *Source:* Whitcomb et al. 2016 [11]/with permission of Elsevier.

biomarkers are present in a subject change over time, as seen in all progressive disorders. The stages are useful for classifying the patient's disease state and trajectory, as well as tracking severity indicators. All etiologies of chronic pancreatitis go through progressive stages, although in individual cases acute pancreatitis may not be seen. Etiologies are also important since the likelihood of progressing from one stage to the next is strongly affected by etiology.

Stage A. ***At Risk***. This stage includes all patients with risks for chronic pancreatitis who have no signs or symptoms of diseases and who have not had an episode of acute pancreatitis. The patient may have dysfunction of some physiologic processes, but the body is able to adapt and compensate for the dysfunction without signs and symptoms of disease.

Stage B. ***AP-RAP***. This stage includes all subjects with at least one episode of acute pancreatitis (AP; designated as the *sentinel* AP *event*, SAPE; see below) or recurrent acute pancreatitis (RAP) with complete resolution and without irreversible damage to the ducts or parenchyma. However, this is a high-risk stage for progression to chronic pancreatitis,

DM, and pancreatic ductal adenocarcinoma (PDAC).

Stage C. ***Early CP***. This stage includes all patients with both biomarkers of chronic pancreatitis and exclusion of other disorders or diseases with features that overlap the characteristics of chronic pancreatitis. Early CP is distinct from Established CP in that the features are reversible. The patient may have symptoms of one or more underlying disorders, but has not met criteria for chronic pancreatitis as a disease.

Currently, Stage C can only be diagnosed in retrospect because the biomarkers are nonspecific and progression is uncertain using traditional definitions and an imaging approach to CP diagnosis. Other names for this stage include "possible CP" and "probable CP." In contrast, a precision medicine approach defines the essence of the underlying process with a probability estimate of progression. Furthermore, the genetics can be used to determine and, in concert with specific biomarkers, help diagnose a *clinical disorder* that, if left untreated, will progress to a disease state.

Stage D. ***Established CP***. Established CP includes patients who have characteristic features of chronic pancreatitis that are irreversible but the gland has sufficient ductal and acinar cell function to sustain nutritional needs without the requirement of pancreatic enzyme replacement therapy (PERT). In addition, other disorders or diseases with features that overlap the characteristics of CP (differential diagnosis, below) should be excluded.

Stage E. ***End-Stage CP***. A patient has reached end-stage chronic pancreatitis when exocrine function is lost from a CP-associated fibroinflammatory process to the point that it requires PERT. Features of this stage may also include fibrosis, calcifications, and DM type 2 or type

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3c [12–14]. This stage is also important because it defines the end-stage disease features for individual patients since not all features are present in everyone.

Diagnosis

A diagnosis is the art or act of identifying a disease in a patient from its signs and symptoms. Diagnosing a disease or disorder involves meeting predetermined criteria.

Diagnostic Criteria

Diagnostic criteria are a list of disease features that must exist in a subject in order to diagnose the subject with a disease. These criteria are typically defined by expert opinions and established as consensus statements by various organizations or societies. They typically included signs and symptoms of the disease, biomarkers, and pathologic features. The criteria also include degrees of severity and features that distinguish the disease from other disorders or diseases with overlapping features.

Pathologic Diagnosis

A pathologic diagnosis is the diagnosis of a disease based on tissue analysis (including culturing of pathogenic organisms). Because there are overlapping features of CP and other disorders it is not possible to diagnosis CP with certainty from tissue samples. Pathology is not the gold standard for diagnosing CP [15]. A diagnosis also requires the presence of clinical and functional elements.

Syndromes

A *syndrome* is a descriptive group of clinical signs and symptoms that occur together and characterize a particular abnormality or condition. A disease can be defined as syndromes without knowledge of the etiologies, pathogenic components, or mechanisms. AP, RAP, and CP are clinical syndromes.

Differential Diagnosis

The differential diagnosis is a list of conditions and diseases that have overlapping signs and symptoms. The differential diagnoses for CP include autoimmune inflammation, inflammation and fibrosis arising from the islets related to long-standing diabetes mellitus, renal disease causing secondary effects on the pancreas, medications that alter the immune system (e.g., cyclosporin), age-related atrophy or fibrosis, intraductal papillary mucinous neoplasm, acinar cell cystadenoma, the desmoplastic response to pancreatic neoplasm, and inflammation upstream of a duct-obstructing mass [10]. The traditional diagnosis of CP required the underlying disorder to advance to the point that it could be nothing else. But since this stage is irreversible, only supportive treatments are available (e.g., insulin and PERT). In precision medicine the genetic and genomic information provides insights into the mechanism of pathogenesis and can also provide insights into the probability of the differential diagnosis [16]. This approach supports clinical decisions as further work-up and treatments can be targeted to one diagnosis or another, based on the likelihood that the diagnosis is correct and the effect of the treatment (i.e., an inexpensive and benign treatment can be started if there remains some uncertainty, whereas a more expensive and radical treatment should be delayed until the diagnosis is confirmed with a high degree of confidence).

Etiology

Etiology defines the cause or origin of something. In inflammatory diseases of the pancreas this may include the etiology of mechanism dysfunction, a disorder, a disease, or a syndrome. The difference between a risk and an etiology is whether or not there are biomarkers of abnormal activity linked to the factor that defines a disorder or disease. The TIGAR-O list (List 1) summarizes known risk/etiologies for RAP and CP [17].

Biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [18,19]. For CP, most biomarkers are normal biological molecules that are in the wrong place or amount [20]. They also tend to be nonspecific, requiring panels of biomarkers to be considered. In some cases biomarkers are more pancreas-specific, such as serum trypsin, amylase, lipase, or CA19-9 for pancreatic cancer, although exceptions always exist.

Classification of Chronic Pancreatitis

Chronic pancreatitis can be classified by structural severity, etiology, or functional stage:

Cambridge Classification of duct imaging. The Cambridge Classification was originally developed to correlate endoscopic retrograde cholangiography (ERCP) images with pathologic progression [21]. The criteria was later expanded to CT images and MRCP

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Table 38.1 TIGAR-O Version 2 risk/etiology classification – Short form. The list summarizes common factors associated with RAP and CP. It is used as a "checklist" to systematically document all factors that contribute to pancreatic disorders and diseases within a patient, and therefore highlights targets for therapy. The long form is available as an open access manuscript [17].

Toxic-metabolic
Alcohol-related (susceptibility and/or progression)
3–4 drinks/day
5 or more drinks/day
Smoking (if yes, record pack-years)
Non-smoker (<100 cigarettes in lifetime)
Past smoker
Current smoker
Other, NOS
Hypercalcemia – (ionized calcium levels >12.0 mg/dL or 3 mmol/L)
Hypertriglyceridemia
Hypertriglyceridemic risk – (Fasting >300 mg/dL; non-fasting >500 mg/dL)
Hypertriglyceridemic acute pancreatitis, history of (>500 mg/dl in first 72 hours)
Medications (name)
Toxins, other
Chronic kidney disease (CKD) – (CKD Stage 5 – end stage renal disease; ESRD)
Other, NOS
Metabolic, other
Diabetes mellitus (with the date of diagnosis if available)
Other, NOS
Idiopathic
Early onset (<35 years of age)
Late onset (>35 years of age)
Genetic
Suspected; No or limited genotyping available
Autosomal dominant (Mendelian inheritance – single gene syndrome)
PRSS1 mutations (Hereditary pancreatitis)
Autosomal recessive (Mendelian inheritance – single gene syndrome)
CFTR, 2 severe variants in trans (cystic fibrosis)
CFTR, <2 severe variants in trans (CFTR-RD)
SPINK1, 2 pathogenic variants in trans (*SPINK1*-associated familial pancreatitis)
Complex genetics – (non-Mendelian, complex genotypes +/– environment)
Modifier genes (list pathogenic genetic variants)
PRSS1-PRSS1 locus
CLDN2 locus
Others:
Hypertriglyceridemia (list pathogenic genetic variants)
Other, NOS
Autoimmune pancreatitis (AIP) / Steroid-responsive pancreatitis
AIP Type 1 – IgG4-related disease
AIP Type 2
Recurrent acute pancreatitis (RAP) and severe acute pancreatitis (SAP)
Acute pancreatitis (single episode, including date of event if available)
AP etiology – Extrapancreatic (excluding alcoholic, HTG, hypercalcemia, genetic)
Biliary pancreatitis
Post ERCP
Traumatic
Undetermined or NOS
Recurrent acute pancreatitis (number of episodes, frequency, and dates of events if available)
Obstructive
Pancreas divisum
Ampullary stenosis
Main duct pancreatic stones
Widespread pancreatic calcifications.
Main pancreatic duct strictures
Localized mass causing duct obstruction

images [22–25]. The 1984 Cambridge Classification system does not correlate with pancreatic function [14] or pain [26] and is therefore falling out of use as the technology for other imaging modalities improve.

TIGAR-O Etiologic Classification. TIGAR-O is an acronym for **T**oxic (including alcohol, smoking, hypertriglyceridemia), **I**diopathic, **G**enetic, **A**utoimmune, **R**ecurrent/Severe AP and **O**bstructive etiologies [17] (Table 38.1). In general, autoimmune and obstructive do not fit the mechanistic classification of chronic pancreatitis but are important both for consideration in the differential diagnosis and for treatment [1].

Functional Stage Classification. Functional classification systems are even more arbitrary than structural ones. This is because the definition of EPI is based on vague clinical signs and symptoms until the late stages, and the threshold for pancreatic insufficiency is also dependent on the metabolic and nutritional needs, the diet and intestinal anatomy and health, and adaptability. Furthermore, the tools for measuring pancreatic function often do not correlate with each other and no adequate test exists [27]. Several approaches are in

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common use including the M-ANNHEIM classification [28] and PROCEED [29].

Classification of Pancreatitis Using Machine-Readable Codes

Medical care is progressing slowly as the complexity of complex conditions becomes evident and new techniques provide massive amounts of information that cannot be assimilated, understood, and utilized by humans in efficient and organized ways. The advances in computers allow data to be stored, organized, and transformed into something useable by humans. However, the premise that "smart computers" can take blocks of unorganized data and solve complex diseases has stalled as limits in natural language processing (NLP), machine learning (ML), and artificial intelligence (AI) have failed to bring clarity out of chaos. And one of the many challenges is that the definitions and organization of data is based on the old Western medicine concepts arising from the germ theory of disease and the scientific method of population-based case-control studies using poorly defined syndromes as classifiers.

Challenges of Multiple Object Identifiers and Classification Systems

The goal of basic science research is to translate findings into clinical research, and from clinical research into clinical practice. The reverse is also important, translating observations in clinical practice back to clinical research to generate new hypotheses, and then test the hypotheses using basic research techniques. In the middle of these translations are the terms and descriptions of data tags to be translated. Future success requires better harmonization of data terms and discipline from physicians and scientist to use them consistently.

Progress in medicine is intimately linked to advances in digital technology. This means that there needs to be better synchronization between advancing science, medicine, and electronic tags to specific disorders, diseases, biomarkers, and complications. The synchronization must also be mechanism- and disorder-based to achieve advantages of precision medicine, and existing data that is in a usable form must have the describers from different systems harmonized so that there is seamless interoperability.

Digital taxonomy systems use object identifiers (OID) to identify objects such as a code system or a value set that represents a group of concepts. The current challenges are that there are multiple classification systems and there are major overlaps of objects with different concepts and codes for the same thing in different systems. The problem is further confounded by the fact that most terms are from modern Western medicine concepts and definitions used by physicians and scientists are not always used appropriately and that outdated terms and concepts are not purged at the end of their natural life cycle. Furthermore, many codes are nonspecific, so that clarity on the subject's disorder is obscured.

Codes, Code Systems, and Value Sets

Successful interoperability is dependent on either using common code systems for data capture or through mapping the unique codes to an interoperable code system [30]. Code systems are a collection of concepts (ideas) with unique identifiers that are logically structured. This may be highly hierarchical systems or more complex and nuanced systems (e.g., ICD-10). The code system structure provides each concept with a code-system-specific meaning, a concept identifier (a code), and a string description (the name, and a definition of the concept meaning). Specific code systems used in electronic health records and health information technology include ICD-10-CM, CPT, SNOMED CT, RxNorm, and LOINC. Other systems used in biology include various GenBank, RefSeq etc for genetic information, the Gene Ontology knowledgebase (GO), and many more. These systems encode content and enable computer-based systems to find and utilize data without human supervision. It has been noted that the best approach for measure developers is to reduce the number of mapping steps required by focusing on content that measured entities can easily capture during clinical care, where metrics that are useful in the care of the patient match those used in quality assessment and decision support systems [30].

Some Limitations

One of the key code systems used in the United States is the International Classification of Disease (ICD) system. This illustrates the challenge of transitioning from traditional "disease" definitions to defining disease mechanisms. Consider ICD-10 codes for chronic pancreatitis in the K86 class. The primary diagnoses are limited to K86.0 (Alcohol-induced CP), K86.1 (Other CP), K86.8 Other specified diseases of pancreas (which are not billable codes in the United States) and K86.9 (Other specified diseases of the pancreas). K86.1 includes "Pancreatitis (inflammation of pancreas), chronic; exocrine pancreatic insufficiency (K86.81); Chronic pancreatitis NOS [not specified elsewhere]; Infectious chronic pancreatitis; Recurrent chronic pancreatitis; Relapsing chronic pancreatitis" without distinction between these very

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different entities. K86.9 is even worse as "synonyms" terms include "Aseptic necrosis of pancreas, Atrophy of pancreas, Baggenstoss change of pancreas [31], Calculus of pancreas, Exocrine pancreatic insufficiency (also coded as K86.81), Fat necrosis of pancreas, Fibrosis of pancreas, Hemorrhage of pancreas, Mass of pancreas, Necrosis of pancreas, Pancreas – baggenstoss change, Pancreatemphraxis, Pancreatic acinar fistula, Pancreatic aseptic necrosis, Pancreatic atrophy, Pancreatic calculus, Pancreatic cirrhosis, Pancreatic exocrine insufficiency (see K86.81), Pancreatic fistula, Pancreatic hemorrhage, Pancreatic infantilism, Pancreatic insufficiency, Pancreatic mass, Pancreatic necrosis."

Another system is the SNOMED-CT. This is a general clinical reference system containing more that 357,000 healthcare concepts with unique meaning and logic-based definitions organized into hierarchies. In pancreatic disease, for example, there is a "parent/child" relationship type that includes parent concept "Disorder of the pancreas (3855007)" with child concepts "Atrophy of the pancreas (88281007); Baggenstoss change of the pancreas (61221008); Bard-Pic syndrome (45019006); Calculus of pancreas (15402006); Complication of transplanted pancreas (79369007); Congenital malformation of the pancreas (23497701); Congenital pancreatic enterokinase deficiency (10866001); Cyst of pancreas (31258000); and Cystic fibrosis of the pancreas (235978006)." This system does not include disorders of the pancreas from most of the etiologies in the TIGAR-O list [17], and partially overlaps diagnoses in ICD-10.

One of the keys to precision medicine is genetics. Specific human genetic variants can be coded using RefSeq identifiers (rsID), but more complex genetic variants, including copy number variants and large deletions or rearrangements, are not captured by these codes. Furthermore, the interpretation of the effect of genetic variants is primarily traditional autosomal dominate or recessive disease with genetic variants within the coding region identified as pathogenic (disease-causing alone), likely pathogenic, uncertain, likely benign or benign [32]. There is no commonly accepted way to grade the effects of "risk" variants, which are only disease-associated under specific conditions and are often tied to regulatory elements of gene expression rather than changing the amino acid sequence of the gene product (i.e., for protein coding genes). ClinVar is a public archive of genetic variants with free access to reports on the relationships between human genetic variations and phenotypes, with supporting evidence. But even here, the strength of evidence is variable, the effects of variants may be tissue-/disease-specific and risk factors, which are critical in understanding complex diseases, are seldom included or noted to have effects since the sequence reports are largely from *traditional* gene testing companies. Genetic data is not well integrated into the electronic health records in formats that are easily accessible.

A Way Forward

One issue that plagues ML applications comes from lack of clean, well-structured data. Inclusion of IT-minded folks in study design/data collection may solve many issues of data cleaning, harmonization, and interpretation that remain a major barrier.

A solution to the larger problem of interpreting complex, multi-code, multi-concept data is the use of "expert systems" [33]. An expert system is a computer program that uses available information, heuristics, and inference to suggest solutions to problems in a particular discipline following the recommendations of experts in the field. In brief, this approach takes extensive genetic data, patient demographics, health histories, biomarkers, images, etc. and integrates them using sequential framing, modeling and trajectory approaches that an expert would use. In the case of pancreatic disease, cell-based models would be used based on an understanding of acinar cell, duct cell, islet cell, neurons and the nervous system, inflammatory cells biology as parallel process (see Fig. 38.1, stages D and E), with cross-system integration (e.g., loss of some acinar cell function with loss of islet function). This is now feasible and may be an early example of true personalized medicine.

Conclusions

Health information technology has already linked ML and AI to assist in areas of reviewing and interpreting images (e.g., CT, MRI, pathology, colonoscopy). However, there is a lag in the development of useful clinical decision support tools in early diagnosis and accurate, mechanistic classification of complex disorders, such as pancreatic disorders and subsequent diseases. The first barrier to progress in complex disorders includes the concepts upon which many of the coding systems have been built, translation between genetics, genomics, biomarkers, systems biology, and human disorders that lead to chronic diseases and all their nuances. The second barrier is the proper use of terms and codes, including genetics, in the clinical arena where patient care is more important that billing codes, and where billing codes are inherently inadequate tools for disease management. A third barrier is the medical literature, where the descriptions of concepts, patient context, and complete data are inadequately coded so that studies can be seamlessly harmonized and NLP can be more useful because the authors adhere to a new HIT-enabling writing structure.

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This chapter does not present the answer to these problems and barriers. It is intended to enhance recognition of these barriers by highlighting limitations of the current systems with concepts that must be integrated into new systems. In the meantime, progress can be made in the old fashion way of using the nonlinear, experience-based, heuristic thinking of expert physicians and scientists to begin bridging the gaps between the present and the future.

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39

Molecular Understanding of Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is a clinically described syndrome that is characterized by consistent cellular stress or repeated bouts of pancreatic injury that result in pancreatic atrophy, fibrosis and duct distortion, a chronic pain syndrome (suggesting neural injury and responses), and eventually loss of both exocrine and endocrine function. Depending on the proposed etiology of the disease, there can be other secondary characteristics including calcifications, duct centric inflammation with either lymphocytes or neutrophils, or primarily an obstructive phenotype. Focusing on the etiology of the injury and the subsequent pathologic response is important to direct our understanding of the molecular mechanisms of CP.

Risk Factors in Chronic Pancreatitis

Although the diagnosis of CP is due to a convergence of common pathological features seen at the end-stage of the disease, there are distinct risk factors for CP (Fig. 39.1). These risk factors have been described by the TIGAR-O classification [1]. They include genetic and environmental factors, obstructive etiologies such as anatomical or traumatic features, and immune-mediated etiologies. The typical organ response to injury and cellular stress promotes recovery and regeneration of the pancreas following injury. However, with repeated injury or prolonged cellular stress, the organ response may become pathologic and drive cellular loss and fibrotic replacement of exocrine and endocrine cells. A proper understanding of the molecular mechanisms of CP requires that we address both the specific etiology, with its associated genetic and epigenetic modifiers, as well as the common pathologic response mediated through both parenchymal cells of the pancreas and mesenchymal cells, including the immune cells and the pancreatic stellate cells [2].

The current attempts to define CP focus on a clinical description of the end histologic appearance of the pancreas, resulting from an immune-mediated response to stress or injury coupled to a fibrogenic wound response. Although such a definition is useful clinically, it belies the complexity of the process leading to CP. Pancreatitis is an inflammatory disorder that involves a complex immunologic cascade of events. Environmental cues shape the initiation and progression of the immune system to accelerate or limit the immune response. The immunologic response can be modulated by epigenetic and genetic factors that alter the progression of the disease. The inflammatory response is modulated by cytokines and chemokines, produced by injured acinar cells, that act as recruiting molecules for an immune repertoire. There are likely multiple modifying factors and intervening steps that impact an individual patient's clinical course but at some point, progression becomes similar because the end result of this process is a similar histological pattern. In this chapter, we will focus on the current understanding of these two distinct stages of disease development, specific etiologies and the immune-activated fibrogenic response. The first stage of CP development relates to specific risk factors, and the second stage is the organ fibrogenic response to injury.

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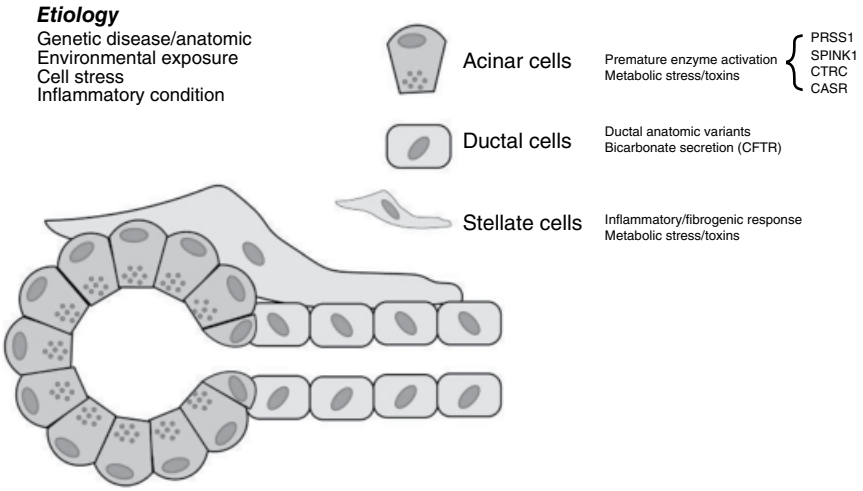


Figure 39.1 Several etiologies exist for chronic pancreatitis. Specific etiologies affect unique cell types within the pancreatic parenchyma, leading to repetitive injury.

Sentinel Acute Pancreatic Event Model

A disease model hypothesis has been proposed as a framework for understanding how different risk factors including environmental, genetic, and toxin mediated injury could impact progression toward CP. The model is the sentinel acute pancreatitis event hypothesis (or SAPE hypothesis), and it uses the TIGAR-O risk classification system, referring to Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis, and Obstructive [1]. In this model, risk factors impact the pancreas through alterations in stress responses by the parenchymal cells (acinar and duct cells). There are also wound healing responses within the pancreas, including the activation of the inflammatory (neutrophils and lymphocytes) and matrix remodeling systems (macrophages and stellate cells) to allow regeneration to occur. Once the risk factors overcome the adaptive mechanisms within the pancreas, injury overtakes the protective regenerative mechanisms, and clinical acute pancreatitis ensues. Repeated bouts of acute pancreatitis can lead to an injury-wound response cycle that over time causes loss of pancreatic cells and replacement with a fibrotic matrix that is promoted by macrophages and stellate cells. The progression of parenchymal tissue destruction and fibrosis is the pathological phenomenon of CP, graphically represented in Fig. 39.2.

Epigenetics as a Modifying Factor in Chronic Pancreatitis

Epigenetics is the control of gene expression that does not involve a change in the primary DNA sequence. In other words, epigenetics refers to modifications of DNA, for instance by methylation, or of chromatin structure through the posttranslational modification of histone proteins. The posttranslational modification of histones can alter chromatin structure or may alter the affinity transcription factors to promoter regions. The epigenome can have significant effects on human health as well as disease susceptibility, and epigenetic alterations can be induced through environmental and prenatal exposures to toxins or stressors. Epigenetic changes can be stable and allow "memory" of past stresses to impact future exposures. Epigenetic alterations may be the result of "subclinical" stresses on the pancreas that over time allow molecular remodeling of stress responses to other stimuli. These "subclinical" stresses may alter the epigenetic pattern of genes with little or no immediate effect on gene expression; however, the gene may develop an altered response in gene expression when exposed to a new specific environmental cue. In the case of CP, there are likely situations of epigenetic change that evade clinical notice until the time of exposure or triggering of risk factors, which then induce the typical destructive, fibrogenic response of the disease. In experimental models of pancreatitis, chronically stressed animals (such as with ethanol exposure [3], a fatty diet [4], or genetic mutation [5]) have an altered response to acute injury compared to animals that have no chronic stress. Ethanol has been shown to affect the action of several epigenetic proteins including the histone acetylases CREB and CBP [6] as well as the histone deacetylases [7]. An epigenetic acetylation mechanism was implicated for controlling acute pancreatitis [8]. Delayed recovery was demonstrated in mice treated with the antiepileptic drug and histone deacetylase inhibitor valproic acid (VPA). VPA is thought to be a definite cause of pancreatitis, especially in pediatric patients [9,10]; however, the mechanism by which VPA induces pancreatitis was unknown. In fact, chronically treating experimental animals with VPA

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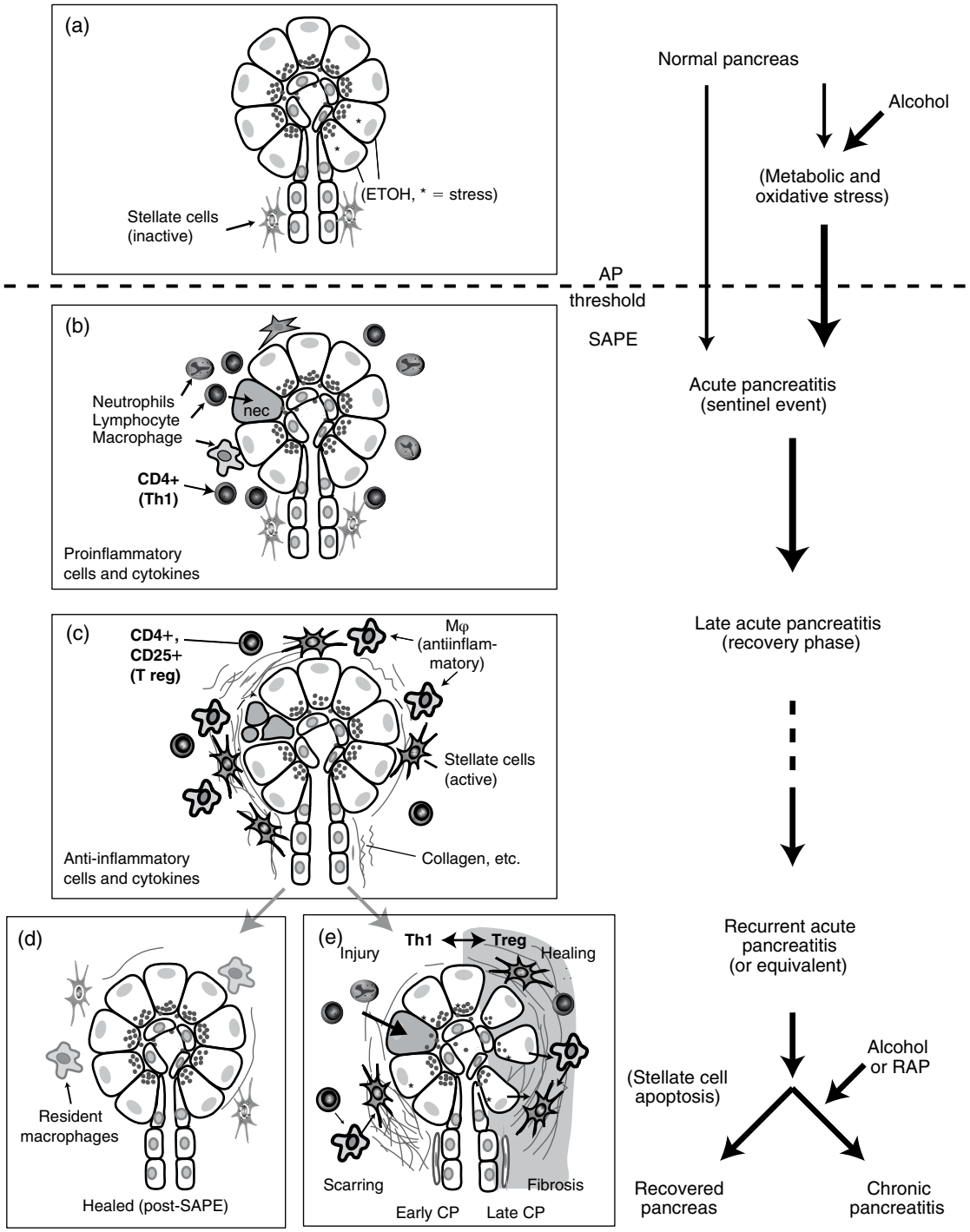


Figure 39.2 Sentinel acute pancreatitis event (SAPE) hypothesis model. (a) Normal pancreas. If the subject is a heavy alcohol user, the acinar cells are under metabolic and oxidative stress (indicated by asterisks) but histology remains relatively normal. Alcohol increases the risk of crossing the acute pancreatitis (AP) threshold (bold line crossing the dashed line). (b) Acute pancreatitis with pancreatic injury and infiltration of proinflammatory cells. (c) Late acute pancreatitis is dominated by anti-inflammatory cells that limit further injury by proinflammatory cells and products, and promote healing. This includes activation of stellate cells, which produce collagen etc. (d) Recurrent acute pancreatitis (RAP): acinar cell injury or other factors that activate an acute inflammatory response (Th1) are immediately countered by an anti-inflammatory counterresponse (Treg) which, among other things, drives fibrosis. This vicious cycle results in both continued injury (top) and further fibrosis (bottom) leading to (e) extensive acinar cell loss and sclerosis (right) characteristic of chronic pancreatitis (CP). Both genetic factors and environmental factors play a role in this process by increasing susceptibility to acute pancreatitis, altering the severity and duration of acute pancreatitis and altering the healing processes that drive fibrosis. *Source:* Adapted from Whitcomb 2004 [3].

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does not induce pancreatitis [11]. However, animals treated with VPA that are then subjected to an additional injury-provoking stimulus, develop pancreatitis. Thus, VPA predisposes the host to pancreatitis by altering the epigenetic landscape and thereby inhibiting the recovery mechanisms that allow regeneration to occur.

Environmental Exposures as Modifying Factors in Chronic Pancreatitis

A mechanism thought to initiate pancreatic injury is through environmental exposures. The exposures include alcohol ingestion and byproducts of smoking [12]. The exposures do not by themselves induce pancreatitis, but they pathologically alter acinar cell responses to stressors. The prototypic example is heavy and frequent alcohol ingestion, which has long been known as a major risk factor for both acute and chronic pancreatitis [13,14]. However, only a minority of binge drinkers develop pancreatitis. Ethanol has been shown to affect pancreatic cell types either through its direct effects or through its metabolites. Ethanol or its metabolites can sensitize the acinar cell to pathologic calcium signals [15] mitochondrial dysfunction [16,17], impairment of autophagic or lysosomal responses [18], or the induction of the UPR with increased expression of XBP1 (a key regulator of ER function) [19,20]. Ethanol appears to increase ER stress visualized by ER swelling and UPR induction, and there is an impact on protein trafficking and on some of the structural components of zymogen granules [21]. Ethanol converts a physiological stimulus to the acinar cell into a pathological stimulus, with adverse outcomes, including premature intra-acinar activation of digestive enzymes and acinar injury [22,23]. This effect could be due to the increased expression of digestive enzymes such as trypsinogen, chymotrypsinogen, or lysosomal cathepsin B and to lysosomal fragility [24].

Genetic Influences in Chronic Pancreatitis

A second mechanism shown to mediate the pathologic response in the pancreas is through repeated injury by specific insults in a susceptible patient with genetic risk factors. Genetic or epigenetic alterations may allow the nonclinical or clinical repeated injury to occur which over time results in the destruction of the pancreatic parenchyma and replacement by fibrosis through repeated activation of immune and fibrotic responses. This replacement results in the loss of exocrine and endocrine pancreatic function. Hereditary pancreatitis is a prime case example of this mechanism. Hereditary pancreatitis is caused by a mutation within the cationic trypsinogen gene (*PRSS1*), the primary proteolytic enzyme responsible for activating pancreatic digestive enzymes or zymogens [25]. These gain of function mutations lead to premature trypsinogen activation. There are several mutations identified but the most common are R122H and N29I. The penetrance of the disease is about 80%. Although these mutations place an individual at a higher risk of developing CP and there is variable expressivity, the disease course and ultimate outcome are also dependent on additive risk factors, including environmental and metabolic stressors. Environmental exposures or other genetic modifiers are thought to alter the disease course as individuals with the same genetic mutation can have significantly different disease courses, despite having similar histopathology [26]. Monozygotic twin studies attest to this level of discordance, whereby the same genetic mutation in the *PRSS1* gene causes profound pancreatic disease in one twin, while the other has no evidence of disease into adulthood [27]. In order to study mechanisms underlying pancreatitis pathogenesis by these genetic mutations, several groups developed hereditary pancreatitis mouse models by manipulating human or mouse trypsinogen genes [28–32]. In addition to the *PRSS1* mutations and hereditary pancreatitis, there are other genetic mutations associated with increased risk for CP [33]. They include mutations within the *CFTR* (cystic fibrosis transmembrane conductance regulator) and *SPINK1* (serine protease inhibitor Kazal type 1) genes. As with *PRSS1* mutations, identical mutations within these genes do not predict similar disease course for affected individuals. Pathogenic variants in the *SPINK1*, *PRSS1*, *CTRC*, and *CFTR* genes can lead to earlier disease onset and worsened clinical outcomes in CP patients with varying etiologies such as idiopathic, alcoholic, and smoking-associated CP [34,35]. Overall, these observations suggest a complex disease process that will require careful analysis of multiple factors that impact disease progression.

Inflammatory Response in Chronic Pancreatitis

The secondary phase of progression to CP involves the inflammatory and fibrotic responses to chronic stress or repeated injury (Fig. 39.3). Recently, progress has been made in understanding this aspect of CP. Injury within the pancreas results in damaged acinar cells that will either repair or undergo cell death through necrosis or apoptosis. The damaged cells promote a sterile inflammatory response to mediate the recovery and regeneration process [36]. The inflammatory response is signaled

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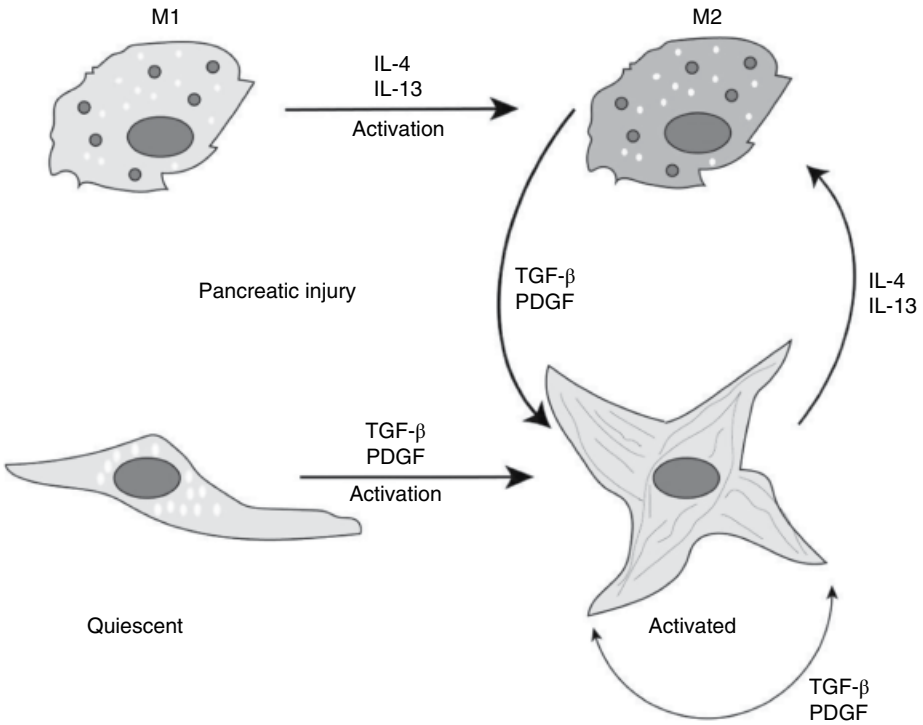


Figure 39.3 Pancreatic injury activates resident immune cells as well as pancreatic stellate cells to promote pancreatic recovery. However, persistent injury or pathologic signaling between macrophages and stellate cells leads to persistent activation and fibrogenic replacement of the pancreatic parenchyma.

by cytokines released from injured acinar cells and mediated by neutrophils, monocytes, lymphocytes, and macrophages which mediate the resolution of the damaged cells and promote the regeneration of the pancreas [37]. During progression of CP, inflammation appears to be mediated by different immune cells depending on the experimental model used [38–40]. Those immune cells including neutrophils, macrophages, and T-cell subsets play multiple roles depending upon disease progression in acute, severe acute, or chronic pancreatitis [38,39,41,42]. These cells will produce additional inflammatory mediators such as TNFα, IL-1β, Il-6, IL10, and MCP1. Initially these signals are produced by damaged acinar cells but with repeated injury and activation of other resident pancreatic cells such as macrophages and stellate cells, there appears to be a shift towards cytokine production from activated immune and stellate cells that promotes and allows progression towards CP. Neutrophils are thought to activate trypsinogen and allow progression towards severe injury in acute pancreatitis; however, in CP, T cells and macrophages are the predominant immune cell infiltrates [43,44]. Neutrophils and macrophages can play a dual role during inflammation, either releasing cytokines such as IFN-g leading to a proinflammatory phenotype repressing regeneration but are also responsible for repair signals necessary for regeneration to occur [45]. T cells are thought to help control the immune-mediated destruction initiated in CP demonstrated by the secretion of IL-10 by these T cells [46]. However, IL-17 or IL-22-secreting T-cell subset (Th17 or Th22) promotes fibrogenesis by activating pancreatic stellate cells (PSC) and contributes to the progression of CP [39,47]. Macrophages can promote healing and regeneration, depending upon macrophage polarity [48]. However, alternatively activated M2 macrophages can play a pathogenic role in CP in both rodents and humans [38]. Furthermore, pancreatic immune cell analyses using unbiased single-cell immune analysis technologies reveal novel disease-relevant immune subpopulations. Single-cell RNA/T-cell receptor sequencing analysis of pancreatic immune cells isolated from pancreatic tissues of CP patients who underwent total pancreatectomy identified hereditary versus idiopathic CP-specific novel T cell and myeloid immune subsets and T cell receptor repertoire changes. This study provides insights into human CP-specific immunopathogenic mechanisms and etiology subtype-specific immunotherapeutic targets in CP [49]. Determining unique immune subsets and their signals to neighbor cells during the disease course that can either promote or suspend disease progression is critical to a better understanding of immunopathogenic mechanisms and identifying novel therapeutic targets for healing.

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Fibrogenesis in Chronic Pancreatitis

The fibrogenic response during CP is influenced by mesenchymal cells known as the pancreatic stellate cells (PSC), along with immune cell interactions. PSC have emerged as a critical player in mediating pancreatic recovery after injury [50]. PSC are localized to the periacinar region and, at baseline (i.e., the quiescent state), they are characterized by vitamin A droplets [51]. In response to injury, PSC undergo transient activation and take on a fibroblast-like role to secrete extracellular matrix (ECM), particularly collagen [52,53], which is a necessary substrate scaffold for proper regeneration and recovery. The hallmarks of pancreatic injury and recovery are regenerative structures called acinar to ductal metaplasia (ADM) [54,55]. The stroma surrounding ADM is composed of activated PSC (aPSC) that function to remodel ECM and are thought to coax ADM to redifferentiate into new acinar cells. Aberrant regulation of PSC has been implicated in the pathogenesis of CP and pancreatic cancer [52,56–58]. PSC are not only activated by acinar cell injury but can be activated by cellular stress and ethanol byproducts. TGFβ appears to be a major contributor to fibrotic properties of PSC by increasing collagen and fibronectin expression but also by inhibiting metalloproteinases (MMP). Once activated, PSC initially help to remodel the parenchyma through the removal of matrix proteins by MMP. PSC not only produce MMP but also the inhibitors of MMP called tissue inhibitors of metalloproteinases (TIMP). A balance of these two factors likely affects the progression toward fibrosis. The destruction of the matrix releases growth factors and cytokines that signal adjacent cells and stimulate parenchymal healing through interactions of the immune and exocrine and endocrine pancreatic cells. PSC not only orchestrate the destruction of matrix but also help orchestrate the regeneration of the framework to allow regenerating acinar and duct cells to proliferate and repopulate the parenchyma. However, if PSC remain activated through repeated injury to the pancreas or aberrant cell signaling from adjacent cells such as macrophages, a pathogenic response can ensue. The response perpetuates the remodeling of the ECM and replaces acinar tissue with fibrosis, leading to the loss of pancreatic exocrine function. PSC in CP models have been shown to respond to adjacent macrophages that produce higher levels of TGFβ and PDGFβ suggesting that the macrophage-PSC interaction may be important in regulating pancreatic fibrogenesis [38]. PSC communicate with cytokine-producing T cells (Th22 and Th17) by expressing their receptors in order to promote fibrosis in CP [39,47]. STAT3 activation is a prominent signaling molecule found in activated PSC, and the inhibition of the Jak/STAT pathway via ruxolitinib has been shown to reduce the severity of experimental CP [59], suggesting a potential therapeutic strategy for CP.

Conclusions

There are several risk factors and progressive steps that lead to the histopathological disease known as CP. They include a sentinel pancreatic event in a susceptible host that perpetuates a progressive low-grade injury. The injury results in pancreatic fibrosis and loss of physiologic function. Alternatively, several repeated injury events of acute pancreatitis may lead to chronic injury and fibrotic replacement of the pancreatic parenchyma. Several animal models have been developed to help target specific aspects of injury and disease progression for the study of CP. Although healthy caution is indicated when using animal models to mimic disease states in humans, with careful attention to the limitations of the experimental model, one may begin to understand aspects of this complex, multifaceted disease. The animal model systems used most frequently are cost-effective rodent models of pancreatic injury leading to inflammation and fibrosis reminiscent of histologic changes in CP (e.g., duct ligation, chemical or biological exposures) [60–65]. However, for certain etiologies such as CFTR disease, the rodent models do not mimic the human condition, and other models (such as the porcine or ferret model for CFTR) must be used. Genetic models of CP exist and include overexpression or reduced expression of genes that allow the histopathologic appearance of CP. Beyond animal models, our understanding of CP would be enhanced by the characterization of heterogeneous human microenvironments using unbiased analysis techniques.

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Natural History of Recurrent Acute and Chronic Pancreatitis

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Introduction

Pancreatitis, especially chronic, is a low prevalence disease. Consequently, the focus of epidemiologic studies of pancreatitis has primarily been to define the disease at the level of individual patients. In the past two decades, the importance of understanding the distribution of risk factors and disease at the population level has been recognized. This has enabled determination of disease estimates and understand the relationship between acute pancreatitis (AP) and chronic pancreatitis (CP) at the population level. Demonstration that subsets of patients with AP develop recurrent acute pancreatitis (RAP) and/or progress to CP provides empiric evidence that these conditions represent stages of a disease continuum. Knowledge of the risks and factors associated with disease progression will help in risk stratification, prediction, and developing strategies for altering the natural history of disease.

This chapter will focus on the burden of disease, natural course and survival of AP, RAP, and CP. For AP, the emphasis will not be on the severity and outcome of the initial attack, but rather the risk of readmissions, recurrences, and progression to CP. In CP, the prevalence and natural history of clinical features, i.e., pain, endocrine and exocrine insufficiency, bone health, and the risk of pancreatic cancer will be discussed. Finally, we will summarize available data on the quality of life.

Natural History After First Attack of AP

Disease Burden, Etiology, and Severity

AP is one of the leading gastrointestinal causes of hospitalization in the United States [1]. The estimated incidence of AP in recent studies is 30–50 per 100,000 population. AP affects all age groups, but is most frequent in middle-aged and older individuals [2]. Gallstones and excessive alcohol consumption account for about 60–70% of all cases, the latter being more common in men when compared to women. Other etiologies include metabolic factors (hypertriglyceridemia, hypercalcemia), endoscopic retrograde cholangiopancreatography (ERCP), medications, genetic mutations (*PRSS1*, *SPINK1*, *CFTR*, *CTRC*), obstructive causes (such as pancreatic duct stricture, etc.), and trauma. In 10–25% patients no identifiable etiology is found on evaluation [2]. The two main determinants of mortality in AP are the presence of infected necrosis and organ failure, especially when persistent (>48 h) or involving more than one organ [3]. The risk of death increases with age and comorbidities [4]. Increased morbidity is seen in patients with local complications who do not have organ failure [5].

Readmissions

After the first attack of AP, about 20–30% patients are readmitted to hospital (Table 40.1). The reason for readmission differs based on time since discharge from the hospital. Vipperla et al. [6] differentiated between early (<30 days after index AP) and late (>30 days) readmissions and found that early readmissions were more likely due to smoldering symptoms from AP and/or local complications, whereas late admissions were more likely to be due from recurrent AP episodes. Younger age, alcohol use and/or alcohol-related etiology, non-private medical insurance, increased length of stay during index admission, and discharge to long-term care facilities have been identified as predictors of readmissions [6–8].

The Pancreatitis Activity Scoring System (PASS) was developed in 2017 as a tool to measure disease activity

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Table 40.1 Summary of recent studies examining rates and risk factors for readmission after a first attack of acute pancreatitis.

Author, year, design	Cohort size	Follow-up time (months)	Readmission rate (%)				Time to readmission (months)	Risk factors for readmission
			Overall	Alcoholic	Biliary	Idiopathic		
Yadav et al., 2014 [7] Retrospective	5239	39.0	22	40	15	32	Unclear	Younger age Alcoholic etiology Subsequent diagnosis of CP
Vipperla et al., 2014 [6] Retrospective	127	36.0	34	60	29	59	1.3	Younger age Male gender Alcoholic or idiopathic etiology Severe disease at index attack
Garg et al., 2018 [8] Retrospective	243816	Unclear	16	Not stated			Unclear	Younger age Non-private medical insurance Discharge to long-term care facilities Increased length of stay

CP: chronic pancreatitis.

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and better predict the prognosis of AP. PASS incorporates organ failure, systemic inflammatory response syndrome (SIRS), abdominal pain, opiate requirement and diet tolerance, with each component having a different weight according to their prognostic importance [9]. In a prospective study examining the predictive utility of PASS, a score of >60 was highly associated with readmission within 30 days of AP discharge [10].

These data suggest that focused discharge planning may reduce the risk of early readmissions—i.e., ensuring that the patients' symptoms are well controlled and they have received counseling for behavior modification. In patients with severe AP, close follow-up with relevant specialists (e.g., nutrition, gastroenterologist, surgeon) is helpful to determine the need and timing of cross-sectional imaging, duration of enteral feeds, and "step-up" therapy. Many patients with severe AP need short-term stay at a transitional care facility or rehabilitation unit prior to safe discharge home.

First Recurrence

The risk of recurrent AP (RAP) after the first attack has been evaluated in several, mostly retrospective, population and nonpopulation based studies (Table 40.2). The overall risk of a subsequent attack of AP is ~20% during a median follow-up period ranging from 4 to 8 years. Similar to the first attack, among patients with a second attack of AP, alcohol, gallstones, and idiopathic are the most common etiologies [11–13]. When compared with the first attack of AP, subsequent recurrence is generally milder with an overall lower mortality [14].

The risk of recurrent attack is highest among patients with alcohol etiology (35–40%) followed by idiopathic and biliary AP (both 10–20%) [11–13]. Takeyama et al. noted that the risk of subsequent recurrence was directly related to continued alcohol consumption—the risk was highest in patients who continued drinking at the same level, and lowest among patients who stopped drinking completely [15]. Contrary to what many physicians may believe, counseling against alcohol consumption has a significant impact on patient behavior. This was tested empirically in a randomized controlled trial (RCT), where repeated counseling of patients led to a significant decrease in the risk of abdominal pain attacks, AP episodes and hospitalizations [16].

After an attack of biliary pancreatitis, the risk of recurrence can be dramatically reduced by early cholecystectomy. This has been demonstrated in RCTs, as well as in meta-analyses of published data [17]. In patients with mild biliary pancreatitis, cholecystectomy should be considered as close to the attack of AP as possible, preferably during the same admission. In patients with severe AP, cholecystectomy should be delayed until resolution of inflammatory changes in the pancreas/pancreatic area. In patients with pancreatic/peripancreatic collections that need drainage, a surgical approach (preferably laparoscopic or minimally invasive) to address this along with a cholecystectomy should be considered [18]. In patients with another known etiology, i.e., medications, hypertriglyceridemia, hypercalcemia, etc., addressing the inciting cause will decrease the risk of recurrence [19].

Tobacco abuse has been a consistent association with the risk of recurrent AP (odds ratio 1.5–2) [11,13,20]. Therefore, after an attack of AP, patients should be informed about this risk and counseled for tobacco cessation. This will be especially relevant in patients in whom the cause was alcohol, hypertriglyceridemia, genetic or idiopathic, or if the AP attack was moderate to severe. Individual studies have also shown that age and severity of initial attack may also play a role in recurrent attacks [11,13,20].

The burden of recurrent AP at a population level is not well defined. Using information on the total number of admissions for AP in the USA and applying the incident AP rates from California, approximate number of recurrent attacks can be estimated [1,21]. Among the 275,000 annual admissions for AP in the USA, approximately 150,000–160,000 would be incident attacks, while the remaining 115,000–125,000 would represent RAP (first or subsequent recurrences), readmissions for ongoing symptoms or complications of AP, or acute CP.

Subsequent Recurrences

Alcohol is the most common etiology of subsequent recurrences, followed by idiopathic pancreatitis, genetic causes, hypertriglyceridemia, and underlying CP as other important causes. The role of pancreas divisum and sphincter of Oddi dysfunction in causing initial or recurrent AP attacks is controversial [22].

Approximately one-third of patients who have a recurrence after the first attack of AP will have one or more subsequent recurrences. Burden of recurrent AP was further quantified in in two previous studies. Among 562 patients with a first attack of alcoholic AP who survived the index admission, Sand et al. reported at least one recurrence in 260 (46%) patients. Among these patients, 133 (51%) had only one recurrence, 49 (19%) had two recurrences, 39 (15%) had three recurrences, and 39 (15%) had four or more recurrences [23]. Among patients who underwent a cholecystectomy for presumed biliary pancreatitis, Trna et al. noted the risk of subsequent attacks to be related to the presence of abnormal liver function tests and documentation of gallbladder stones or sludge. Among patients who did not have either, 26% had a second attack, and 9% had a third attack of AP [24]. Although few empiric data is available, the risk of

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Table 40.2 Summary of recent studies examining the rate and risk factors for development of recurrent acute pancreatitis (RAP) after a first attack of acute pancreatitis.

Author, year	Cohort size	Follow-up time (years)	RAP rate (%)				Time to recurrence (months)	Risk factors for RAP
			Overall	Alcoholic	Biliary	Idiopathic		
Lankisch et al., 2009 [12] Prospective	532	8.0	17	33	12	14	Unclear	Younger age Alcoholic etiology Male gender
Yadav et al., 2012 [13] Retrospective	7456	3.3	29	52	18	26	7.2	Younger age Alcoholic etiology Tobacco use
Bertilsson et al., 2015 [11] Retrospective	1457	4.2	23	37	17	24	5.1	Alcoholic etiology Severe disease at index attack Tobacco use
Ahmed Ali et al., 2016 [20] Prospective	669	4.8	17	Not stated			5.0	Younger age Idiopathic etiology Tobacco abuse Severe disease at index attack

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multiple attacks of AP seems high in patients with genetic mutations (e.g., *PRSS1*, *CFTR*) [25]. The risk of recurrences would also be higher in patients with uncommon causes of AP, such as hypertriglyceridemia, hypercalcemia, etc., especially if the underlying cause is not corrected, but definitive data on the burden of attacks in these patients is limited.

Diabetes and Exocrine Insufficiency After AP

Recent data have documented that AP increases the risk of diabetes mellitus (DM) and exocrine pancreatic insufficiency (EPI) irrespective of severity. In two population-based studies patients with mild AP were about two times more likely to develop DM than age- and sex-matched controls [26,27]. In a systematic review of 24 prospective studies, the pooled prevalence of newly diagnosed DM after the first episode of AP was reported to be 23% (95% CI 16–31%), and increased with the duration of follow-up [28]. The risk of DM after AP is greater in patients with severe AP, necrotizing pancreatitis and in those with alcohol etiology. The mechanisms leading to DM are not well defined.

With regards to EPI, a meta-analysis of 39 studies reported that the pooled prevalence of EPI after an index episode of AP was 35% and the prevalence was greater during the time of AP hospitalization [29]. The risk of EPI increased with disease severity, presence of necrosis, and alcohol etiology.

Quality of Life After AP

Several studies have demonstrated that AP deleteriously impacts quality of life. In a single-center prospective study of 91 patients, patients who experienced AP had a significantly lower physical healthcare-related quality of life (HRQOL) as compared to controls even after 14 months of AP [30]. Factors associated with lower physical HRQOL included the presence of ongoing abdominal pain and use of analgesics, disability, and smoking. Multiorgan failure was the only disease-related factor associated with a lower physical HRQOL.

Progression to CP

Many studies evaluating the natural history after a first attack of AP have determined the risk of progression to CP (Table 40.3) [11–13,20]. In a meta-analysis of 14 studies consisting of 8492 patients, Sankaran et al. reported that following a sentinel attack of AP the pooled prevalence of RAP was 22% (38% for alcohol etiology, 17% for biliary etiology) and of CP was 10% [31]. The three factors consistently shown to have an independent effect on disease progression have been alcohol etiology, tobacco abuse, and RAP. The association with severity of AP is less consistent and has been noted in some studies.

Lankisch et al. noted that progression to CP occurred almost exclusively in patients with alcohol etiology [12]. However, in other studies progression was also noted with nonalcoholic or idiopathic CP, albeit at a lower rate. The role of tobacco, especially in combination with alcohol in disease progression is important. Ali et al. reported that while the cumulative risk of progression to CP overall was 7.6%, it was 18% among current smokers, and increased to 30% in current smokers who also had alcohol etiology [20]. Therefore, including the counseling of tobacco cessation along with alcohol abstinence should be emphasized. Genetic factors also seem to play a role in the development of CP, but outside of hereditary pancreatitis, little empiric data is available [25].

Perhaps the strongest risk factor for disease progression is RAP, and the risk of progression in these patients is ~30–40%. Bertilsson et al. noted that among patients who transitioned to CP, 74% had at least two AP attacks, and 54% had more than two attacks. When compared with alcohol or tobacco (hazard ratio between 2 and 3), the risk of progression to CP in RAP is much higher (hazard ratio ~6) [11].

Natural History of Chronic Pancreatitis

Disease Burden, Demographics, and Etiology

Recent population studies estimate that the incidence of CP ranges from 4 to 14 per 100,000 per year, and the prevalence ranges from 42 to 73 per 100,000 population [19,32]. The prevalence of CP peaks at the age of 45–55 years and has a male predominance [32]. Alcohol is the most common cause of CP worldwide (frequency ~40–70%), followed by idiopathic etiology (frequency ~20–30%) [19]. Smoking is a well-recognized factor for CP and works in a dose-dependent manner—the risk of CP is fivefold greater in those smoking over 35 pack-years compared to never smokers [33]. The role of genetic factors is increasingly recognized and mutations in some susceptibility genes (*PRSS1*, *SPINK1*, *CFTR*, *CTRC*, *CPA*, *CASR*) are found in 10–15% of CP patients. Alcoholic CP is seen more commonly in men, while the other etiologies are more evenly distributed in both sexes [33]. The diagnosis of CP is preceded by AP in at least 50% of patients [34]. This has been well demonstrated in patients with hereditary and alcoholic CP, in whom AP precedes the progression of CP by 10 years [19].

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Table 40.3 Summary of recent studies examining the incidence and risk factors for development of chronic pancreatitis after acute pancreatitis.

			CP rate (%)					
Author, year	**Cohort size**	**Follow-up time (years)**	**Overall**	**Alcoholic**	**Idiopathic**	**RAP**	**Time to CP (months)**	**Risk factors for RAP**
Lankisch et al., 2009 [12] Prospective	532	8.0	4	13	0	22	Unclear	Alcoholic etiology Recurrent acute pancreatitis Tobacco use
Yadav et al., 2012 [13] Retrospective	7456	3.3	13	28	10	32	10.4	Alcoholic etiology Recurrent acute pancreatitis Tobacco use
Bertilsson et al., 2015 [11] Retrospective	1457	4.2	5	17	6	Not stated	5.1	Alcoholic etiology Recurrent acute pancreatitis Severe disease at index attack Tobacco use
Ahmed Ali et al., 2016 [20] Prospective	669	4.8	8	Not stated			21.0	Younger age Idiopathic etiology Tobacco abuse Severe disease at index attack

AP: acute pancreatitis; CP: chronic pancreatitis; RAP: recurrent acute pancreatitis.

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Natural History of Pain

Abdominal pain is the hallmark of CP, and often prompts patients to seek medical attention. A recent systematic review of 42 studies demonstrated that 88% of CP patients experience abdominal pain at some point during the disease course [35]. Emerging data has demonstrated that the temporal nature of pain is a more important determinant of patient outcomes than the intensity of pain [36,37]. On cross-sectional assessments of abdominal pain in CP patients, approximately 60–70% have constant pain and 30–40% have intermittent pain; however, 60% alternate between pain patterns during the disease course [36,37]. Constant pain is associated with lower quality of life, higher rates of disability, and greater need for resource utilization (e.g., hospitalizations, pain medications) as compared to intermittent pain [36–38]. This effect is independent of the intensity of abdominal pain.

The mechanisms of pain in CP are complex, multifactorial, and poorly understood. Pain can be due to structural complications in the pancreas (pancreatic duct obstruction from stricture or stone, pancreatic inflammation, pseudocyst) or peripancreatic organs (bile duct stricture, duodenal obstruction). Resolution of these complications does not always result in pain control, and many patients with painful CP do not have these structural complications, suggesting sensitization of peripheral and/or central nociceptive pathways [33]. However, differentiating visceral pancreatic pain from central nervous system alterations is challenging in clinical practice, and novel pain assessment tools (e.g., comprehensive pain assessment score, pancreatic quantitative sensory testing) are being investigated to better classify pain profiles and to more effectively guide treatment choices.

Although medical management with nonopioid analgesics is the first step in the management of painful CP, this is often insufficient. In a recent US population study, 25% of CP patients are prescribed opiates and CP had the highest prescription rates among all GI disorders [39]. This is concerning, given the adverse events associated with opioid use. Endoscopic and surgical interventions are needed in a subset of patients with pain refractory to noninvasive interventions. In a US population-based study, 22% of CP patients required endoscopic procedures and 11% underwent surgical interventions over 10-year follow-up; however, a higher proportion of patients receive endoscopic and/or surgical interventions at referral centers [40].

One aspect that has recently been investigated is the interaction of psychiatric comorbidities with pain in CP. In a recent retrospective US cohort, patients with CP had sevenfold greater risk of anxiety (37%) and fivefold greater risk of depression (47%) compared with the general population [41]. The presence of psychiatric comorbidities in CP patients has been associated with higher pain prevalence, pain severity, and pain interference scores [42]. These data indicate that psychiatric comorbidities should be evaluated in CP patients, and their management is likely to improve pain management.

The concept of pain *burn-out* in CP was proposed by Ammann et al. decades ago, based on the observation that over 80% of patients with alcoholic CP became pain-free at a median of 5 years from disease onset. In recent years, an accumulating body of evidence has emerged that refutes this theory. In a large single-center retrospective cohort of 279 CP patients, 47% still complained of abdominal pain at a median period of 12 years from disease onset [43]. In multivariate analysis, this and other studies have shown that disease duration is not associated with pain relief [37,43].

Approximately 1 in 10 patients experience a painless disease course, with the majority of these (57%) having idiopathic/genetic etiology [35]. Patients with painless CP are diagnosed when undergoing abdominal imaging for other reasons and are found with calcifications and/or significant ductal changes. In general, these patients do not benefit from endoscopic or surgical interventions.

Diabetes Mellitus

Diabetes mellitus (DM) is a well-known complication of CP. In a recent systematic review of 15 studies, the incidence of new-onset DM was 15% within 3 years and 33% after 5 years of CP diagnosis [44]. In prospective studies with longer follow-up, the cumulative incidence of DM is 40–50% at 10 years and >80% at 25 years [40,45]. The pathogenesis of DM in CP has been thought to be a result of progressive parenchymal fibrosis with impaired insulin secretion. Several epidemiologic studies have supported this theory, by demonstrating that the risk of DM increases with certain CP specific characteristics (disease duration, calcifications, exocrine insufficiency, pancreatic surgery) [46,47]. This pathophysiologic paradigm has been challenged by recent large cross-sectional multicenter studies that reported an increased risk of DM in CP with traditional type 2 DM risk factors (age, overweight/obesity, family history of DM, dyslipidemia) [46,47]. This has suggested that DM in CP, at least in a subset of patients, may be a subtype of type 2 DM, and future studies are needed to better define the mechanisms of DM in CP.

Diabetes in CP is difficult to treat and about half become insulin dependent [44]. The risk of all-cause mortality and hospitalizations in CP patients with diabetes is greater than in patients with type 2 DM [48].

Exocrine Pancreatic Insufficiency

Initially CP patients lose pancreatic enzyme output, measured by direct or indirect pancreatic function tests, but maintain adequate digestive capacity, quantified by

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normal coefficient of fat absorption (CFA ≥ 93%). The term exocrine dysfunction (stage I and II) has been coined for these patients, who do not have symptoms or vitamin deficiencies, and would not benefit from treatment [49]. As pancreatic function loss reaches near total (>90%), patients develop abrupt and marked impairment in digestive capacity (CFA < 85%), with clinical manifestations, and micronutrient deficiencies [50]. This state of insufficient digestive capacity due to severe loss of pancreatic function represents exocrine pancreatic insufficiency (EPI, stage III and IV) [49] The burden of EPI in CP is difficult to estimate, given the absence of simple and accurate tests to diagnose EPI in clinical practice. A recent US population study showed a cumulative incidence of 30% at 10 years of follow-up [40]. In other series, the prevalence of EPI ranges from 35% to 75%, with higher risk in alcoholic CP and with longer disease duration [51]

EPI from CP is frequently experienced as diarrhea, foul-smelling stools, flatulence, meteorism, abdominal discomfort/pain, and weight loss. Persistent malabsorption can cause deficits of fat-soluble vitamins A, D, E, and K, calcium, magnesium, zinc, thiamine and folic acid. Fortunately, EPI can be treated with the initiation of pancreatic enzyme replacement therapy (PERT), which has been shown to improve symptoms, nutritional status and quality of life. A minimal dose of at least 40,000 USP units of lipase with each meal is recommended. Despite its importance, a recent US study of administrative claims demonstrated that only 6.5% of CP patients receive any testing for EPI, and that among those treated with PERT, only 32% are prescribed appropriate dosing [51]. In this study, seeing a GI physician and formal testing for EPI were strong predictors for prescribing PERT and using an appropriate dose.

Metabolic Bone Disease

Long-term malnutrition from EPI and CP can lead to metabolic bone disease. In a systematic review of 10 studies reporting osteopathy in CP, the prevalence of osteopenia was 40% and of osteoporosis was 23% [52]. Similar estimates were reported in a recent multicenter US study of 282 patients with definitive CP, in which 39% had osteopenia and 17% had osteoporosis at the time of baseline DXA scan [53]. Risk factors independently associated with osteopathy included underweight body mass index, older age, female sex, and white race [53]. In a large VA cohort, CP was independently associated with greater risk of total fractures (5%), vertebral fractures (1%), and hip fractures (2%), compared to non-CP controls [54]. Therefore, assessments of bone mineral density are recommended for CP patients. However, this is often underperformed, and a recent single center study showed that a dual-energy X-ray absorptiometry test (DXA) was performed in only 21% of CP patients [55].

Pancreatic Cancer

Within the first 2 years of CP diagnosis, there is an excess of pancreatic cancer diagnosis, that may represent early cancers misdiagnosed as CP [56]. When excluding patients diagnosed with pancreatic cancer within 2 years of CP diagnosis, a meta-analysis of 13 observational studies showed that the risk of pancreatic cancer in CP is 16-fold greater than in the general population [57]. Even when excluding pancreatic cancer patients diagnosed within 5 years of CP, patients with CP still have eightfold greater risk of pancreatic cancer [57]. In a recent US population based study, the cumulative incidence of pancreatic cancer from initial CP diagnosis was 2% at 2 years and 3% at 5 years [58]. Age, obesity, and pancreatic ductal dilation are risk factors associated with higher incidence of pancreatic cancer [58].

Quality of Life

CP is a debilitating disease that negatively impacts quality of life. Factors that significantly decrease quality of life include constant pain, disability/unemployment, current smoking, and other comorbidities [38]. In a multicenter prospective study, anxiety and depression were also noticed to negatively impact quality of life in CP [42].

Survival

The overall survival and the standardized mortality ratio in CP patients is two- to fourfold higher when compared with the general population [59]. Most patients die from nonpancreatic causes such as cancers and cardiovascular diseases.

Conclusion

Studies in the past two decades have provided an insight into the population distributions and natural history of different stages of pancreatitis. Readmission to hospital is frequent after AP. After the first attack of AP, about 1 in 5 patients develop a recurrence and 1 in 10 progresses to CP. Alcohol and tobacco abuse are the main predictors of recurrence, and these along with RAP are the main predictors of progression to CP. Abdominal pain is the main symptom of CP, and a significant fraction of these patients develop exocrine and/or endocrine insufficiency during the disease course. CP is an established risk factor for pancreatic cancer, although, the absolute risk of this is low.

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Pediatric Recurrent Acute and Chronic Pancreatitis: Role of Pancreas Divisum

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Pediatric Pancreatitis

The incidence of pediatric acute pancreatitis (AP) has increased over the last several years, affecting approximately 1 in 10,000 children. Acute recurrent pancreatitis (ARP), characterized as two or more discrete episodes of AP, is reported in ~15% to 20% of children following an initial AP episode. Chronic pancreatitis (CP), in which children have imaging or functional evidence of irreversible pancreatic damage, is estimated to have an incidence of ~2 per 100,000 children per year. ARP and CP are considered as a disease continuum. They are both associated with significant disease burden. Children with ARP or CP experience frequent abdominal pain, emergency room visits and hospitalizations. They undergo numerous endoscopic and surgical procedures. Overall, diagnostic and therapeutic approaches are limited.

Risk Factors

Genetic Factors

Gene variants are the leading risk factors in recurrent attacks of pancreatitis in childhood affecting approximately 50% of children with ARP and 75% with CP. The genes most commonly associated with pediatric pancreatitis are: cationic trypsinogen (*PRSS1*), serine protease inhibitor Kazal-type 1 (*SPINK1*), chymotrypsin C (*CTRC*), and carboxypeptidase A1 (*CPA1*).

Obstructive Factors

These include biliary obstructive factors (gallstones, choledochal cyst) and anatomical abnormalities—e.g., pancreas divisum, pancreaticobiliary malunion (Table 41.1). Pancreas divisum (PD) is found in 14.5% of the INSPPIRE (International Study Group of Pediatric Pancreatitis in Search for a Cure) population, which is higher than in the normal population (~7%), but does not have an association to known pancreatitis gene mutations, suggesting that PD itself may be a risk factor. Although children frequently undergo endoscopic interventions, pancreatic sphincterotomy or minor papillotomy for PD, it is not clear whether they help prevent recurrent attacks. Therapeutic endoscopy was found most helpful when the pancreatic duct was impacted with stones in children with PD. A prospective and randomized study similar to the SHARP (Sphincterotomy for Acute Recurrent Pancreatitis) trial in adults with PD would be beneficial to assess whether therapeutic endoscopy would be helpful for this subset [1–5].

Pancreas Divisum

Anatomical Description

Pancreas divisum (PD) is the most common anatomical variant of the pancreatic duct system and occurs in 4–14% of the population. It occurs as a result of the failure of fusion of the dorsal and ventral pancreatic ducts during embryonic development. There are two types of PD: complete and incomplete. In complete PD, there is no connection between the dorsal and ventral ducts. The ventral duct drains the uncinate process and part of the head of the pancreas into the major papilla. The dorsal pancreatic duct drains the head, body, and tail of the pancreas and opens into the minor papilla. Incomplete PD occurs when a small branch of the ventral duct communicates with the dorsal duct. In both types of PD, the minor papilla drains the majority of the pancreas. This leads to increased intraductal

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Table 41.1 Etiology of pediatric pancreatitis.

- Congenital anomalies – periampullary obstruction: choledochal cyst, abnormal union of the pancreaticobiliary junction, pancreas divisum
- Gallstones, choledocholithiasis
- Tumor
- Ascariasis
- Infectious
- Drugs
- Trauma
- Systemic/metabolic disease
- Familial, idiopathic

pressure, which can lead to the development of recurrent bouts of pancreatitis.

Clinical Symptoms, Diagnostics, and Treatment

The majority of patients with PD remains asymptomatic. Between 5% and 10% of patients with PD develop clinical symptoms of acute and chronic abdominal epigastric pain and recurrent pancreatitis documented by elevated amylase, lipase, and C-reactive protein. The diagnosis of hereditary pancreatitis and cystic fibrosis should be excluded. Diagnostic magnetic resonance cholangiopancreatography (MRCP) can show a progressive dilation of the Wirsung's duct in the head of the pancreas but sometimes can fail to show PD (Fig. 41.1) [6].

Treatment is aimed at improving the drainage of the dorsal duct. This may be achieved by endoscopic retrograde cholangiopancreatography (ERCP), assisted papillotomy and/or stent insertion, or by surgical approaches [7]. An overview of the authors' experience with PD management is summarized in Table 41.2.

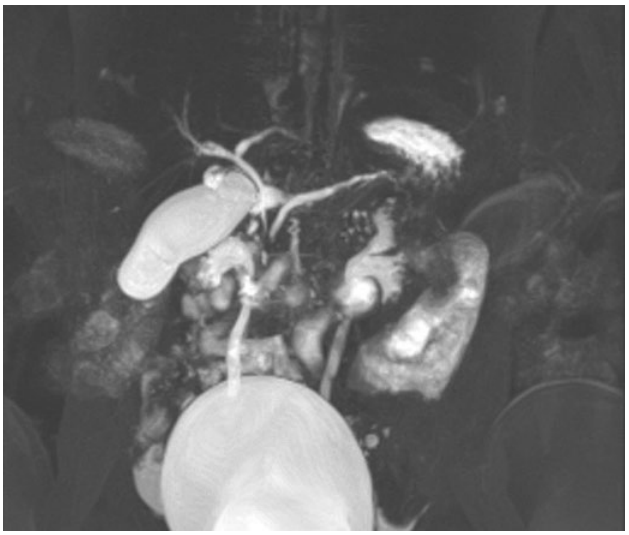


Figure 41.1 Magnetic resonance cholangiopancreatography (MRCP) of a 4-year-old girl with pancreas divisum.

It is stated in the published literature, that the first choice of treatment for patients with symptomatic PD is ERCP papillotomy [8]. However, no randomized studies have been performed to warrant this approach [9]. ERCP papillotomy may result in symptom improvement [6]. However, if ERCP papillotomy is unsuccessful or cannot be performed, surgical treatment is indicated [10,11].

Surgical Treatment

Indication for surgery in pediatric PD is very rare. It is only considered in patients with repeated bouts of pancreatitis, abdominal pain, and failure to thrive after ERCP has failed to improve the symptoms.

The plethora of surgical techniques (transduodenal sphincteroplasty, Puestow's procedure, Frey's procedure, Kausch/Whipple's procedure, duodenum-preserving resection of the pancreatic head, and total pancreatectomy) complicates the clinical decision-making process about which surgical method should be performed.

A promising surgical procedure in patients with PD is duodenum-preserving resection of the pancreatic head (DPRPH) [6], a reliable method to preserve the duodenum and limit resection of pancreatic tissue. To perform duodenum-preserving pancreatic head resection safely, preservation of the mesoduodenal vessel as well as the posterior superior pancreatoduodenal artery is important, and Kocher's maneuver should be avoided for this reason. DPRPH is ideally performed using an ultrasonic surgical aspirator (Fig. 41.2) and a Roux-en-Y pancreatojejunoanastomosis is created (Fig. 41.3).

DPRPH was first introduced by Prof. Beger for chronic pancreatitis in an adult patient [10]. The application has expanded to precancerous lesions and pancreatic head tumors with low malignancy.

Schneider followed this report with a study of 36 patients who underwent DPRPH for symptomatic PD. After the surgical intervention, 50% of the patients were completely pain-free and 31% had a significant reduction of pain. The procedure was specifically chosen because of the underlying duct anomalies and major pathomorphological changes in the pancreatic head [12].

DPRPH is an alternative technique to other resective or drainage procedures after failure of the nonsurgical interventional treatment. The scarce published cases of children with PD indicate that sphincteroplasty may not be sufficient in preventing pancreatitis. Puestow's procedure is preferred to the DPRPH in the presence of a dilated pancreatic duct; however, it is surgically challenging and has a lower success rate.

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Table 41.2 An overview of patients with pancreas divisum, published in Snajdauf et al. [6].

Patient	Sex	Age (y)	Variant of PD	Successful papillotomy	Management	Recurrence of pancreatitis
1	F	4	Complete	Yes, no improvement	DPRPH	No after surgery
2	M	14	Complete	Yes (minor)	Papillotomy	No
3	F	6	Incomplete	Yes (minor)	Papillotomy	No
4	M	12	Complete	Yes (major)	Papillotomy	No
5	F	11	Complete	No	Conservative	Mild
6	M	14	Complete	No	Conservative	Mild
7	M	2	Incomplete	No	Conservative	Mild

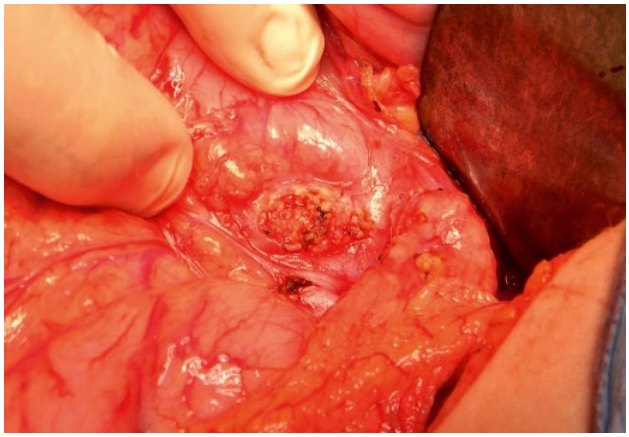


Figure 41.2 Duodenum-preserving resection of the pancreatic head (DPRPH) was performed using an ultrasonic surgical aspirator.

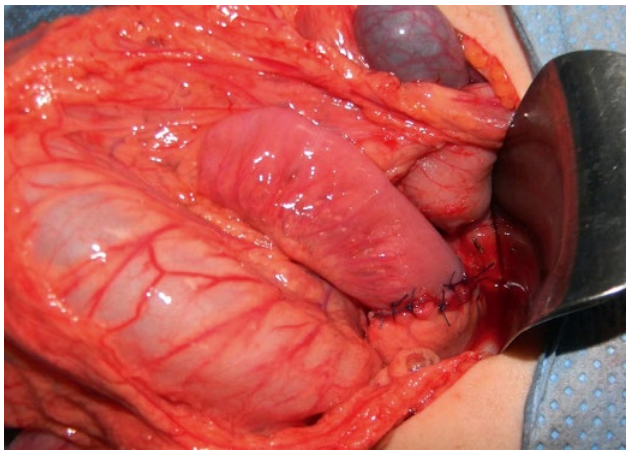


Figure 41.3 The rest of the pancreas was drained into the jejunum by means of a retrocolic single end-to-end, Roux-en-Y pancreaticojejunostomy.

DPRPH is a technically demanding (especially concerning the separation of the head of the pancreas from the duodenum) and time-consuming procedure. However, it is very effective when the obstruction lies in the head of the pancreas. When the head of the pancreas is removed, the recurrent bouts of pancreatitis are cured [13]. Furthermore, the risk of pancreatic insufficiency is very small, as only the head of the pancreas is removed. DPRPH may be superior in other aspects, such as the need for postoperative blood replacement, length of hospital stay, exocrine function impairment, postoperative weight gain, and quality of life [14,15]. Postoperative weight gain and quality of life are outcomes of utmost importance in pediatric patients. Continuing normal growth after such procedures is key because impeded development has dire social and psychological impacts on the child.

Complications and Controversies with Resection of the Pancreas

Partial or total resection of the pancreas can have severe complications in growing children. Thus, surgical treatment is only indicated when its potential benefits outweigh the risks of complications and the impaired quality of life caused by recurrent pancreatitis. The most frequent complications of pancreatic surgery in children and adults are exocrine and endocrine dysfunction of the pancreas, diabetes mellitus, gastrointestinal dysfunction (e.g., delayed gastric emptying), impaired quality of life, persisting impairment of nutritional status, abdominal pain, fatigue, change in stools, and local surgical site-related complications such as pancreatic fistula or bleeding [16–22].

To our knowledge, only a few cases of children treated surgically for PD have been published. Snajdauf et al. presented a case of a girl who underwent DPRPH for PD and she was reported to be in a good state of health 7 years after the operation. Her alimentary status and somatic growth rates were within the normal population range and she had no reported gastrointestinal dysfunction, no symptoms of diabetes mellitus, and did not

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require any dietary restrictions [6]. O'Rourke and Harrison reported an 8-year-old girl who presented with recurrent bouts of acute pancreatitis and, after multiple failed attempts at ERCP, was referred for surgical intervention. She underwent an open sphincteroplasty of both the major and minor papillae and at a follow-up period of 22 months was symptom-free [23]. Neblett reported eight children who underwent surgical treatment for symptomatic PD. Seven patients underwent transductal sphincteroplasty, and two of these patients further underwent longitudinal pancreaticojejunostomy due to recurrent symptoms. Pancreaticojejunostomy was performed as a primary procedure in one patient. The indication for this was a ductal stenosis at the union of the ducts of Wirsung and Santorini [24]. This suggests that the cause of outflow obstruction in PD may lie in the head of the pancreas. Rabinovich et al. presented the largest series to date on pancreatic procedures performed in children. They reported 72 operative interventions in 62 patients over a 12-year period. Nine patients were treated operatively for PD with recurrent bouts of pancreatitis. Unfortunately, the long-term follow-up data were not reported in this study [25]. Shukri presented a series of seven children with PD over a span of 20 years. One patient in this group was treated surgically. Initially a transduodenal papilloplasty was performed through the accessory papilla. However, due to a recurrence of pancreatitis 1 year later, Puestow's procedure was performed [26]. Schneider reported 28 patients treated surgically for symptomatic PD. The group included one child, a 12-year-old boy treated by sphincteroplasty of the minor papilla. However, due to persisting symptoms caused by an isolated ductal stenosis the patient underwent further segmental resection 23 years later [12].

Conclusions

Surgery is not required in most pediatric patients with pancreas divisum. Patients with a milder form of pancreatitis respond well to ERCP papillotomy or pancreatic duct stent insertion. Surgery should only be performed if ERCP therapy fails. Transduodenal sphincteroplasty, Puestow's procedure, Frey's procedure, Whipple's procedure, or total pancreatectomy are the most preferred procedures worldwide. A duodenum-sparing technique (duodenum-preserving resection of the pancreatic head) seems to be a promising choice for pancreas divisum, although the numbers of operated patients are low and more experience is needed in the future.

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Clinical and Laboratory Diagnosis of Chronic Pancreatitis

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Introduction

For centuries the pancreas was a "terra incognita" hidden behind the stomach and its pathophysiological role remained obscure. In 1761 Jean-Baptista Morgagni described the first case of chronic pancreatitis in his book *De sedibus et causis morborum* and it took a further 60 years until Kuntzmann was able to connect fatty stool to diseases of the pancreas. Even in the twenty-first century the time interval between the onset of symptoms and the diagnosis of chronic pancreatitis is unacceptably long and this is mainly caused by the fact that routine blood tests are usually not helpful in diagnosing chronic pancreatitis and that clinical symptoms are often nonspecific. The modern clinical concept of clinical chemistry for pancreatic diseases began in 1929 with the introduction of serum amylase (diastase) measurements [1]. Thereafter Comfort and coworkers [2] combined clinical observations, surgical findings, and autopsy studies to characterize chronic pancreatitis and first reported a chronic relapsing course of the disease. They also commented on its frequent association with longstanding alcohol intake, its common onset in the third and fourth decade of life, and the typical complications of the disease such as exocrine and endocrine pancreatic insufficiency.

Clinical Presentation

With a global incidence of 34 (CI 23–49), a prevalence of 13.5 to 52.4 per 100,000 population and a frequency of 0.04% to 5% among all autopsies, chronic pancreatitis represents a rather common disorder of the gastrointestinal tract [3,4]. Chronic pancreatitis also accounts for a substantial morbidity and healthcare costs. Although most patients with chronic pancreatitis are treated as outpatients, in 2017 there were almost 20,000 (ICD-10: K86) hospital admissions for chronic pancreatitis in Germany alone (Federal Statistics Office). This does not include those patients who were coded as having acute pancreatitis, including those reporting an acute episode of chronic pancreatitis (55,221 cases). Evaluating records from the United States, United Kingdom, the Netherlands, and Finland confirmed an increasing number of annual hospital admissions amounting to a 30% increase within 6 years [5]. This substantiates the high socioeconomic significance of the disease. Mortality from chronic pancreatitis is reported to be 12.8–19.8%, over a mean observation period of 6.3–9.8 years [6–8]. Total mortality in the same studies was reported to be 28.8–35%. Continued alcohol consumption results in a significantly reduced survival rate. The number of patients who leave the workforce and abandon gainful employment due to prolonged illness or continued alcohol consumption, or become disabled and are forced to retire prematurely during the course of the disease amounts to 40%. The 10-year survival rate is 70% and the 20-year survival rate is 45% in comparison with 93% and 65%, respectively, for an age-adjusted cohort [9].

Investigating the time interval between the onset of symptoms and the diagnosis of chronic pancreatitis a median interval of 30–55 months was reported in alcoholics [10,11]. In nonalcoholics the diagnosis was even more delayed (median 81 months) and frequently only established if complications of the disease such as pseudocysts or gastric outlet obstruction occurred. The major reason for this delay lies in the natural course of the disease. The clinical presentation of patients with chronic pancreatitis is highly dependent on the stage of

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the disease. It varies between severely ill patients with symptoms of an acute abdomen to slowly progressing cachexia. Often the first signs of the disease which prompt the patient to seek medical attention are belt-like abdominal pain that frequently radiates to the back, loss of body weight (in 80%), and steatorrhea (in less than 50%) [12].

Several attempts have been undertaken to establish histological and morphological criteria that clearly define chronic pancreatitis. Unfortunately an exact correlation between clinical symptoms, morphological signs, and histological criteria is still not at hand.

Etiology

In Western countries alcohol consumption is assumed to be the leading cause (42% to 68%) of chronic pancreatitis [13]. The prevalence of chronic pancreatitis clearly correlates with the alcohol consumption in a given population [14].

It is reported that 24.1% of all patients suffering from acute pancreatitis will progress to chronic pancreatitis [15]. Of those, 48.2% have alcoholic pancreatitis and smoking was identified as the only independent but dose-dependent risk factor for disease progression [16]. With regard to the etiology of chronic pancreatitis, more recent studies suggest that in addition to alcohol consumption smoking increases the risk and can independently cause chronic pancreatitis [17].

The second most common form of chronic pancreatitis (25%), as of today, is so-called idiopathic pancreatitis [18,19]. Patients without an identifiable risk factor for chronic pancreatitis are classified as having idiopathic pancreatitis. This group is constantly decreasing since Comfort and Steinberg reported in 1952 an inherited form of chronic pancreatitis that follows an autosomal dominant inheritance pattern and knowledge about genetic susceptibility factors is accumulating [2]. Hereditary pancreatitis represents a genetic disorder closely associated with mutations in the cationic trypsinogen gene and presents with a disease penetrance of ≈ 80% [20]. Shortly after the identification of mutations in the trypsinogen gene associated with chronic pancreatitis another important observation was made by Witt et al. [21]. They found mutations in the *SPINK-1* gene (encoding the pancreatic secretory trypsin inhibitor, PSTI) to be associated with idiopathic chronic pancreatitis in children. *SPINK-1* mutations can be frequently detected in patients who do not present with a family history of pancreatitis and are devoid of classical risk factors for chronic pancreatitis [22,23].

Cystic fibrosis is an autosomal-recessive disorder with an estimated incidence of 1 : 2500 characterized by pancreatic exocrine insufficiency and chronic pulmonary disease. The extent to which the pancreas is affected varies between a complete loss of exocrine and endocrine function to clinically normal pancreatic function. Recurrent episodes of pancreatitis occur in 1–2% of all patients with cystic fibrosis who have normal exocrine pancreatic function and much more rarely in patients with exocrine pancreatic insufficiency. That means that *CFTR* changes that would not cause cystic fibrosis still confer a twice increased risk of developing pancreatitis.

Metabolic disorders associated with hypertriglyceridemia above 1000 mg/dL can be responsible for the development of recurrent episodes of pancreatitis [24], but even lower triglyceride levels pose a significant risk [25]. In addition to dietary restrictions, fibrates, and rescue treatments by lipidapheresis and glucose/insulin infusion to lower triglyceride levels, the antisense oligonucleotide volanesorsen has been approved for the treatment of familial chylomicronemia syndrome, a genetic disorder leading to lipoprotein lipase deficiency resulting in severe hypertriglyceridemia. In a prospective, randomized open-label trial the risk for developing episodes of pancreatitis was markedly reduced in the treatment group compared to placebo, although the trial was not powered for this endpoint [26]. In a few cases chronic calcifying pancreatitis has been reported due to hypercalcemia in patients with untreated hyperparathyroidism. The underlying mechanism of hyperparathyroidism-associated pancreatitis is most likely related to the established role of calcium in the premature, intracellular activation of digestive proteases [27].

Pain

Pain is the most commonly encountered symptom in chronic pancreatitis (80–95% of patients) [28]. Up to 50% of patients with chronic alcoholic pancreatitis may suffer from chronic pain, while the remaining portion presents with intermittent attacks followed by pain-free intervals or have never experienced severe pain due to pancreatitis [19,29]. Most patients report continual, numb pain lasting for more than 24 hours and 68% report epigastric pain (Fig. 42.1). Pain, which can radiate to the back is reported in 39%, to the left upper quadrant in 50%, and to the right upper quadrant in 32%. About 6% of patients feel their pain radiating between the shoulders. In general, patients with abdominal pain take a "jackknife" posture to relax abdominal musculature affected by peritonitis. In chronic alcoholic pancreatitis a relationship between alcohol ingestion and recurrent pain has been described. Pain often begins between 12 and 48 hours after ceasing alcohol intake.

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Figure 42.1 Erythema ab igne in a female patient aged 45 years suffering from chronic alcoholic pancreatitis.

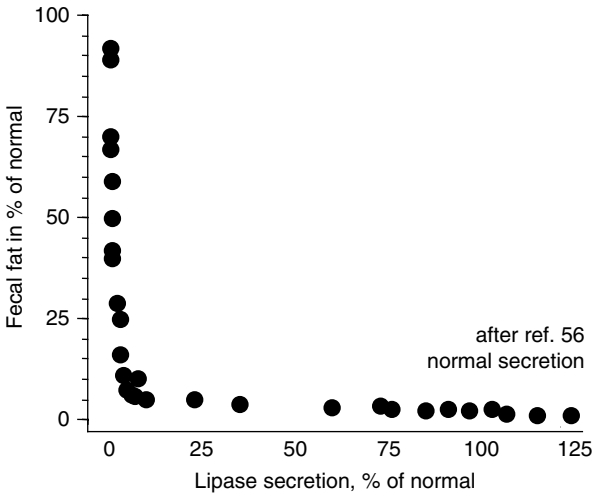


Figure 42.2 The graph illustrates the reduction in lipase secretion, which is paralleled by an increase in fecal fat. With rare exceptions, steatorrhea and azotorrhea only occur if there is greater than 90% reduction in pancreatic lipase and trypsin secretion. *Source:* Adapted from [39].

Malabsorption, Weight Loss

Fat excretion of patients with pancreatic steatorrhea frequently exceeds that of patients with other causes of steatorrhea. Leaking oily stool from the anus is virtually pathognomonic of exocrine pancreatic insufficiency. In general, weight loss is a cardinal symptom of pancreatic exocrine insufficiency with steatorrhea whereas hypoproteinemia or malabsorption of the fat-soluble vitamins is less common. So far there have only been a few publications that have reported decreased bone mineral density, but no comparison to an age-matched control cohort was included [30,31]. Overt steatorrhea occurs in approximately 30% of patients with chronic calcific pancreatitis.

With rare exceptions, steatorrhea and azotorrhea (excessive discharge of nitrogenous substances in the feces or urine) only occur when the reduction in lipase and protease secretion, respectively, surpasses 90% [32,33] (Fig. 42.2).

In alcoholic chronic pancreatitis it will usually take 10 to 20 years until severe exocrine insufficiency develops, but according to DiMagno and coworkers lipase secretion will decrease more rapidly than protease secretion. In decompensated chronic pancreatitis with less than 5% of the normal enzyme output, about 40% of nutrients from a readily digestible low caloric meal are malabsorbed and enter the colon.

Endocrine Insufficiency

More rarely patients seek medical attention because they develop diabetes mellitus with a loss of endocrine function or cachexia as the initial symptoms of chronic pancreatitis. A history of diarrhea with recent onset of diabetes mellitus should always raise the suspicion of chronic pancreatitis as the underlying cause. The symptoms of diabetes "of other specific types" according to the WHO classification system released in 2003 (e.g., loss of insulin production due to diseases of the exocrine pancreas) are similar to those of diabetes mellitus of other causes. Overall 45% of the patients with chronic pancreatitis suffer from overt diabetes. The cause of chronic pancreatitis bears no relationship to the subsequent likelihood of developing diabetes, but it does seem to influence the time lag between onset of pancreatitis and onset of diabetes. Alcoholics show symptoms of endocrine insufficiency earlier than nonalcoholics [7]. Diabetes mellitus is also an independent predictor of mortality in patients with chronic pancreatitis. The underlying pathophysiology of diabetes in chronic pancreatitis is the loss of insulin-secreting cells often combined with a peripheral and hepatic insulin resistance. Oral antidiabetics and especially metformin might therefore have a role in the treatment of these patients but control of blood sugar levels should be achieved with exogenous insulin supplementation.

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Jaundice

In 10–40% of cases with chronic pancreatitis a benign dominant stenosis of the common bile duct develops due to inflammation of the pancreatic head or due to pancreatic pseudocysts or phlegmons, all of which require either endoscopic or surgical intervention. An asymptomatic increase in alkaline phosphatase is the most common laboratory manifestation of a stenosis of the common bile duct secondary to chronic pancreatitis. Jaundice may develop later. However, a raised alkaline phosphatase or increased bilirubin alone does not always point to extrahepatic cholestasis but might be a symptom of parenchymal liver damage caused by hepatitis, steatosis, or even liver cirrhosis. Endoscopic intervention is clinically indicated if the patient presents with jaundice or cholangitis and in order to prevent secondary biliary cirrhosis, whereas surgery is indicated, if a malignant cause for jaundice cannot be excluded.

Laboratory Diagnosis

Even after two centuries of pancreatic research a diagnostic serum marker for chronic pancreatitis is not available. Usually the diagnosis is made by a combination of imaging procedures such as ultrasound, endoscopic ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), or MRCP in combination with exocrine and endocrine function tests.

Serum Tests for the Diagnosis and Etiological Characterization of Chronic Pancreatitis

The simplest, noninvasive tests would be to measure exocrine pancreatic enzymes or hormones in fasting blood samples. Total serum amylase, as opposed to pancreatic isoamylase or salivary isoamylase, has been measured routinely since 1929, but it is of little use for the diagnosis of chronic pancreatitis. Since amylase secretion into the gut decreases in chronic pancreatitis it has been hypothesized that low serum pancreatic amylase could be used to diagnose chronic pancreatitis. Unfortunately, pancreatic isoamylase is completely normal in many patients with mild to moderate chronic pancreatitis and the sensitivity was reported to be only 60% with a variation between 12% and 100 % depending on the severity of the disease [34]. The same problems apply to the measurement of lipase and trypsin. Therefore pancreatic serum enzyme testing lacks diagnostic accuracy as well as specificity.

Provocation tests, in which serum levels of pancreatic enzymes are measured after stimulation of pancreatic secretion by a secretagogues or parasympathomimetics, have been found to be rather insensitive, nonspecific, burdened with great interindividual ranges and therefore just as unreliable as markers for chronic pancreatitis. At most they are abnormal in 25% of patients suffering from chronic pancreatitis and at least the same proportion of healthy volunteers show abnormal test results [35,36].

A promising approach to diagnosing chronic pancreatitis by means of a blood test comes from the use of a multitude of markers measured on a common platform, a so-called biomarker signature. In a three-tiered prospective discovery and validation design, Adam and Beyer et al. described a multivariable prediction model based on blood plasma and serum metabolomics. The signature is comprised of eight metabolites measured on GC-MS and LC-MS/MS platforms and pancreatitis subjects were distinguished from non-pancreas disease control subjects with an AUC of 0.85 (95% CI 0.81–0.89) in EDTA-plasma or 0.87 (95% CI 0.81–0.95) in serum [37]. Similarly, a protein-based signature unique for chronic pancreatitis was identified by group from Stanford using the Luminex® assay [38].

Pancreatic Exocrine Function Tests

Tests for exocrine and endocrine pancreatic function serve as a second line of diagnostic tools for chronic pancreatitis. Reduced exocrine function can precede overt morphological changes and therefore the sensitivity to detect early changes is higher for exocrine pancreatic function tests than for imaging studies. These patients have exocrine pancreatic insufficiency because enzymes and chime do not mix appropriately and their fat digestion is accordingly impaired. However, excreted enzymes, for example elastase or chymotrypsin in stool, will appear normal.

Several tests for exocrine pancreatic function are now well established in the diagnostic workup of patients with suspected chronic pancreatitis. Assays can be divided into direct and indirect methods depending on the technique used for determining enzyme output (via duodenal tube or indirectly). When pancreatic function is measured directly the stimulated output of enzymes and bicarbonate into the small intestinal lumen is collected via a nasoduodenal tube and then quantitated. Indirect methods detect a decreased amount of pancreatic enzymes in stool or serum or, alternatively, evaluate the digestion of synthetic substrates by pancreatic enzymes, which also indicate impaired exocrine function when reduced (Table 42.1). The disadvantage of indirect tests for pancreatic function is that they cannot distinguish between structural or functional abnormalities. The situation after gastrectomy can serve as a good example of when an impaired synchrony between pancreatic secretion and the gastrointestinal passage of

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Table 42.1 Direct and indirect pancreatic function tests.

	Pancreatic function test
Direct	• Secretin–cholecystokinin test • Endoscopic secretin test
Indirect	*Serum tests*: • Pancreolauryl test • NBT-PABA test (commercially discontinued) *Fecal tests*: • Fecal elastase • Chymotrypsin • Stool weight • Fecal fat quantification

food will signal exocrine insufficiency on pancreatic function tests without any structural damage to the pancreas (pancreatico-cibale asynchrony) [39].

Direct Pancreatic Function Tests

Secretin–Cholecystokinin Test

Pancreatic enzyme activity as well as bicarbonate concentration are measured in the duodenal juice after stimulation with the enterohormones secretin (1 CU/kg KG i.v.) and cholecystokinin (CCK; 25–100 ng/kg KG). The secretin–cholecystokinin test was the gold standard for pancreatic function testing. Its overall sensitivity and specificity is 90%. The combined secretin–CCK test is no longer used since pharmaceutical CCK preparations for human use are no longer marketed (at least not in most countries). Some authors used a standardized test meal (Lund test) rather than hormone stimulation of the exocrine pancreas but this more "physiological" approach is ultimately less sensitive in detecting early functional changes and bicarbonate cannot be measured in the collected chyme. As early as 1982 Gregg suggested a new method to determine exocrine pancreatic function by collecting pancreatic juice after intravenous secretin stimulation during ERP [40]. Until 2003 no larger series of this promising approach had been conducted until DiMagno and coworkers presented a modified version of the endoscopic pancreatic function test investigating 412 subjects. The overall accuracy of the endoscopic secretin test was 79% with positive and negative predictive values of 73% and 85%, respectively [41]. One possibility to overcome the limitations of invasive function testing might be secretin-stimulated MRI. Intravenous application of secretin causes the rapid washout of bicarbonate-rich fluid from the exocrine pancreas which can be quantified semiquantitatively but is significantly reduced in patients with impaired exocrine function. Sensitivity of secretin-stimulated MRI was calculated to be 69% while the specificity was 90%. As MRI is becoming an alternative to CT scan examination for the diagnosis of chronic pancreatitis, secretin-MRCP could become a valuable diagnostic tool [42,43].

Noninvasive Pancreatic Function Tests

Fecal Elastase-1

Pancreatic elastase accounts for 6% of protein in pancreatic juice. Compared to other serine proteases this enzyme is highly stable during its passage through the gut and can be detected with a five- to sixfold concentration in stool (median concentration of 1200 µg/g). Fecal elastase is measured using an enzyme-linked immunoassay (ELISA) and there are human-specific polyclonal and monoclonal test kits without cross-reactivity commercially available. It is therefore not necessary for the patient to discontinue enzyme supplementation treatment because it would potentially contain traces of pork elastase. The overall sensitivity of fecal elastase testing is 63% for mild exocrine insufficiency and rises to 100% for severe exocrine insufficiency if compared to the gold standard of the secretin–cholecystokinin test [44]. Biochemically the elastase 1 assay is a misnomer since the human pancreas expresses elastase 2 and 3 isoforms but not elastase 1 isoform known only from pigs.

About 5% of chymotrypsin secreted into the duodenum can be recovered enzymatically active in the feces and measured by a colorimetric enzyme reaction employing the substrate *N*-glutaryl-L-phenylalanine-*p*-nitroanilide (GNPNA). Sensitivity and specificity is regarded to be equal or lower compared to fecal elastase but false negative results occur in 4% of patients with severe exocrine insufficiency, 15–18% of patients with moderate exocrine insufficiency, and 25–40% of patients with mild pancreatic insufficiency [44,45].

Another noninvasive approach to evaluate pancreatic exocrine insufficiency is the assessment of CO_2 exhalation after digestion of 13 labelled synthetic substrates such as mixed triglyceride, triolein, and hiolein, which are enzymatically cleaved by pancreatic enzymes in the duodenum, and the 13 CO_2 component, which is rapidly resorbed on can therefore be detected in exhaled breath over time [46]. In patients with severe exocrine insufficiency sensitivity of the detection of mixed triglycerides is 92% to 100%, but in patients suffering from mild impairment of exocrine function sensitivity it is reduced to 46% [47]. However, in addition to the detection of pancreatic insufficiency these tests can be used for clinical workup of chronic diarrhea or to monitor the efficacy of enzyme supplementation [48].

Fecal fat quantification by the classical van de Kamer (alcohol extraction) technique is the standard test to determine steatorrhea as a characteristic symptom of

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reduced exocrine function. After a 90% loss of exocrine function fat excretion in stool significantly increases as a sign of fat maldigestion. A mild or intermediate impairment of exocrine function is usually clinically compensated for. The van de Kamer test has fallen out of favor with patients, nurses, and technicians because it requires extensive handling of large amounts of smelly stool.

Evaluation of Endocrine Function

Overt diabetes occurs in approximately 20% of patients suffering from alcoholic chronic pancreatitis 6 years after disease onset. Ten years after disease onset about 50% of alcoholic pancreatitis patients display signs of impaired glucose metabolism with diminished insulin production [49]. Pancreatic endocrine function should be evaluated by measuring HbA_{1c}, fasted glucose or by means of an oral glucose tolerance test according to the guidelines of the WHO for the diagnosis of diabetes mellitus. Type 3c diabetes mellitus on the background of CP can be diagnosed if exocrine insufficiency is also present and type 1 diabetes and insulin resistance are unlikely [50].

Genetic Testing

In addition to an evaluation of exocrine and endocrine function considerable attention is now paid to the etiology of the disease. Recent results from molecular and genetic studies suggest that a significant number of patients with chronic pancreatitis suffer from a genetically determined or inherited disease. This is mainly true for patients who were formerly classified as suffering from idiopathic pancreatitis, for patients with an onset of the disease before the age of 25, or those with a positive family history for chronic pancreatitis or pancreatic cancer. Patients who suffer from chronic pancreatitis due to mutations in the cationic trypsinogen gene are burdened with a 70- to 140-fold increased risk to develop pancreatic cancer, particularly if they smoke. Whether, this is also true for patients who carry *SPINK-1* or *CFTR* mutations needs to be determined. Genetic testing for the most common and clinically relevant trypsinogen gene mutations (N29I and R122H or R122C) can be recommended for chronic pancreatitis patients who have first-degree relatives suffering from pancreatitis or pancreatic cancer, for patients with chronic pancreatitis or recurrent bouts of acute pancreatitis before the age of 25 years and no identifiable risk factor [3]. Genetic testing for clinically unaffected relatives is not indicated and should only be performed within Ethics Committee approved research protocols. A much more detailed analysis of the genetic risk factors of pancreatitis is found in other chapters of this volume (Table 42.2).

Table 42.2 Implications for genetic testing.

Indications for genetic testing in idiopathic or hereditary pancreatitis
• Recurrent (2 or more) episodes of ***acute*** pancreatitis without identifyable cause or etiology,
or
• Idiopathic ***chronic*** pancreatitis – especially in children and young adults under the age of 25 years,
or
• Pancreatitis in a patients with a positive family history of ***pancreatitis*** (one or more first- or second-degree relatives)

In conclusion, even in the twenty-first century the diagnosis of chronic pancreatitis is made by a combination of clinical symptoms, imaging procedures such as ultrasound, EUS, CT, and MRCP, and exocrine and endocrine function tests. Therapy is restricted to symptom control for the lack of a causal treatment strategy and the time point from first symptoms to diagnosis has not been significantly shortened during the last 15 years. Biomarkers or tests are urgently needed but currently not available.

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43

Abdominal Imaging for the Diagnosis of Chronic Pancreatitis

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Introduction

In 2016, a mechanistic definition for progression of chronic pancreatitis (CP) was proposed [1], with defined conditions of early, established, and end-stage CP. Regarding the diagnoses of the last two conditions (definite CP), they are easily diagnosed with identified parenchymal findings such as parenchymal loss (glandular atrophy), chronic inflammation, and fibrosis of the pancreas, in addition to ductal findings such as beading, dilated side-branch radicals, enlargement of the main pancreatic duct (MPD), and dystrophic intraductal calcifications. Diagnostic imaging modalities include transabdominal ultrasonography (US), endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging/cholangiopancreatography (MRI/MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) [2,3]. Furthermore, for the diagnosis of early CP, EUS plays a major role in elucidating subtle changes in the pancreatic parenchyma [4–6]. Although some guidelines for CP recommend CT or MRI for the first-line diagnosis of CP and either test should be the first choice for the diagnosis of CP [7,8], this chapter also describes the significance of minimally invasive tests such as US and plain abdominal radiography.

Transabdominal Ultrasonography

The simplest and least invasive imaging modality is US, which is regarded as the first imaging procedure when a patient has symptoms that suggest CP. Nevertheless, it must be understood as a limitation that, because of its low accuracy, US is useful only for the diagnosis of advanced CP [9]. A definite CP diagnosis based on US images is made when US shows a pancreatic duct stone, multiple or diffuse pancreatic calcifications, or obvious deformation of the pancreas with irregular dilation of the pancreatic duct [5] (Fig. 43.1). However, because a CP diagnosis based on US is susceptible to the effects of gastrointestinal tract fats and gas, its sensitivity is not high: 48–83% [10,11]. Consequently, some cases require other imaging procedures for CP diagnosis. It is also noteworthy that the usefulness of US for diagnosing early CP has not been established.

Recently, the performance of US-based CP diagnosis has been improved by the combined use of US elastography, which measures pancreatic stiffness [12]. US elastography, a new diagnostic tool, measures tissue elasticity (stiffness) by evaluating distortion and waves occurring after the addition of the external vibration energy to the tissue through manual compression and heartbeat. The pancreatic stiffness that is measured based on the shear wave elastography has been reported as correlated with CP progression [13].

Plain Abdominal Radiography

Plain abdominal radiography, a noninvasive and simple modality, can be used to diagnose radiopaque pancreatic calculus. Furthermore, it offers superior cost-effectiveness for the follow-up of patients with CP with evidence of a stone (Fig. 43.2) and those who experience a stone for the first time. The frontal view of the abdominal radiograph has presented difficulty for independently detecting pancreatic stones in some cases. Consequently, three-view abdominal radiography (i.e., frontal, left, and right views) has been adopted to improve this process [14–16]. The proportion of pancreatic calcifications in patients with CP is estimated as 17–60.8%; few patients

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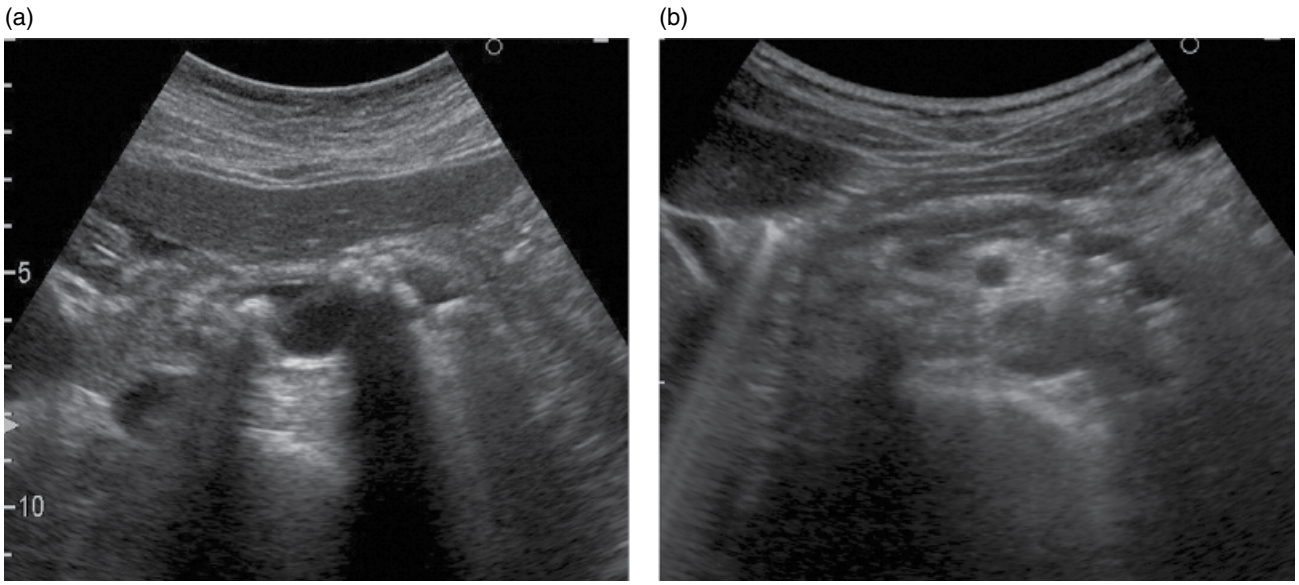


Figure 43.1 Transabdominal ultrasound images of the definite chronic pancreatitis (a and b). Both images of transabdominal ultrasound show multiple stones in the dilated pancreatic duct with atrophic parenchyma.

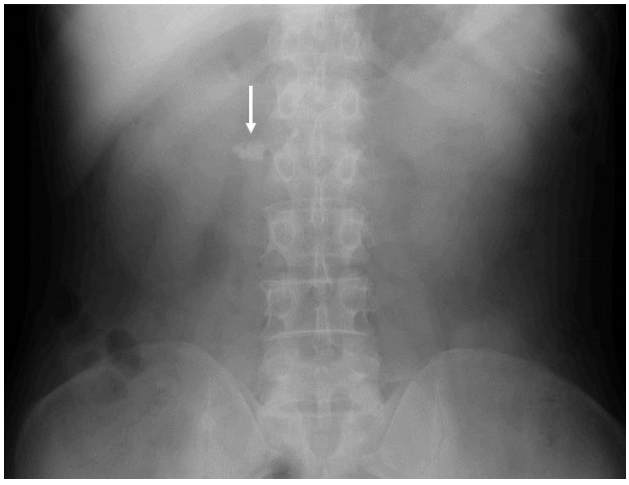


Figure 43.2 Plain abdominal radiography in patient with definite chronic pancreatitis. A pancreatic stone is seen (arrow).

are diagnosed with CP based only on abdominal radiography findings [17,18]. However, a diagnosis of noncalcified CP using this modality is difficult to reach.

Computed Tomography

Cross-sectional imaging is the most commonly used method to establish a diagnosis of CP. Actually, CT is a highly objective and minimally invasive imaging test. Furthermore, gastrointestinal fats and gas have little effect on the diagnostic performance of CT. A study in which several radiologists read CT images of 39 patients with CP based on the Cambridge classification and for which their interobserver variations were evaluated showed high interobserver reliability, indicating limited variation among CP diagnoses [19]. Therefore, CT is an excellent method for visualizing pancreatic calcifications/stones. It can also visualize apparent pancreatic alterations that show dilatation of the pancreatic duct with an uneven and irregular outline, which are findings for probable CP diagnosis. A systematic review that compared different imaging procedures in the diagnostic performance for CP showed excellent diagnostic performance of abdominal CT, with sensitivity of 75% (95% confidence interval [CI]: 66–83%) and specificity of 91% (95% CI: 81–96%) [2]. Other studies have also shown high diagnostic performance of abdominal CT for CP diagnosis, with sensitivity of 74–91% and specificity of 78–85% [20,21]. However, it should be understood that the pancreatic duct branches are poorly visualized on CT compared with MRCP or ERCP in some cases. Furthermore, the diagnosis of CP in older adults should be treated with caution, given that calcifications might be associated with other diseases in this population. Recently, the usefulness of virtua1 CT pancreatoscopy has been reported [22]. This modality has been shown to correlate closely with ERCP imaging. Actually, CT has no diagnostic significance for early CP. Furthermore, all imaging must be performed using a multidetector helical CT scanner [23], from the perspective that CP entails a high risk of carcinogenesis.

The classical CT findings in CP are dilatation of the pancreatic duct, pancreatic calcifications, and parenchymal atrophy (Fig. 43.3). Other CT findings include MPD dilatation and dilated secondary radicals. The MPD is

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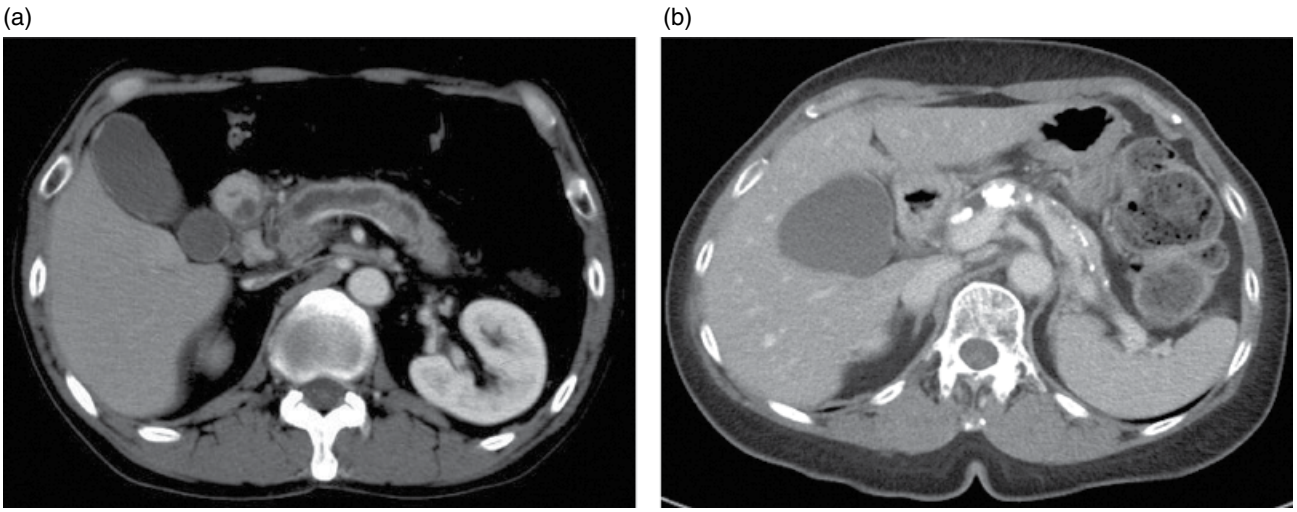


Figure 43.3 CT findings of the definite chronic pancreatitis. (a) CT shows dilated main pancreatic duct with marked atrophic parenchyma. (b) CT shows multiple stones in the dilated pancreatic duct with atrophic parenchyma.

classically beaded and irregular. However, the main duct might also be contoured regularly [24]. Results of an earlier study [25] indicated the frequency and characteristics of CP findings on CT as follows: a dilated pancreatic duct and secondary radicals were the most common findings, found in 68%, pancreatic atrophy in 54%, intraductal calcifications (scattered or clustered, focal, or diffuse) in 50%, pancreatic parenchymal atrophy in 54%, fluid collection in 30%, focal pancreatic enlargement in 30%, biliary duct dilation in 29%, and alterations in peripancreatic fat in 16%. However, normal appearance was identified in 7%, which presents difficulty for this diagnosis modality. In addition, CT is especially helpful in identifying complications of CP, including pseudocysts, portosplenic venous thrombosis, collaterals and arterial pseudoaneurysms, and pancreaticopleural fistulas [26,27].

MRI/MRCP

Actually, MRI with MRCP are widely acknowledged as more sensitive than CT for the detection of ductal and subtle parenchymal changes, especially during early stages of CP [28]. For instance, MRI is better than CT in displaying tissue contrast. Such characteristics evaluate fibrosis of the pancreatic parenchyma based on the enhancement pattern on T1-MRI, diffusion-weighted images [29], or contrast-enhanced MRI. Ductal abnormalities are very specific and reliable MRI signs of CP. The diagnostic ability of MRCP for CP has been reported as similar to that of ERP, with sensitivity of 87.7% and specificity of 94.0%. It is recognized that its diagnostic value is high from the viewpoint of adverse events. Moreover, among patients with CP classified into mild CP based on the Cambridge classification, MRCP identified nonuniform dilatation of the pancreatic duct branches in 79% and 73% of patients with calcified pancreatitis and those with noncalcified pancreatitis, respectively [30]. This finding demonstrates that MRCP can visualize a tiny pancreatic change. A recent meta-analysis has revealed that the diagnostic performance of MRCP is similar to that of ERCP for CP diagnosis, with sensitivity of 78% and specificity of 96% [31]. However, although the diagnostic ability of MRI/MRCP for pancreatic calculus is lower than that of CT (direct diagnosis of this situation using MRI/MRCP is difficult), MRI/MRCP can indirectly diagnose pancreatic calculus based on lucencies in the main pancreatic duct or its branches; its diagnostic performance is higher than 90% [32]. However, this diagnosis should be treated with caution, given that, in some cases, a small stone in the main pancreatic duct and its branches is not visible as a lucent structure on MRI/MRCP [33]. Furthermore, MR elastography has been conducted. It showed a promising technique for detecting and quantifying pancreatic stiffness. It is related to fibrosis and is apparently useful for assessing the treatment response and clinical follow-up of pancreatic diseases [34].

Definite CP diagnoses using MRCP have been made based on the following findings: irregular dilation of the pancreatic duct branches that are unevenly distributed in the entire pancreas, irregular main pancreatic duct dilation, and the presence of a protein plug (Fig. 43.4) [5,6]. In addition to evaluation of pancreatic duct abnormalities, MRI is extremely sensitive for the detection of parenchymal abnormalities. The parenchymal features of CP include, in addition to atrophy, abnormal decreased signal intensity on fat-suppressed T1-weighted images and delayed and limited enhancement after contrast administration, reflecting fibrosis of the pancreatic parenchyma [24,35]. Stimulation

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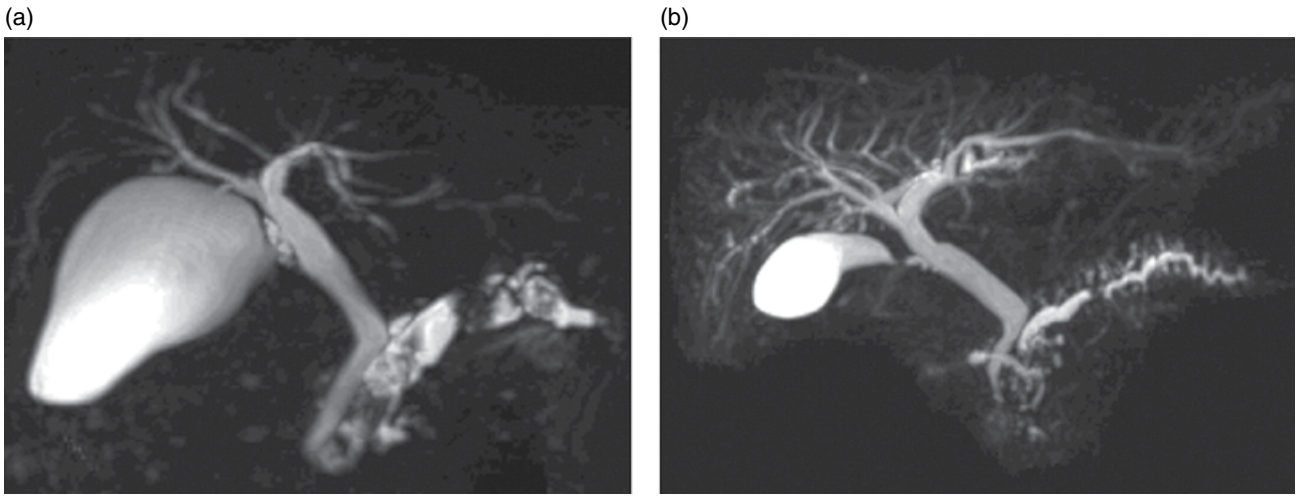


Figure 43.4 MRCP findings of the definite chronic pancreatitis. (a) MRCP shows stones/protein plugs in the dilated irregular main pancreatic duct. (b) MRCP shows irregular dilatation of the main pancreatic duct and side branches in the entire pancreas.

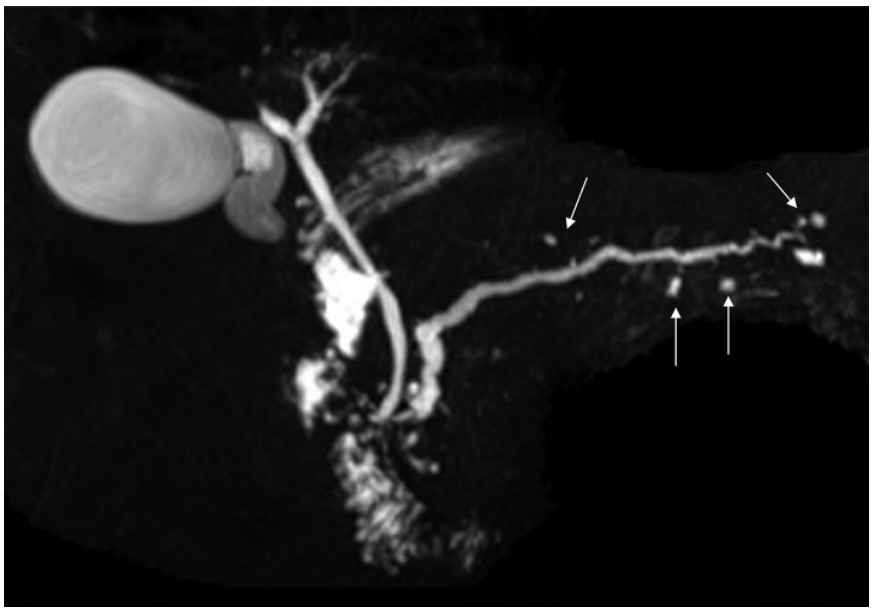


Figure 43.5 MRCP imaging of the early chronic pancreatitis. Several abnormal side branches (dilation, arrows) are found in the body to tail.

of the pancreas using intravenous secretin might improve the diagnostic accuracy for the detection of ductal and parenchymal abnormalities seen in CP.

In addition, MRI/MRCP has high performance for the diagnosis of early CP. Signal intensity changes in the pancreas, as seen on MRI, might precede ductal abnormalities and suggest early CP. Subtle signal intensity decreases within the gland, especially on fat-suppressed T1-weighted images, are extremely important to realize that these parenchymal abnormalities might precede the ductal abnormalities in the early stage [36]. A recent study also showed that T1 mapping can distinguish subtle parenchymal changes seen in early stage CP. It shows promise for implementation in routine imaging protocols for the diagnosis of CP [37]. In addition, in the Japanese criteria for early CP [6], its findings are defined as irregular dilation of at least three pancreatic duct branches, which are taken with an MRCP at a magnetic field strength of 3.0 tesla (Fig. 43.5). Because of the recent progress in MRCP resolution that is associated with the advancement of MRI instruments, MRCP is positioned as an examination method with similar ability to ERCP in these diagnostic criteria. Moreover, high diagnostic performance of secretin-loaded MRCP for early CP has been demonstrated.

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EUS

By enabling detailed observation of the pancreatic parenchyma, EUS plays an important role in early CP diagnosis. In fact, it allows high-resolution imaging and close-up pancreatic observation. Normal pancreatic parenchyma that is visualized by EUS shows a homogeneous echo pattern, with echo intensity that is similar to or slightly higher than that of the liver (i.e., a fine reticular pattern). Moreover, EUS shows no tortuous main pancreatic duct or dilated pancreatic duct branches in an echo of the normal pancreatic parenchyma. The pancreatic duct on EUS shows a slightly hyperechoic wall, which is observed as a uniformly linear echo, with diameter of approximately 2.4 mm (head), 1.8 mm (body), and 1.2 mm (tail) [38]. Abnormal pancreatic images are defined based on these findings.

The Rosemont classification, which was developed based on expert opinion in 2009, has been used widely to diagnose CP with EUS (Table 43.1) [39]. This system assigns different weights (major A, major B, and minor) to different findings. Parenchymal major A criterion included hyperechoic foci with shadowing and well-circumscribed lobularity. In fact, the only ductal major A criterion was MPD calculi. The only parenchymal major B criterion was lobularity with honeycombing. Minor parenchymal criteria were cysts, stranding, nonshadowing hyperechoic foci, and lobularity with noncontiguous lobules. Minor ductal criteria were dilated ducts (body ≥3.5 mm and tail ≥1.5 mm), irregular MPD contour, dilated side branches of 1 mm or more, and hyperechoic duct margin. The diagnosis of CP based on the Rosemont classification was consistent if one of the following was

Table 43.1 The Rosemont criteria.

Parenchymal criteria

- Major A
  - Hyperechoic foci (>2 mm in length/width with shadowing)
- Major B
  - Lobularity (≥3 contiguous lobules = "with honeycombing")
- Minor
  - Cyst (anechoic, round/elliptical with or without septations)
  - Hyperechoic strands (≥3 mm in at least 2 different directions with respect to the imaged plane)
  - Hyperechoic foci (>2 mm in length/width with no shadowing)
  - Lobularity (noncontiguous lobules = "without honeycombing")

Duct criteria

- Major A
  - MPD calculi (echogenic structure[s] within the MPD with acoustic shadowing)
- Minor
  - MPD dilation (≥3.5 mm in body or >1.5 mm in tail)
  - Irregular MPD contour (uneven or irregular outline and ectatic course)
  - Dilated side branches (>3 tubular anechoic structures each measuring ≥1 mm in width, budding from the MPD)
  - Hyperechoic MPD margin (echogenic, distinct structure >50% of entire MPD in the body and tail)

Classification based on endoscopic criteria

- **Consistent with CP**
  - A) 1 major A feature (+) ≥3 minor features
  - B) 1 major A feature (+) major B feature
  - C) 2 major A features
- **Suggestive of CP**
  - A) 1 major A feature (+) <3 minor features
  - B) 1 major B feature (+) ≥3 minor features
  - C) ≥5 minor features (any)
- **Indeterminate for CP**
  - A) 3 to 4 minor features, no major features
  - B) major B feature alone or with <3 minor features
- **Normal**
  - ≤2 minor features, no major features

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present: (i) 1 major A feature + ≥3 minor features; (ii) 1 major A feature + major B feature; or (iii) 2 major A features. All other combinations of features were categorized as suggestive, indeterminate, or normal. The validity of EUS diagnostic items used in the Rosemont classification has been established in a study evaluating risk factors for CP [40]. A recent systemic review indicated the diagnostic accuracy of several imaging procedures, with the implication that the diagnostic performance of EUS is similar to that of ERCP/CT/MRI, with diagnostic accuracy of 81% (95% CI: 70–89%) and a specificity of 90% (95% CI: 82–95%) [41].

For the diagnosis of early CP, the Japan Pancreas Society established the revised EUS criteria for early CP in 2019 [6] based on the Rosemont classification. Early CP has been diagnosed if a patient has two of the following four criteria (Fig. 43.6): (i) lobularity (honeycombing or non-honeycombing), (ii) hyperechoic foci (nonshadowing or stranding, (iii) dilated side branches, and (iv) hyperechoic main pancreatic duct margin. These findings and clinical signs are combined to diagnose early CP. A recent study showed that EUS findings for ECP according to Japan's above criteria, lobularity, and the hyperechoic margin of the pancreatic duct might highly correspond to the pathological findings of chronic inflammation. In addition, although a great limitation in the use of EUS for evaluating CP has been its poor interobserver reliability, especially in diagnosis for early CP, a recent study [42] demonstrated high reliability for the criteria above. Consequently, results suggest that EUS can be useful for diagnosing early CP. Nevertheless, some reports have described the usefulness of EUS elastography (including shear-wave elastography) for CP diagnosis [43]. This modality is particularly useful to distinguish the diagnosis between normal pancreas confused with CP and early CP on B-mode EUS.

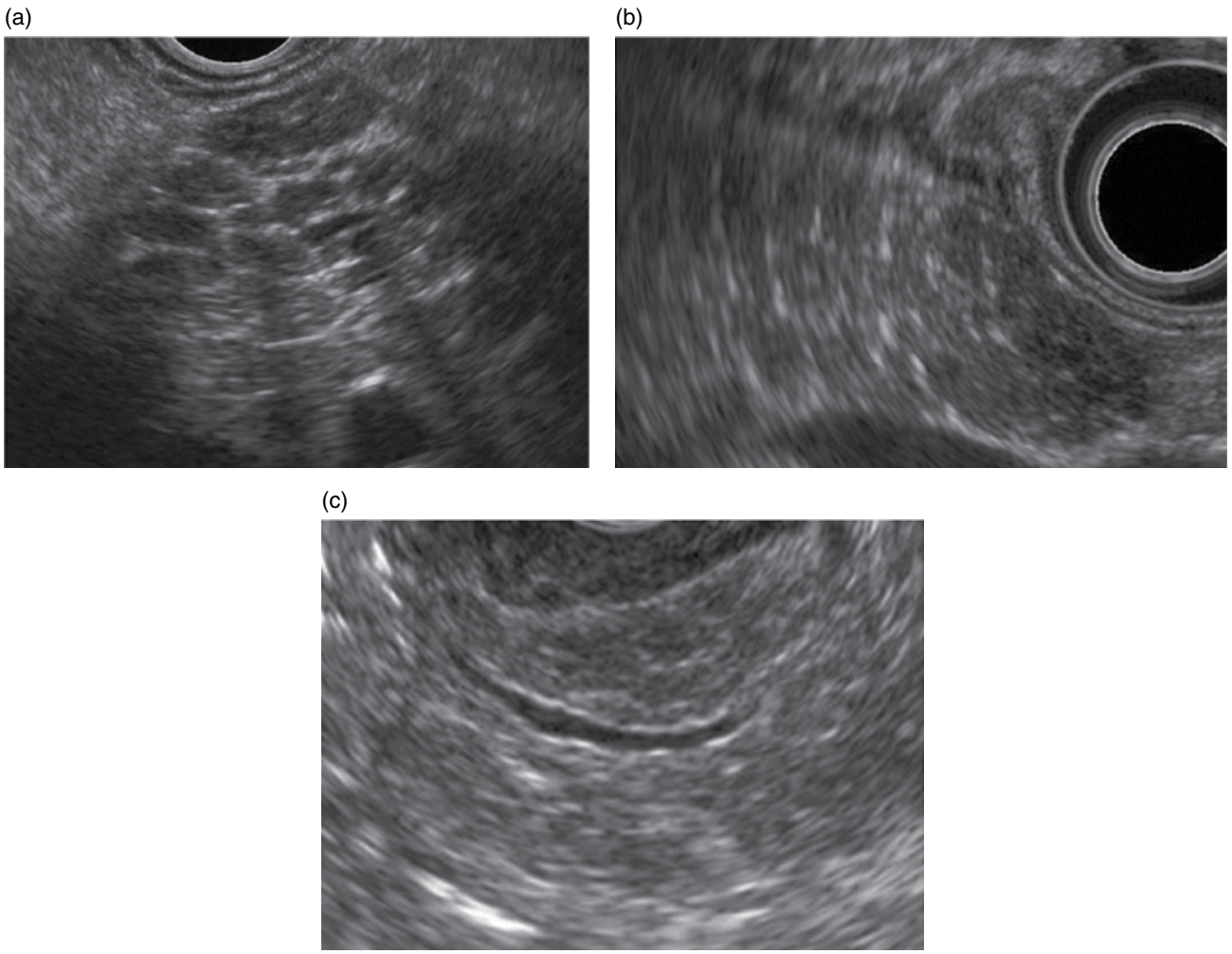


Figure 43.6 EUS findings of the early chronic pancreatitis. (a) Lobularity (honeycomb). (b) Hyperechoic foci without shadow and stranding. (c) Hyperechoic ductal margin.

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As described above, EUS is a useful modality for the diagnosis of CP, especially in the early stage. However, the following points should be noted when applying EUS for CP diagnosis: EUS findings must be interpreted with caution because of the inability to distinguish the clinically and metabolically benign asymptomatic fibrosis from true CP.

Endoscopic Retrograde Cholangiopancreatography

A high-performance modality with high sensitivity and specificity is ERCP [43]. The diagnostic performance of ERCP for CP is better than that of abdominal US and CT, with a sensitivity of 70–90% and a specificity of 89–100% [44,45]. It was reported that an association between pancreatic duct branch changes on ERCP and histological findings of the pancreatic parenchyma in patients with CP who underwent pancreatectomy [46].

However, while ERCP can provide information that is invaluable in managing CP, the development of post-ERCP pancreatitis, a rare but crucial life-threatening complication, is a significant problem in the diagnostic ERCP. Therefore, ERCP as diagnostic imaging has been replaced by MRCP in recent years. Conversely, ERCP has superiority over other modalities in that it enables pathological examination of pancreatic ductal abnormalities. Thus ERCP plays an important role in making a differential CP diagnosis from pancreatic cancer.

The diagnosis of CP by ERP is made on the basis of changes in the MPD and side branches, requiring a quality pancreatogram to most accurately delineate the ductal anatomy [47]. A definitive CP diagnosis based on ERCP is made when the following findings are observed: irregular dilation of the main pancreatic duct with nonuniform and irregular dilation of the pancreatic duct branches that are unevenly distributed in the entire pancreas (Fig. 43.7) [5,6]. In addition, the following are also significant findings unique to ERCP: irregular dilation of the main pancreatic duct and its branches in the papillary

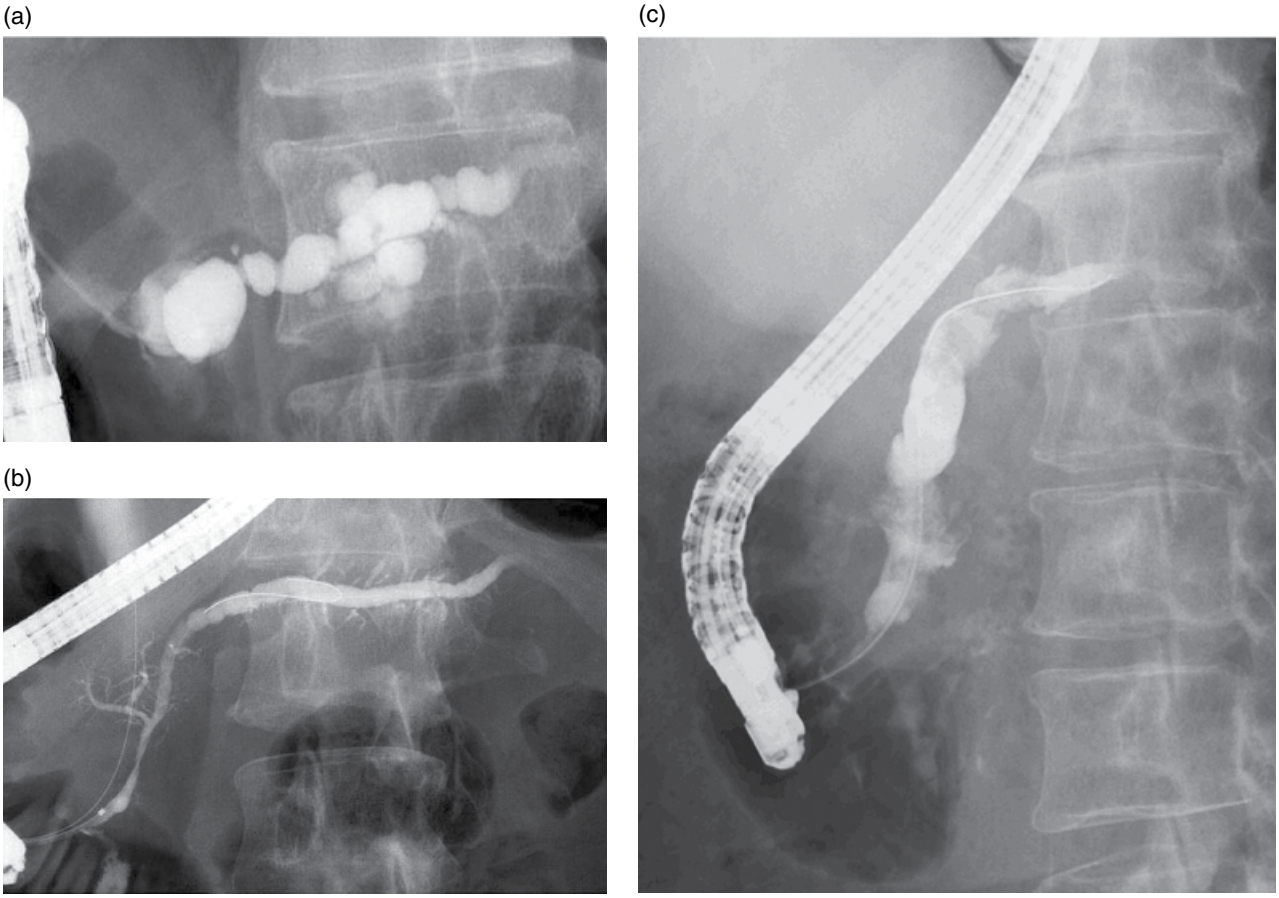


Figure 43.7 ERCP findings of the definite chronic pancreatitis. (a) Marked dilation and irregular of main pancreatic duct. (b) Irregular main pancreatic duct with dilated side branches. (c) Dilated irregular main pancreatic duct with multiple stones.

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side of occlusion or stenosis by a pancreatic stone and a protein plug [5,6]. ERCP findings are also useful for CP-grade classification.

The most accepted criteria for scoring ductal changes on pancreatograms are the Cambridge criteria [47], which grade pancreatograms from normal or equivocal to mild, moderate, or severe CP based on main duct and side branch abnormalities. Main duct abnormalities include dilation, narrowing, strictures, filling defects, and leaks or cavities. The side branch may be of normal length or shortened; its caliber may be normal, dilated, or narrowed, and the contour may be smooth or irregular. The grading is defined as follows: normal, equivocal (normal except for fewer than three abnormal side branches), mild (more than three abnormal side branches but normal main duct), moderate (abnormal main duct with or without branch changes), and severed (as moderate pancreatitis but also at least one of the following: duct obstruction, severe irregularity or dilatation, ductal filling defects, or a cavity) [48]. At the moment, these criteria are often used for MRCP grading, but recent study has shown that there is a lack of strong concordance between ERCP- and MRCP-based grading of CP using the Cambridge criteria. MRCP had moderate to good performance in diagnosing side-branch predominant versus main-duct predominant CP [49]. Thus, it will be required to revise the standard in the future. In addition, for diagnosis of early CP, Japanese criteria for early CP [6] defined the ERCP image of early CP according to the Cambridge criteria: irregular dilation of at least three pancreatic duct branches (Fig. 43.8).

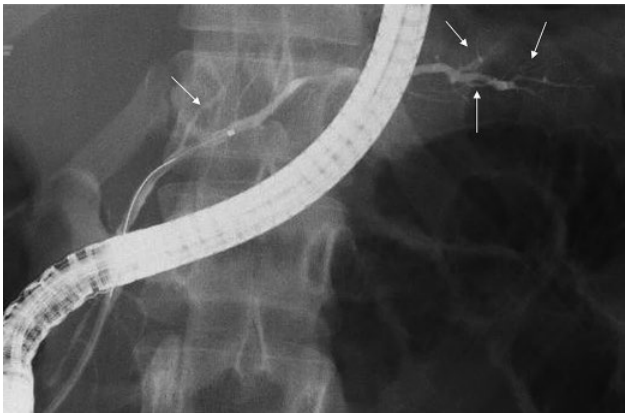


Figure 43.8 ERCP findings of the early chronic pancreatitis. Several abnormal side branches (arrows) with nondilated main pancreatic duct are seen.

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44

Endoscopic Ultrasound for Diagnosis of Chronic Pancreatitis Versus Pancreatic Cancer

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Introduction

Despite recent advances in diagnostic procedures, differential diagnosis of solid pancreatic masses remains a challenge. Chronic pancreatitis increases the risk of pancreatic cancer, thus making more complex the differential diagnosis between both diseases. Essential methods for the diagnosis and differentiation of pancreatic tumors are multidetector CT scan (MDCT), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) and its associated techniques [1]. Among all these diagnostic modalities, EUS associated with guided tissue sampling, elastography, and contrast enhancement has emerged as the key method. The role of EUS and associated techniques in the differential diagnosis between malignant lesions and mass-forming chronic pancreatitis or focal autoimmune pancreatitis is discussed here.

Endoscopic Ultrasound for the Differential Diagnosis of Solid Pancreatic Tumors

EUS provides high-resolution images of both pancreatic parenchyma and pancreatic ducts, and it is considered to be one of the most accurate methods for the diagnosis and staging of chronic inflammatory, cystic, and neoplastic diseases of the pancreas. When compared with transabdominal ultrasound (TUS), EUS can provide images with high resolution by using high-frequency ultrasound due to its proximity to the pancreas. Furthermore, while the TUS imaging of the head and tail of the pancreas is often hindered by intestinal gas, EUS allows the imaging from head to tail of the pancreas by scanning through the gastric and duodenal wall.

The usefulness of EUS in comparison with CT has been reported as well [2,3]. Among 22 studies covering 1170 patients, the median sensitivity of EUS for the detection of pancreatic tumors was 94%. The sensitivity of EUS was shown to be superior to that of CT (98% vs. 74%) in 19 comparative studies ($n = 895$). The sensitivity of EUS was also shown to be superior to that of TUS (94% vs. 67%) in four comparative studies ($n = 259$). All these data are summarized in a recent review from Kitano et al. [4]. Furthermore, the advantage of EUS is more prominent in small lesions. EUS is accepted to be the most sensitive technique for detection of small pancreatic tumors (<2 cm). In a recent systematic review of patients with suspected pancreatic lesion based on indeterminate CT scan [5], EUS detected a pancreatic mass with a mean size of 21 mm in 70% of the patients. The sensitivity of EUS diagnosis of malignancy was 85%; however, specificity remained as low as 58%. In summary, despite recent development of cross-sectional imaging modalities, EUS plays a major role in the detection of pancreatic lesions, especially those so small that they cannot be detected by CT scan.

Once detected, the main point is to characterize the tumor. To differentiate between different types of pancreatic neoplasms by B-mode EUS is challenging. Typically, pancreatic cancer is an ill-defined, hypoechoic, and heterogeneous lesion (Fig. 44.1), but those tumors can often show atypical imaging findings. Inflammatory tumors (mainly in the setting of a chronic pancreatitis) (Fig. 44.2), metastatic tumors (being primary tumor lung cancer, breast cancer, renal cancer, colon cancer), pancreatic lymphomas or solid pseudopapillary tumors are part of the differential diagnosis [4]. Although EUS imaging is not able to

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Figure 44.1 Endoscopic ultrasound of a pancreatic adenocarcinoma, with irregular borders, and infiltration of surrounding vessels.

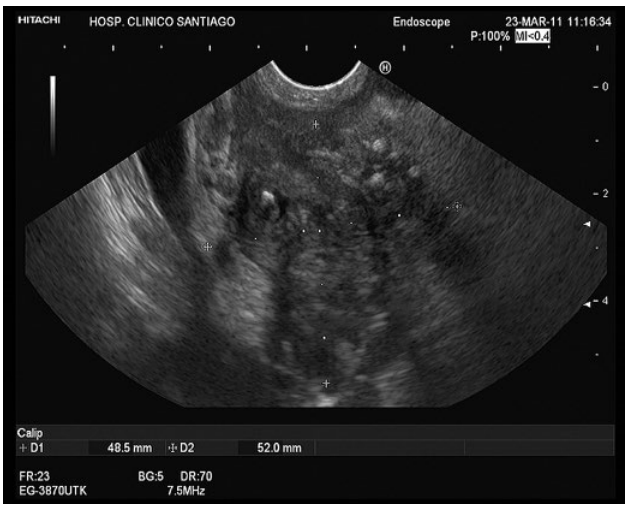


Figure 44.2 Endoscopic ultrasound of a mass-forming chronic pancreatitis showing an irregular heterogenic pattern, predominantly hypoechoic, with no infiltration of surrounding vessels, and the presence of calcifications.

differentiate reliably between malignant and benign inflammatory lesions, echotexture of the lesion and the rest of the pancreas provides very important additional information, such as boundary, ductal characteristics, lymphadenopathy, and vascular involvement. Features favoring a pseudotumor include homogeneous pattern with hyperechoic septations, calcifications, cysts, multilobular appearance, and positive Doppler signals in the lesion (Fig. 44.2). Conversely, as previously stated, pancreatic cancer usually appears as a hypoechoic mass, periductal hypoechogenicity, and displacement of calcifications (Fig. 44.1). The sensitivity and specificity of EUS are 64% and 75%, respectively, for the detection of pancreatic cancer in chronic pancreatitis [6,7]. However, in the presence of a pseudotumor, EUS alone cannot distinguish pancreatic cancer from mass-forming chronic pancreatitis. This is partly because changes like internal and/or peripheral calcifications, typical of advanced chronic pancreatitis, are also present in a proportion of pancreatic malignancies. A recent study showed that lobularity without honeycombing was more frequently observed in cases of pancreatic cancer ($P = 0.018$; OR: 12.65) [8].

Advanced techniques associated with EUS (tissue acquisition, contrast enhancement, and elastography) can improve the diagnostic accuracy of EUS in this context.

Endoscopic Ultrasound-Guided Sampling

The role of EUS-guided sampling in the diagnosis of solid pancreatic tumors has been evaluated in several well-designed studies. Reported accuracy for malignancy ranges from 79% to 92% [9–11]. This accuracy may be even higher using onsite evaluation of the sample by an experienced pathologist [12]. Furthermore, in addition to differentiating between benign and malignant lesions, EUS-guided sampling can also establish the final pathological diagnosis (Fig. 44.3).

New needles have been designed over the last years that increase the diagnostic capabilities of EUS-guided sampling. Recent reported accuracy reaches 90–95%, with the advantage of providing tissue cores, allowing histological evaluation of the samples obtained [13]. Among them Fork-tip, Franseen needle, and Procore™ have shown the best results, with a clear improvement



Figure 44.3 Endoscopic ultrasound-guided sampling of a solid pancreatic tumor (final diagnosis was pancreatic adenocarcinoma).

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shown with the Fork-tip and Franseen needle tip [11]. The ability of these needles to obtain histological and cytological samples has been reported to be superior compared to cytological needles. In fact, both the Franseen-tip and the Fork-tip needles demonstrated excellent diagnostic accuracy (>90%), with or without rapid onsite evaluation [14]. Their high rate of tissue adequacy was not associated with an increase in adverse events, and a smaller number of needle passes were needed, with a single pass resulting in a diagnostic accuracy over 95%. Nevertheless, results of a recent meta-analysis could not establish a clear benefit of core needles over cytological needles in terms of diagnostic accuracy for pancreatic lesions [15].

Some drawbacks of EUS-guided sampling need to be emphasized. The procedure is not feasible in about 6–9% of cases due to vessel interposition, duodenal stenosis, or tumor hardness, particularly in chronic pancreatitis. On some occasions, sample adequacy is not enough for diagnosis. A systematic review of 53 studies reported a negative predictive value of EUS-guided sampling for the diagnosis of pancreatic adenocarcinoma of 60–70% [16]. Hence, a second puncture is needed to exclude malignancy in some cases where the first result was of benignity. Given the high accuracy for the evaluation of pancreatic tumors, it can be concluded that routine EUS-guided sampling can be recommended for the differential diagnosis of solid pancreatic masses [17].

Sensitivity of EUS-guided tissue acquisition is lower in the context of chronic pancreatitis compared to normal surrounding parenchyma. Fritscher-Ravens et al. found that sensitivity of EUS-guided fine-needle aspiration (FNA) in patients with a focal pancreatic lesion without chronic pancreatitis was 89%, while it was only 54% in patients with chronic pancreatitis [18]. Varadarajulu et al. investigated 282 patients with pancreatic solid tumors. Sensitivity of EUS-guided FNA for malignancy was lower in the group of patients with concurrent chronic pancreatitis compared to those without it (73.9% vs. 91.3%; $P = 0.02$). There were no differences in terms of specificity (100% vs. 93.8%), and overall accuracy (91.5% vs. 91.4%) [19]. In a study by Ardengh et al. including 69 pancreatic masses in patients with chronic pancreatitis, EUS-guided FNA increased the diagnostic sensitivity, specificity, and overall accuracy of EUS for the differential diagnosis between inflammatory process and pancreatic adenocarcinoma (72.7% vs. 63.6%, 100% vs. 75.9%, 95.7% vs. 73.9%, respectively) [20]. Takahashi et al., evaluated 62 patients with pancreatic cancer and 15 with focal pancreatitis, reporting sensitivity, specificity, overall accuracy, positive predictive value, and negative predictive value of cytopathologic diagnosis of 82%, 100%, 86%, 100%, and 58%, respectively. They also observed K-ras point mutations in 74% of pancreatic cancers and 0% of focal pancreatitis lesions [21]. Ogura et al. have also shown that the determination of K-ras mutations in EUS biopsy samples can increase the diagnostic accuracy of this procedure, since these mutations are present in 87% of pancreatic cancer, but only in 3% of mass-forming chronic pancreatitis [22]. More recently, Xie et al. identified in their series 44 patients with chronic pancreatitis out of 234 cases submitted for EUS-guided sampling for solid pancreatic lesions, and sensitivity (80% vs. 95%, $P = 0.020$) and accuracy (86% vs. 95%, $P = 0.043$) were significantly lower in patients with chronic pancreatitis compared to those without chronic pancreatitis [23]. Kurita et al. aimed to investigate whether chronic pancreatitis influences the diagnostic ability of EUS-guided sampling for pancreatic lesions ≤10 mm. In a multivariate analysis of factors influencing the accuracy of EUS-guided sampling, chronic pancreatitis significantly lowered the accuracy ($P = 0.048$; OR: 9.21). Among pancreatic cancer patients, the number of chronic pancreatitis patients was significantly higher than the number of patients with benign lesions ($P = 0.023$) [8]. Finally, a recent systematic review and meta-analysis conducted by Abdallah et al. with the aim of evaluating the diagnostic performance of EUS-guided sampling for detecting pancreatic malignancy in chronic pancreatitis showed a pooled sensitivity of 65% (95% CI 52.6–75.6%), and specificity of 96.8% (75–99.7%) [24]. In the same study, the sensitivity of EUS-guided sampling for diagnosing pancreatic malignancy in the absence of chronic pancreatitis was 91.5 vs. 65.3% (OR [95% CI] 5.5 [2.9–10.2]) compared to patients with chronic pancreatitis [24].

Endoscopic Ultrasound-Guided Elastography

Different pathological processes, including inflammation, fibrosis, and cancer, alter tissue elasticity differently, which result in distinct elastographic appearance [25,26]. EUS-guided elastography has been shown to be highly accurate for the differential diagnosis of solid pancreatic tumors. A homogeneous green pattern usually represents normal pancreatic parenchyma. A heterogeneous, predominantly green pattern with slight yellow and red lines is present in inflammatory pancreatic masses (Fig. 44.4). A heterogeneous, predominantly blue pattern with small green areas and red lines and a geographic appearance is present mainly in pancreatic malignant tumors, including pancreatic adenocarcinoma (Fig. 44.5). Finally, a homogeneous blue pattern is found in pancreatic neuroendocrine malignant lesions. Pancreatic cancer can be excluded with a high accuracy in lesions with a predominantly

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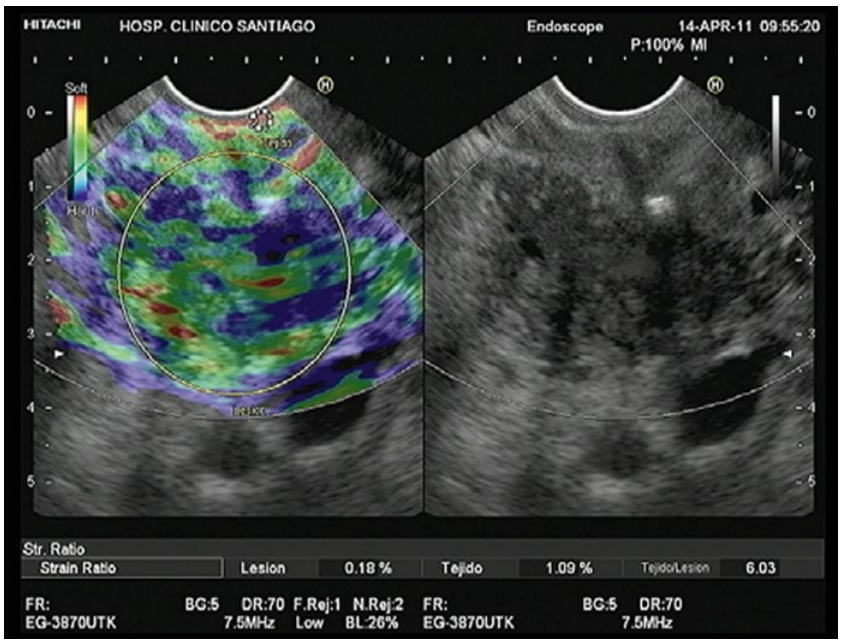


Figure 44.4 Endoscopic ultrasound-guided elastography from a mass-forming chronic pancreatitis, showing the typical green heterogeneous predominant pattern.

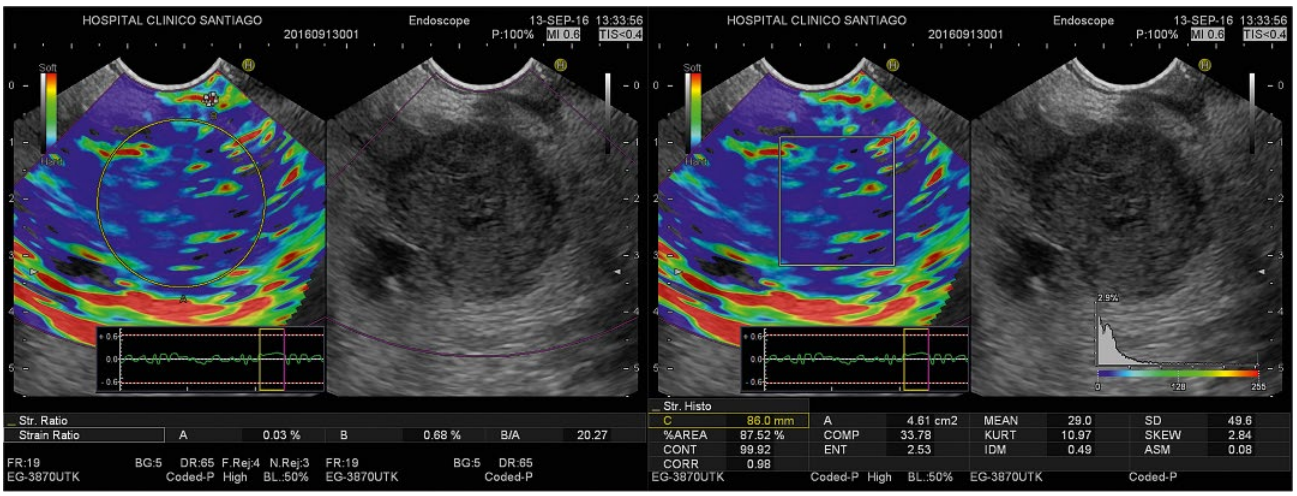


Figure 44.5 Endoscopic ultrasound-guided elastography from a pancreatic cancer, with a heterogeneous blue predominant pattern, showing a strain ratio of 20.27, and a strain histogram of 29.

soft (green) pattern [27]. Chronic pancreatitis can be differentiated from pancreatic cancer by a difference in the elastography appearance in most of the cases. It is important to highlight the different pattern in cases of autoimmune pancreatitis, characterized by a diffuse stiff pattern in the pancreatic parenchyma, not just in the focal mass [25,26].

Elastography can also be evaluated in a quantitative manner by calculating the ratio between the strain in the region of interest and a reference area in surrounding soft tissue (strain ratio) or evaluating the strain histogram of the selected area. Malignant pancreatic masses and neuroendocrine tumors produce higher strain ratios and lower strain histograms than inflammatory masses and normal parenchyma. It has been suggested that a strain ratio of >10 or a mean strain histogram value of <50 is associated with malignancy [26,28,29] (Fig. 44.5). Color patterns, strain ratio, and strain histogram values for the evaluation of solid pancreatic lesions are shown in Tables 44.1 and 44.2.

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Table 44.1 Elastographic patterns classification.

Color and pattern	Stiffness	Malignancy
Homogeneous blue predominant	Hard	Yes
Heterogeneous blue predominant (Fig. 44.3)	Hard	Yes
Heterogeneous green predominant (Fig. 44.4)	Intermediate	No
Homogeneous green predominant (Fig. 44.5)	Soft	No
Heterogeneous green and blue without predominant color	Intermediate hard	Undetermined

Table 44.2 Elastographic values on quantitative evaluation.

Strain ratio	Strain histogram	Malignancy
>10	<50	Yes
<10	>50	No

Different meta-analysis have evaluated the diagnostic performance of EUS elastography for the characterization of malignant pancreatic tumors. Overall, a high sensitivity (92–98%), but a low specificity (67–76%) have been reported [30,31]. No significant advantage of semi-quantitative strain elastography over qualitative strain elastography has been demonstrated. The low specificity can explain the difficult interpretation of cases with chronic calcifying pancreatitis. Calcifications show a hard blue pattern, as expected, so it is important in these cases to evaluate the areas where no calcifications are present. In a recent multicenter study, 50% of solid pancreatic lesions ≤15 mm proved to be soft, and the probability of a soft lesion to be malignant was negligible [32]. Therefore, due to its very high negative predictive value for malignancy, EUS elastography may have a specific value for the evaluation of small pancreatic lesions. A topic of specific interest in the evaluation of chronic pancreatitis cases is the role of elastography to detect blue spots (hard tissue) inside the mass-forming chronic pancreatitis, to target the area of sampling. A study on 54 patients with solid pancreatic lesions, using a 25-gauge EUS needle that was inserted into the most suspicious part of the lesion according to EUS elastography (Fig. 44.6), reported a positive diagnosis of carcinoma in 85% of patients. The diagnostic accuracy, sensitivity, and specificity of the combination EUS-elastography/FNA was 94%, 93%, and 100%, respectively [33].

Endoscopic Ultrasound-Guided Contrast Enhancement

Contrast enhanced harmonic EUS (CEH-EUS) is a methodology to further improve the EUS-based differential diagnosis of solid pancreatic tumors. The development of microbubble-based contrast agents together with technological advances and refinement in ultrasound technology has led to improved imaging of fine vascular structures and visualization of microflow patterns within target lesions [34,35].

Lesions of interest should be reported and documented in terms of their specific contrast enhancement by looking separately into the arterial phase and the venous phase over time. Thereby, the temporal behavior of signals can be assessed and compared with those signals arising from the surrounding tissues (non-, hypo-, iso-, or hyperenhancement) and with its contrast distribution (homogenous or heterogeneous). Besides qualitative descriptions, the intensity of depicted contrast signals can be quantified by the calculation of time–intensity curves both during the wash-in and wash-out phases [36]. Several parameters can be calculated for further reviews such as peak enhancement, rise time, wash-in and wash-out rate, area under the curve, and others.

The main contrast agent available is SonoVue/Lumason (Bracco Imaging, Milan, Italy), containing microbubbles composed of sulfur hexafluoride gas enclosed in a lipid shell. After intravenous injection, the pancreatic arterial phase occurs within 15–30 s before a venous phase starts approximately 30–45 s after injection [36].

CEH-EUS can differentiate the nature of solid pancreatic lesions, particularly pancreatic ductal adenocarcinoma that is typically hypoenhanced (Fig. 44.7). In this regard, pancreatic adenocarcinoma differs from other solid lesions such as neuroendocrine tumors, pancreatic metastases, or pseudotumoral (mass-forming) focal chronic pancreatitis. Both mass-forming chronic pancreatitis and autoimmune pancreatitis present as iso- or hyperenhanced pseudotumors as opposed to the hypoenhanced lesions associated with pancreatic adenocarcinoma. Contrast enhancement can also be used to assess therapeutic response in the treatment of autoimmune pancreatitis [35].

Several meta-analyses have shown the accuracy of this methodology in the differential diagnosis of solid pancreatic tumor, mainly for the detection of pancreatic cancer. Sensitivity ranges from 85% to 90%, and specificities from 80% to 90% [37–39]. A large multicenter trial that included 167 consecutive patients indicated that peak enhancement, wash-in area under the curve, wash-in rate, and the wash-in perfusion index were significantly different in patients with chronic pancreatitis

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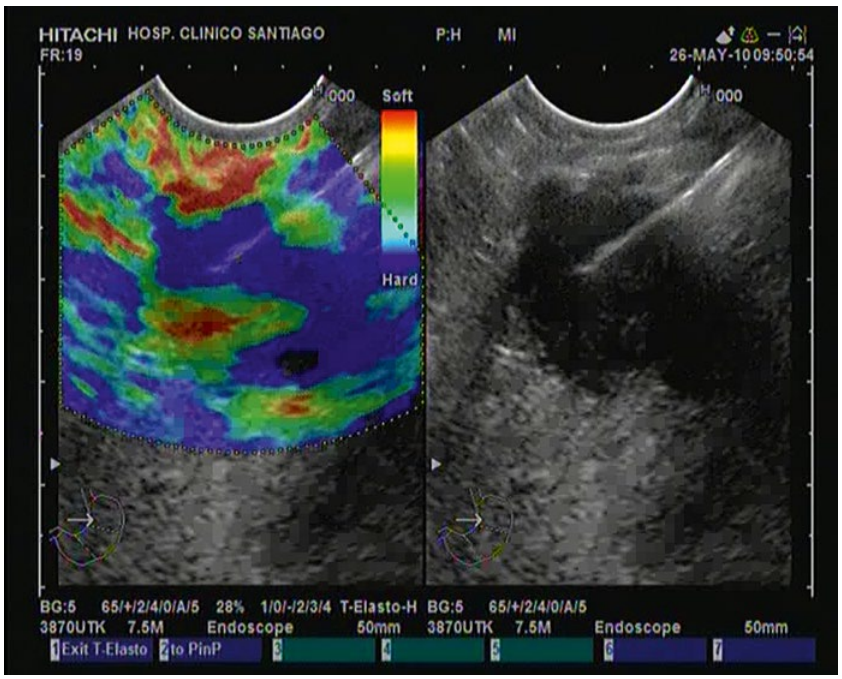


Figure 44.6 Endoscopic ultrasound-guided sampling from a pancreatic solid tumor, guided by elastography (targeting the blue area of the lesion).

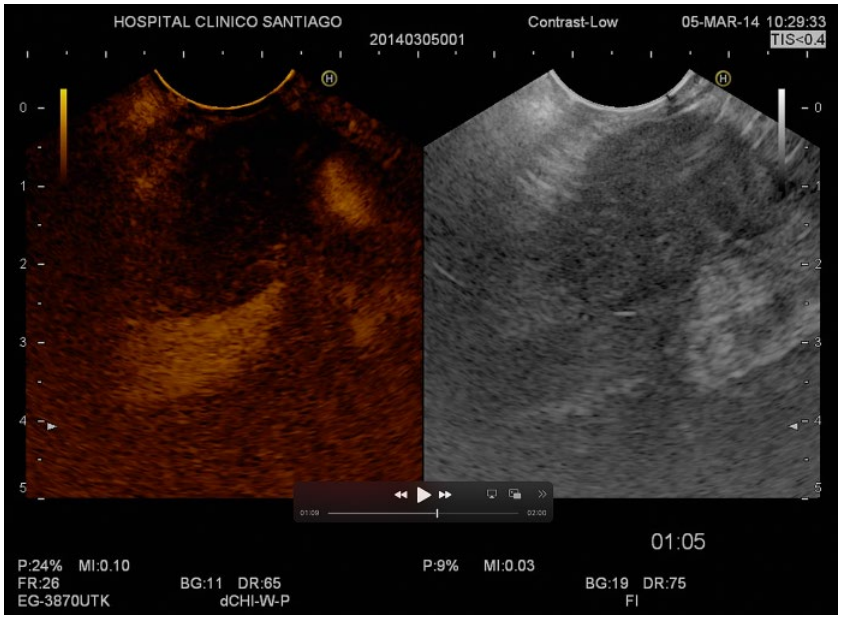


Figure 44.7 Contrast-enhanced harmonic endoscopic ultrasound of a pancreatic solid tumor, a pancreatic adenocarcinoma, showing the typical hypoenhanced pattern.

and pancreatic cancer [40]. Furthermore, using a model of artificial neural networks for the parameters listed above, the authors found an increased sensitivity (94%), specificity (94%), positive predictive value (97%), and negative predictive value (90%). The diagnostic yield of CEH-EUS for the diagnosis of pancreatic cancer versus other tumors in lesions <15 mm has been confirmed in a recent multicenter trial including 219 patients, indicating an overall 89% accuracy [41]. Recently, time–intensity curve analysis has also been used with a high diagnostic accuracy of 91% to characterize focal pancreatic lesions [42].

Contrast-enhanced EUS can also be used for targeting EUS-guided sampling. However, a recent study has shown that diagnostic rates for samples obtained using 22-gauge needles with standard EUS-guides sampling

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and CEH-EUS-guided sampling were not significantly different [43]. However, the use of CEH-EUS may reduce the number of needle passes needed to reach a diagnosis as compared to conventional techniques [44].

Combination of EUS-Guided Advanced Imaging and Tissue Sampling

The combined use of different EUS technologies has been shown to improve the diagnosis of solid pancreatic lesions. A recent meta-analysis selected 17 studies evaluating elastography, contrast enhancement, and tissue sampling for pancreatic lesions. The pooled sensitivity and specificity were for qualitative elastography respectively, 97% and 67%; for strain ratio 98% and 62%; for contrast enhancement 90% and 76%; and for tissue acquisition 84% and 96% [45]. Iglesias-García et al. showed an overall accuracy for malignancy using elastography, CEH-EUS, their combination, and EUS-guided tissue acquisition of 98.4%, 85.5%, 91.9%, and 91.5%, respectively. Importantly, the combination of advanced imaging provided very useful information for establishing the malignant potential of the lesions [28]. Costache et al. conducted a multicenter trial on the combined use of EUS-guided elastography and CEH-EUS. Elastography showed a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 29.63%, 78.65%, 100%, and 80.41%, respectively. Corresponding values for CEH-EUS (considering hypoenhancement as a predictive factor of malignancy) were 98.57%, 77.78%, 92%, 95.45%, and 92.78%, respectively. Combining CEH-EUS (hypoenhancement) and EUS-guided elastography, the sensitivity, specificity, and accuracy were 98.57%, 81.48%, and 93.81%, respectively. Best results were obtained using a sequential clinical algorithm based on the initial use of elastography, followed by contrast enhancement [46].

Conclusions

EUS, CT, and MRI can all provide valuable and complementary information for the differential diagnosis between mass-forming chronic pancreatitis, autoimmune pancreatitis, and pancreatic adenocarcinoma. However, EUS has the unique ability to allow obtaining specimens for histopathological diagnosis safely and accurately, thus playing nowadays a crucial role in the evaluation of patients with solid pancreatic lesions. Advanced imaging (EUS-guided elastography and CEH-EUS) further increase the diagnostic capabilities of EUS in this setting.

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45

Hereditary Pancreatitis and Complex Genetic Causes

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Clinical and Genetic Definitions

Hereditary pancreatitis (HP) is a syndrome that encompasses acute pancreatitis (AP), recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP). A mechanistic definition of CP is useful for framing HP as a process extending from asymptomatic risk to end-stage disease. Chronic pancreatitis is defined both by its essence and its character as "a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" [1]. In addition, "Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia" [1]. The definition was designed to assist in the early diagnosis of CP, the prognosis, and in the type and timing of potential therapies.

Hereditary pancreatitis is defined by clinical presentation in a family or by genetic test results in an affected individual. In families, HP is defined as two or more first-degree relatives or three or more second-degree relatives with recurrent acute pancreatitis (RAP) or chronic pancreatitis (CP) in two or more generations, consistent with an autosomal dominant inheritance pattern. Less commonly, families may appear to follow alternative inheritance patterns (e.g., autosomal recessive and complex). Alternatively, HP can be diagnosed in an individual with pancreatitis and a known pathogenic germline mutation, regardless of family history. Of importance, the penetrance of *PRSS1* hereditary pancreatitis is incomplete and therefore, identification of a pathogenic *PRSS1* mutation in an asymptomatic individual is not sufficient for a diagnosis but does indicate high risk. Some hereditary pancreatitis-appearing families have pathogenic variants in the serine protease inhibitor, Kazal type 1 gene (*SPINK1*), the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), *SPINK1* plus *CFTR*, the chymotrypsinogen C gene (*CTRC*), or a more complex genotype. Therefore, the absence of a pathogenic *PRSS1* variant does not preclude the diagnosis of HP in a family. A diagnosis of HP should always be considered in idiopathic pancreatitis, early-onset pancreatitis, or in a family with multiple affected individuals.

Familial pancreatitis refers to the occurrence of pancreatitis of any cause in a family with an incidence greater than would be expected by chance alone. Familial pancreatitis does not follow an observable monogenic pattern of inheritance. Kindreds with familial pancreatitis may have shared genetic and/or environmental (e.g., alcohol, smoking, stress) risk factors that predispose them to pancreatitis above the general population risk.

Epidemiology

Hereditary pancreatitis is a rare genetic disorder. In 1952, Comfort and Steinburg described a large family with HP [2]. Since this initial report, hundreds of HP kindreds have been identified in several regions in the United States and Europe and in a few families in Japan, Korea, China, Thailand, Malaysia, and South America. The vast majority of HP kindreds identified in the United States are of European ancestry linked to large pedigrees (>500 people), suggesting founder effects. The reason that HP is rare in Africans and Asians is unknown.

The prevalence of hereditary pancreatitis differs by geographic region, and HP has been observed most frequently in the USA and Europe. A national series of HP in France estimated a population prevalence of at least

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0.3 per 100,000 [3]. Since there is autosomal dominant inheritance with high penetrance and founders originating multiple generations in the past, the fraction of CP patients with HP will vary greatly from region to region and country to country.

Clinical Presentation

Hereditary pancreatitis typically presents with acute pancreatitis in early adolescence, with a high risk of progression to chronic pancreatitis by early adulthood (Fig. 45.1). In HP, the phenotypic features are confined to the pancreas, whereas *CFTR*-related disorders affect multiple organs as seen in cystic fibrosis. In patients who develop CP, major comorbidities include pancreatic exocrine insufficiency, diabetes mellitus, and chronic pain syndromes. In comparison to CP of other etiologies, HP has earlier age of onset and appears to have higher cumulative risks for exocrine and endocrine failure in patients who develop chronic pancreatitis, as well as increased risk for pancreatic cancer.

The disease penetrance for a *PRSS1* mutation was estimated as ~80% [4–6]. However, a national series of *PRSS1*-tested patients in France identified a penetrance of 93% [3]. Of note, estimates of penetrance may be inflated by biased study ascertainments. Penetrance may also differ by type of mutation and presence of modifying risk factors. Lifespan is not reduced as compared to the general population, except in patients who develop pancreatic adenocarcinoma [7].

Acute Pancreatitis

The median age of onset of acute pancreatitis is 10–12 years [3,4]. Some studies have shown that the age of symptom onset is earlier in *PRSS1* p.R122H carriers compared to p.N29I carriers and mutation-negative patients [4,5,8]. A multicenter European (EUROPAC) study of 418 subjects from 112 families identified an age of onset of 10 years for the *PRSS1* p.R122H mutation, 14 years for the p.N29I mutation, and 14.5 years in patients without an identified mutation [4]. Severity, length, and frequency of attacks are variable and can vary dramatically by family. In one large kindred, 58% of *PRSS1* p.R122H subjects were <5 years at the age of symptom onset [5]. Shared modifier genes and environmental factors in families contribute to age of onset and severity. For example, disease onset in four twin pairs differed by median of 1 year (range 0–2.4 years) as compared to 7 years (range 2–15 years) in a nonsibling comparison group matched for mutation, gender, and age [9].

At least 83% of patients experience epigastric abdominal pain [3]. The number of reported hospitalizations for acute pancreatitis varies by family and mutations status, with nearly 90% of affected individuals reporting >5 hospitalizations [4,5,8]. The EUROPAC study found a significant reduction in hospital admission rates for patients with a *PRSS1* p.N29I mutation (0.19 per year) as compared to patients with a *PRSS1* p.R122H mutation (0.33 per year) [4]. However, the difference in number of attacks between patients with an p.N29I mutation (1.4 per year) and an p.R122H mutation (2 per year) was not significantly different, suggesting that the p.N29I mutation results in less severe attacks [4]. The same study found that the majority of attacks are ≤7 days in length [4], but smoldering pancreatitis and/or persistence of pain that lasts weeks or months has been reported in patients with hereditary pancreatitis [10].

Chronic Pancreatitis

Recurrent acute pancreatitis progresses to chronic pancreatitis by the second or third decade of life in the majority of patients with hereditary pancreatitis. Rate and severity of pancreatic fibrosis and parenchymal destruction is highly variable, with cumulative incidence of ~50% in a lifetime (Fig. 45.1). A trend exists between the number of attacks and degree of fibrosis, and this process is highly influenced by modifying factors.

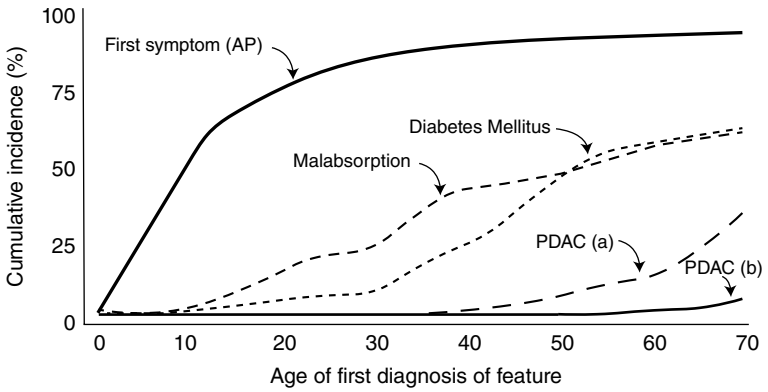


Figure 45.1 Age of onset of first symptoms of acute pancreatitis, pancreatic exocrine insufficiency, pancreatic endocrine insufficiency, and pancreatic cancer (PDAC). PDAC (a) is from Ref. 4 and PDAC (b) is from Ref. 14 with reduced smoking. *Source:* Data from [4] and [14].

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Pancreatic Exocrine Insufficiency

Progression of inflammation and fibrosis eventually leads to pancreatic exocrine insufficiency in a significant subset of patients. Pancreatic exocrine insufficiency occurs when the pancreas cannot supply a sufficient quantity of digestive enzymes to the intestines, leading to maldigestion. The EUROPAC study identified cumulative risks for exocrine failure of 8.4% at 20 years, 37.2% at 50 years, and 60.2% at 70 years, with a median time to malabsorption of 53 years [4]. No significant difference in time to malabsorption was found between men and women [4].

Diabetes Mellitus

As with other forms of chronic pancreatitis, chronic inflammation and progressive fibrosis also lead to islet cell injury. Glucose intolerance progresses to pancreatic endocrine insufficiency from loss of insulin-secreting beta cells. Furthermore, loss of glucagon-secreting alpha cells places patients at high risk for hypoglycemia. Diabetes mellitus from pancreatic exocrine disease and loss of all islet cell types is classified as type 3c. However, acute pancreatitis and pancreatic inflammation also triple the risk of type 2 diabetes, which develops earlier in the clinical course then type 3c [11,12]. The danger of hypoglycemia is enhanced by untreated pancreatic exocrine insufficiency, since the ingestion of nutrients is not well coordinated with digestion and absorption. The cumulative risks for endocrine failure in HP are 4.4% at 20 years, 47.6% at 50 years, and 79.1% at 80 years [4]. Median time to development of diabetes mellitus was 53 years and not significantly influenced by gender and mutation status [4].

Pancreatic Cancer

Hereditary pancreatitis is associated with a >50-fold increased risk for pancreatic adenocarcinoma [4,7,13]. Estimates for cumulative risk for pancreatic cancer at 70 years range from 7.2% to 40% [3,4,13,14]. The risk for pancreatic cancer is highest in smokers and individuals with diabetes mellitus. Smokers with HP have ~twofold increased risk for pancreatic cancer, with development of cancer 20 years earlier than nonsmokers [15]. More recent lower estimates of pancreatic cancer risk may reflect successful counseling of HP families to avoid tobacco [14]. The increased risk for pancreatic cancer appears to result from chronic inflammation rather than a *PRSS1* mutation itself, since all forms of CP are associated with pancreatic cancer, but early-onset pancreatitis in HP remains one of the strongest known risk factors for pancreatic cancer.

Incidence of pancreatic cancer varies extensively between HP families, and some families have high incidences of pancreatic cancer in the absence of clear environmental factors, suggesting the presence of risk and/or protective variants. Annual screening for pancreatic cancer is recommended for patients with *PRSS1*-HP beginning at age 50 or 10 years younger than the earliest familial onset of pancreatic cancer [16].

Management

As with pancreatitis of nongenetic etiology, management is aimed at prevention, reduction of symptoms such as fibrosis, pancreatic exocrine insufficiency and pancreatic endocrine insufficiency, and alleviation of pain. The approach should be based on targeting the underlying genetic factors, minimizing environmental stressors, and considering new therapeutic interventions as indicated. Alcohol, emotional stress, and dietary fat can exacerbate pancreatitis and should be avoided. Patients should also be counseled to refrain from smoking, which doubles the already increased risk for pancreatic cancer [14,15]. Antioxidants may reduce pain in a subset of patients [17]. Common recommendations include a low-fat diet with multiple small meals a day and to maintain good hydration to reduce the risk of an attack, but these recommendations are not based on strong evidence and a normal diet is possible with appropriate pancreatic enzyme replacement therapy.

Pancreatic exocrine insufficiency should be anticipated and managed with early initiation of pancreatic enzyme replacement therapy. The diagnosis of pancreatic exocrine insufficiency currently relies on clinical suspicion from abdominal bloating, diarrhea, steatorrhea, deficiency of fat-soluble vitamins or vitamin B12, or unexplained weight loss. The most common diagnostic tests include measuring low levels of human fecal elastase, low serum trypsinogen levels, or the clinical response to a trial of pancreatic enzyme replacement therapy.

Diabetes mellitus is common both in patients with pancreatitis and in the general population. In HP, type 3c diabetes mellitus typically develops years after the onset of CP. The diagnosis is challenging, and standardized protocols are not widely accepted. However, the clinical context of advanced CP, especially with pancreatic exocrine insufficiency, should indicate caution and a multidisciplinary approach involving endocrinologists and pancreatologists. The destruction of the islets may limit the use of some antidiabetic medications, and the use of insulin must be balanced with the ingestion and digestion of the meal, which may require the addition of pancreatic enzyme replacement therapy.

In the absence of pancreatic cancer, the primary indication for surgery is pain. Total pancreatectomy with islet cell autotransplantation (TPIAT) can be

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considered in younger patients with intractable, narcotic-dependent pancreatic pain [18,19]. Total pancreatectomy without islet autotransplantation can be considered in older patients with chronic pancreatitis for 20 years or more to reduce pain and as a last resort to reduce the risk of developing pancreatic cancer [20,21]. The need and timing of this radical procedure requires both experience with the procedure and clear prognostic understanding of what will happen with, and without TPIAT.

Molecular Genetics

In 1996, a missense mutation in the cationic trypsinogen gene (*PRSS1*) was identified in a large hereditary pancreatitis family [22]. Mutations in *PRSS1* have since been identified in 65–100% of HP kindreds with an estimated penetrance of 80%. Since this discovery, additional genes associated with recurrent acute and chronic pancreatitis have been identified, particularly *SPINK1*, *CFTR*, and *CTRC* [23–26] (Tables 45.1 and 45.2). Other important genes that have been associated with chronic pancreatitis include *CLDN2*, *CASR*, *CTSB*, *CPA1*, *GGT1*, and *TRPV6* [27–29]. Disease mechanisms for many of the genes associated with pancreatitis are complex, and gene–gene and gene–environment interactions are not fully defined.

PRSS1

Cationic trypsinogen is the most abundant isoform of trypsinogen (~65%), followed by anionic trypsinogen (*PRSS2*, ~30%) and mesotrypsinogen (*PRSS3*, ~5%) [30]. Trypsinogen is the inactive zymogen of trypsin, a digestive enzyme and regulator of all pancreatic zymogens, except amylase and lipase. The trypsinogen activation peptide maintains the inactive enzyme until it is cleaved by enterokinase or another trypsin, generally in the duodenum. Self-destruction (autolysis) occurs at p.R122, which is located on the single chain that links the two globular domains of trypsin. Two calcium-binding pockets serve as "on–off" switches in response to calcium concentrations, inducing distinct conformational changes. Increased calcium concentrations facilitate trypsin activation, whereas reduced calcium levels permit autolysis.

PRSS1 gain of function mutations fall into two categories: (i) premature activation of trypsin in the pancreas; or (ii) resistance to degradation. The importance of *PRSS1* mutations is demonstrated in transgenic mice with early-onset acinar cell injury and dedifferentiation, inflammatory cell infiltration, and progressive pancreatic fibrosis [31]. Many of the less common *PRSS1* variants found in patients with pancreatitis do not appear to be gain-of-function mutations. Instead, they may represent coding region variants causing protein misfolding, and triggering an unfolded protein stress response that drives fibrosis in a poorly defined way [32].

Table 45.1 Genes associated with pancreatitis.

Gene	Chromosome	Type of mutation	Mechanism
CTRC	1	Loss of function	Diminished trypsin degradation in pancreas
CASR	3	Loss of function; Inappropriate localization	Elevated pancreatic calcium levels Hypothesized premature activation of trypsin
SPINK1	5	Loss of function	Diminished trypsin degradation in pancreas
PRSS1	7	Gain of function	Premature activation of trypsinogen in pancreas
		Loss of function	Misfolding-induced endoplasmic reticulum stress; associated with nonalcoholic, early-onset CP
TRPV6	7	Loss of function	May alter calcium homeostasis in pancreatic acinar cells
CFTR	7	Loss of function	Loss of or diminished bicarbonate conductance leads to detainment of trypsinogen in the pancreas
CPA1	7	Loss of function	Misfolding-induced endoplasmic reticulum stress; associated with nonalcoholic, early-onset CP
CTSB	8	Unknown / Gain of function	Hypothesized to induce premature activation of trypsinogen
CEL	9	Loss of function	The CEL-HYB recombination allele originating from a crossover between CEL and pseudogene CELP is associated with an increased risk for pancreatitis
CLDN2	X	Altered regulatory element	Unknown; associated with alcoholic CP

CP: chronic pancreatitis.

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Table 45.2 Genotypephenotype correlations and multiorgan syndromes.

Genotype (variants)	Phenotype (syndromes)	Comment
PRSS1	Hereditary pancreatitis	Genetic counseling recommended
$CFTR^{sev}$/$CFTR^{sev}$	Cystic fibrosis (CF)	Manage with a CF center
$CFTR^{sev}$/$CFTR^{m\text{-}v}$	Atypical CF	Manage with a CF center
SPINK1/*SPINK1*	Familial pancreatitis	Usually progresses to severe CP
$CFTR^{bicarb}$/$CFTR^{any}$	Pancreas/sinus/CBAVD	Newly defined syndrome
$CFTR^{any}$/*SPINK1*	RAP/CP	Pancreas only
CTRC/*SPINK1*	RAP/CP	Pancreas only – not well studied
CASR/*SPINK1*	RAP/CP	Pancreas only – not well studied

CFTR: sev, severe mutations (typically functional class I–III); m-v, mild-variable mutations, (typically *CFTR* functional class IV); bicarb, bicarbonate conductance-disrupting variant (e.g., p.R75Q); any, either severe, mild-variable, or bicarbonate-disrupting variants; CP: chronic pancreatitis; RAP: recurrent acute pancreatitis; CBAVD: congenital bilateral absence of the vas deferens.

The most common *PRSS1* mutations are p.R122H and p.N29I (~90%). Less common mutations include p.A16V, p.R122C, p.N29T, p.D22G, and p.K23R. Mutations have primarily been identified in exons 2 and 3, but rare variants have also been identified in the 5′UTR, introns 1–4, and exons 4 and 5 (see http://www.pancreasgenetics.org). Copy number variations of the *PRSS1-PRSS2* locus have also been associated with chronic pancreatitis [33].

SPINK1

The serine protease inhibitor, Kazal type 1 (*SPINK1*; *PST1*) is a trypsin inhibitor secreted from pancreatic acinar cells. Loss-of-function mutations in *SPINK1* reduce its protective function and predispose to pancreatitis [34]. Mutations are found in ~2% of the population and confer a 12-fold increased risk for pancreatitis [34]. Still, less than 1% of *SPINK1* carriers develop pancreatitis. Biallelic loss of function mutations in *SPINK1* may lead to autosomal recessive pancreatitis. However, the majority of affected patients with *SPINK1* mutations are heterozygous, indicating the presence of complex gene–gene and gene–environment interactions [35]. For example, *SPINK1* can act as a disease modifier, and compound heterozygosity for pathogenic variants in *SPINK1/PRSS1* and, more commonly, *SPINK1/CFTR* has been reported [25,36].

SPINK1 mutations are detected in ~20% of patients with idiopathic chronic pancreatitis. The most common high-risk haplotype identified in the United States and Europe is *SPINK1* p.N34S. The *SPINK1* IVS3 +2T>C splicing variant is common in East Asian populations.

CFTR

Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) are common among patients with idiopathic chronic pancreatitis. *CFTR* mutations may impair both chloride and bicarbonate conductance (e.g., severe mutations), or only bicarbonate conductance [36,37]. Homozygosity or compound heterozygosity for two "severe" *CFTR* mutations generally causes cystic fibrosis (CF), while "mild-variable" or other mutations are associated with RAP, CP, pancreas sufficient CF and CFTR-related disorders [38]. *CFTR* carriers that develop pancreatitis are also likely to have an additional genetic (e.g., *SPINK1*, *CTRC*) or other (e.g., pancreas divisum) risk factors [25,36]. CFTR-associated pancreatitis is considered in Chapter 4.10. The use of CFTR modulators in pancreatic sufficient CF suggest that specific new therapies may be available in the future [39].

CTRC

Chymotrypsinogen C (*CTRC*) is a digestive enzyme and the primary regulator of trypsin. The action of chymotrypsinogen C is twofold and dependent on calcium concentrations. In the calcium-rich duodenum, chymotrypsin C promotes trypsinogen activation, but in solutions with lower calcium concentrations, it mediates trypsin degradation [40]. As with *SPINK1*, chymotrypsin C is believed to protect the pancreas from premature trypsin activation, with genetic defects increasing the risk of trypsin-mediated pancreatitis [41,42]. Two mutations, p.R254W and p.K247_R254del, were found to be overrepresented in patients with idiopathic or hereditary chronic pancreatitis [41]. The c.180T>G variant has been identified in about 10.8% of persons of European ancestry in North America and moderately increases the risk of progression from recurrent acute to chronic pancreatitis, particularly in the presence of alcohol, tobacco, or *PRSS1*/*SPINK1* mutations [43]. The independent effects of pathogenic *CTRC* variants appears to be low, but they clearly increase the risk of CP in the context of other risk factors such as

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pathogenic *CFTR* variants [25], and can contribute to familial clustering of CP cases.

Complex Genetics

Single-gene or Mendelian diseases are caused by highly penetrant pathogenic mutations in a single gene that follow a clear pattern of inheritance (e.g., autosomal dominant, autosomal recessive). Mendelian forms of pancreatitis, such as *PRSS1*-HP, are rare. Instead, most patients have a complex etiology resulting from multiple low-to-moderate effect risk alleles in combination with environmental and physiologic risk factors. Complex risk variants are defined as variants with variable effect sizes, ranging in frequency from rare to common, that do not cause disease in isolation. Instead, the combination of multiple interacting risk variants and other factors work in concert to initiate the disease process. In patients with pancreatitis, several common risk variants have been identified, including the *CTRC* c.180T>G (p.G60=) and *SPINK1* p.N43S variants (described above), a *PRSS1-PRSS2* haplotype [44], risk alleles in *CLDN2* [44], and the CEL-HYB risk allele [45]. Heterozygous carriers of *CFTR* variants associated with cystic fibrosis or a CFTR-related disorder have also been associated with an increased risk for pancreatitis as a part of a complex etiology [46]. Known risk factors for pancreatitis are outlined in the Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive Pancreatitis Risk/Etiology Checklist (TIGAR-O_V2) [27], which functions as an organizational tool to document and track patient risk and etiological factors. Although the identification of complex risk variants may lend insights into a patient's disease process, the quantification of risk to develop pancreatitis in asymptomatic patients or to progress to severe disease in symptomatic patients based on multiple complex variants and nongenetic factors remains challenging and imprecise.

Genetic Testing and Counseling

When a patient or family is suspicious for hereditary pancreatitis, a (minimum) three-generation pedigree should be collected, including family history of pancreatitis, age of onset, age at diagnosis for multiple pancreatic episodes, and pancreatic cancer [47]. Other information valuable for assessment of a family includes smoking and alcohol exposure, diabetes mellitus, pancreatic insufficiency, male infertility, cystic fibrosis, chronic sinusitis, and nasal polyps [47]. Calculation of risk in a family depends on genotype, pattern of inheritance in the family, and environmental exposures (e.g., tobacco, alcohol).

Indications to offer genetic testing in a symptomatic patient include unexplained recurrent acute pancreatitis and/or chronic pancreatitis, a first- or second-degree relative with pancreatitis, and/or unexplained pancreatitis in a child requiring hospitalization. Genetic testing is commercially available for several genes, including *CASR*, *CEL*, *CFTR*, *CLDN2*, *CPA1*, *CTRC*, *GGT1*, *PRSS1*, *PRSS2*, *SBDS*, *SPINK1*, and *UBR1*. Deletion/duplication analysis should be considered in a proband if a mutation is not identified from sequencing or targeted mutation analysis.

Genetic testing should always be preceded and followed by appropriate genetic counseling. Results may have implications for patient risk, risk to other family members, and family planning [48]. Another concern for genetic testing in this patient population, especially in the United States, is insurance discrimination [48]. The *Genetic Information Nondiscrimination Act of 2008* (GINA, Pub. L, 110–233) protects against genetic discrimination in health insurance and employment in the United States, but does not cover life, disability, or long-term care insurance. Patients and families should understand the benefits, limitations, and costs of genetic testing before the test is ordered. Therefore, clinicians must understand the consequences of genetic testing and should provide counseling directly or refer patients to a genetic counselor to obtain appropriate informed consent.

Genetic testing in a symptomatic patient can clarify etiology and provide information on risk for related complications, such as pancreatic cancer. Identification of a responsible mutation may clarify risk for family members and provide information relevant to family planning. *PRSS1*-related hereditary pancreatitis follows an autosomal inheritance pattern, and each child of a parent with a *PRSS1* mutation, has a 50% or 1 in 2 chance to inherit the deleterious allele. About 80% of individuals who inherit a *PRSS1* mutation develop pancreatitis. Therefore, each child of a parent with a *PRSS1* mutation has a ~40% chance of developing hereditary pancreatitis. However, variation in penetrance and severity exists between HP kindreds, and family history should always guide interpretation of results and risk calculation. Identifying a responsible genetic mutation in a family may also expedite diagnosis of family members and prevent unnecessary evaluation for other etiologies.

Predictive genetic testing in an asymptomatic individual is available when a mutation has been identified in a close family member. Testing for this mutation can clarify risk to develop pancreatitis and risk to descendants. Genetic testing may also identify family members who would benefit from lifestyle interventions to reduce risk and severity, such as avoidance of alcohol, smoking, and fatty foods.

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A negative test result in a patient from a family with a known mutation reduces but does not remove the risk for hereditary pancreatitis. Families may share additional, unidentified risk factors that predispose to pancreatic disease. Furthermore, not all hereditary pancreatitis-appearing families have an identifiable mutation. In a family without an identifiable mutation, genetic testing of asymptomatic family members will be uninformative, and discussions of risk must be tailored according to the presentation of disease within the family.

Genetic Testing in Children

The decision to pursue genetic testing in a child is the responsibility of the parents or legal guardian. When a child is 7 years or older, the child should provide assent for genetic testing. Testing of a symptomatic child can explain or confirm the diagnosis of pancreatitis and prevent unnecessary further evaluations.

Predictive genetic testing for hereditary pancreatitis is generally not recommended for patients less than 16 years of age. There are no clear medical benefits to identifying asymptomatic carriers at a young age and waiting to pursue testing gives the patient the opportunity to make an informed adult decision. Predictive testing to identify children that would benefit from diet, lifestyle, medication, or surveillance interventions has been advocated [49]. However, avoidance of pancreatitis risk factors, particularly fatty foods, alcohol, tobacco, and stress, are advised for all children regardless of mutation status.

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Epidemiology and Pathophysiology of Tropical Chronic Pancreatitis

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Introduction

In 1937, Kini [1] published a report on chronic calcific pancreatitis from India. Similar findings in autopsy studies were reported from southern India in 1954 [2]. While the features presented in those report were strikingly similar to the report on 45 malnourished patients from Indonesia published a couple of decades later, the credit for describing tropical (chronic) pancreatitis (TCP) as a distinct entity rests with Zuidema [3,4]. These patients were from economically weaker sections and were suffering from protein calorie malnutrition.

GeeVarghese [5,6] provided a detailed description of features that constituted TCP based on his analysis of patients in Kerala, southern India. This body of work now forms the framework on the basis of which our understanding of TCP resides.

TCP is considered a distinct subtype of CP comprising calcifying, nonalcoholic CP afflicting younger, generally malnourished individuals from the tropical regions of Asia [7–11], Africa [12–15], and even South America [16,17]. A male predominance was also noted [18–20]. However, there has been the occasional report of the disease from developed nations more often due to diagnosis of the disease in migrants arriving from the developing world [21]. In the past, the entity has been referred to by numerous terminologies including tropical calcific pancreatitis, tropical pancreatic diabetes, nutritional pancreatitis, juvenile pancreatitis syndrome, Afro-Asian pancreatitis, tropical calculous pancreatopathy, and fibrocalculous pancreatopathy, or fibrocalculous pancreatic diabetes (FCPD). However, the terminology most commonly employed today is TCP [22,23]. GeeVarghese summarized the natural history of TCP in the adage, "recurrent abdominal pain in childhood, diabetes around puberty and death at the prime of life" [5]. Barman and colleagues presented the triad of symptoms that comprised TCP, namely, abdominal pain, maldigestion and steatorrhea, and diabetes mellitus [24].

To date, there remains a paucity of large-scale epidemiological data on the prevalence of TCP. A field study from Kerala in southern India, involving 28,567 inhabitants, determined the prevalence of TCP to be 1:793 in that region [8] based on well laid out criteria for diagnosis of the disease. The study revealed that contrary to previous hospital reports, TCP in Kerala appeared to have a female preponderance (male: female ratio of 1:1.8), older age at disease onset (mean 23.9 yr), and evidence of milder disease. Prior attempts at understanding the nature of the disease had included hospital studies and a couple of monographs published by GeeVarghese [5,22] based on his experience of more than 1500 patients with the disease. The criticism by Balaji et al. [8] of these prior studies was the possibility that their findings were potentially influenced by need for healthcare (patients presenting only when symptomatic) as well as access to healthcare being preferentially available to males.

A large nationwide study from India that included 1086 CP patients has determined that idiopathic CP is now the most common subtype of the disease in the country (accounting for 60% of cases) [25]. This finding is not too dissimilar from the 70% of patients from India and China labeled to have idiopathic CP based on a survey in the Asia-Pacific region [9]. Interestingly, in the study by Balakrishnan et al. [25], when well-defined criteria for TCP were applied, TCP was found in only 3.8% of patients. The authors conjectured that these findings

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may reflect a prior overrepresentation of the disease owing to the interchangeable use of the terms idiopathic CP and TCP with the possibility that the true incidence of TCP lies somewhere in between this wide variation. The declining incidence of TCP has been noted in other studies from India, too [26,27]. Whether this is a reflection of improving socioeconomic conditions accompanied by improved nutrition [25,28], an increase in smoking and alcohol consumption amongst youngsters [26], or simply a better elucidation of the entity "idiopathic CP," leading to more individuals fitting these criteria rather than TCP [29], may remain a question left unanswered.

Pathophysiology

The initial documentation of cases of TCP in malnourished patients from the tropics and from financially weaker sections of society [1,4] instinctively led researchers to focus on dietary components as a cause for the disease [30]. Over the years, detection of TCP in apparently healthy individuals with a normal nutritional status (as per their body mass index) [31,32] has led to micronutrient deficiency being more intensively investigated. Eloquent studies teasing out pathological changes [33] and genetic mutations and comparing these with other subtypes of CP have heralded a possibly more objective approach to the understanding of the entity [34,35].

Pathology

Gross appearance of the gland depends on the duration of disease, degree of fibrosis, the presence of cysts, and location and size of calculi [36]. With the passage of time, the gland undergoes uneven fibrosis and atrophy often leading to an eccentric ductal location [23] with the gland often left appearing finger-like with a nodular and irregular surface [37].

One of the hallmarks of TCP is the presence of large calculi composed of 95.5% calcium carbonate (mainly in the form of calcite [38]), a small amount of calcium phosphate and traces of magnesium, urate, and oxalate distributed throughout the ductal system varying in color, shape, and size [23]. The calculi possess an amorphous nidus and a cryptocrystalline periphery [39]. The biochemical and structural nature of calculi in TCP is not too dissimilar to those in other subtypes of CP [23]. The larger stones tend to form toward the head with their size decreasing toward the tail region.

On microscopic examination, the hallmark of TCP is the degree of intralobular fibrosis [33] that is uniform throughout the pancreatic parenchyma [40]. Nair [36] suggested that TCP was characterized by a lack of inflammation suggesting the terminology of "tropical calcific pancreatopathy" to be more appropriate. However, these findings have not been corroborated by others. Shrikhande and colleagues [33] compared the histologic appearance of TCP versus alcoholic CP (ACP) and idiopathic CP and uncovered similar histological features and a comparable inflammatory cell reaction in all three subtypes of CP although the extent of the pathological change was variable in the individual types. The degree of endophlebitis and plasma cell density was significantly higher in TCP [33]. This finding of plasma cell infiltration of the pancreas is in keeping with the report of Nagalotimath who also found a lymphocyte infiltration mainly around the ducts [37]. Cyriac and colleagues [41] have recently demonstrated that stellate cell activation occurs in a similar manner to other subtypes of CP. Total fatty replacement of parenchyma has been noted to be a striking feature in TCP, seen exclusively in diabetics with gross atrophy of islets of Langerhans [40]. Moreover, in patients with established diabetes secondary to TCP (FCPD) histopathological examination as well as immunohistochemistry have revealed varying extents of acinar atrophy and parenchymal destruction [23] along with paucity of alpha and beta cells and reduction in glucagon positivity and areas of nesidoblastosis [37,42].

An interesting observation in the pathological assessment of tissues of patients with TCP when compared with alcoholic and idiopathic has been the increase in neural tissue and neural alterations associated with progression of the disease toward a stage amenable to surgery [43], a hallmark of pain accompanying CP [44]. It is not only the neural alterations that are identical but other histologic aspects including the degree of endophlebitis, overall density of plasma cells, and inflammatory cell reaction leading to the inference that independent of the underlying etiology, the pathologic changes accompanying CP eventually reach a common immunologic stage beyond which CP appears to progress as a single distinctive entity [33].

Nutrition (Including Cassava)

The initial reports of TCP originating from regions in the developing world coupled with the clinical picture of young emaciated patients, intuitively led clinicians to focus on the nutritional aspect, or more specifically, protein calorie malnutrition [4,12,45]. However, over the years, possibly a more objective approach to investigating the role of malnutrition as a causative agent has led pancreatologists to infer that malnutrition, in

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itself, is not the main cause for TCP [46] and the nutritionally deprived state may rather be an effect of the malabsorption associated with disease [47,48]. Patients with kwashiorkor, do not develop features of TCP [23,49]. Moreover, while malnutrition exists in many other countries in the world, there are no reported cases of TCP/FCPD from them [50], while on the flipside TCP cases have been reported even among patients from well-nourished families [23]. Nonetheless, cause or effect, malnutrition remains a major issue in TCP and addressing it in its entirety forms an essential part of the workup and management of patients with TCP [51].

While malnutrition may not be the only etiological factor in the causation of TCP, it is very likely that micronutrient deficiency, along with varying degrees of macronutrient deficiency and oxidant stress are cofactors in the causation of TCP.

Cassava Toxicity

Cassava (tapioca, *Manihot esculenta* Crantz) was implicated as a cofactor in the causation of TCP based on three hypotheses, namely, the geographic coincidence of cassava being the staple diet of the low socioeconomic class of people in Kerala and the high incidence of TCP reported there [52]; the cyanogenic glycoside composition of cassava (93% linamarin and 7% lotaustralin), which requires sulfur derived from the sulfur-containing amino acids (such as cysteine and methionine) for its detoxification—believed to be inherently deficient in malnourished individuals [53]; and experimental induction of hyperglycemia on feeding cyanide to rats [30] or hypoinsulinemia and histopathological changes of necrosis, hemorrhage, and fibrosis of the exocrine and endocrine portions of the pancreas in dogs fed on cassava [54].

While the activity of the cyanogen detoxifying enzyme, rhodanase, has been shown to be reduced accompanied by a decrease in sulfur-containing amino acids and antioxidants such as glutathione in TCP patients [55], neither this study [55], nor any of the other case-control or cohort clinical studies [49,56,57] were able to conclusively prove the role of cassava consumption in the causation of TCP. Besides, TCP has been reported even from regions where cassava is not consumed [9,25]. Even in the experimental setting, long-term ingestion of tapioca by rats failed to result in the development of diabetes or pancreatitis [58].

Antioxidants (Including Micronutrients)

It has been hypothesized that escalating oxidative stress within the acinar cells as a result of cytochrome p450 superfamily induction, deficiency of micronutrients required to maintain stores of reduced glutathione, and exposure to bioactivated chemicals [59,60] plays a role in the development of CP.

In TCP patients, the surrogate marker for p450I activity, namely, theophylline clearance was found to be faster in cases as compared to controls [61]. Additionally, the bioavailability of ascorbic acid and beta-carotene that predispose to pancreatic oxidative stress was found to be significantly reduced in South Indians (from Chennai) with TCP as compared to patients with CP from Manchester [35]. Girish and colleagues [62] observed enhanced lipid peroxidation with concomitant decrease in antioxidant status in patients with TCP as compared to healthy subjects. Moreover, in the same study, they noted that zinc deficiency appeared to affect the oxidative status in patients with TCP. The same group also noted a correlation between zinc deficiency and exocrine and endocrine insufficiency in CP patients [63]. They observed a marked effect of diabetes in zinc levels in patients with TCP as compared to those with ACP [63]. Other postulated mechanisms by which zinc deficiency could contribute to the progression of CP include reduction of free radical scavengers, increased collagen deposition, and possibly an alteration in immune function [64].

Genetics of TCP and Familial Clustering

The finding of an aggregation of patients with TCP in certain families [65], reported as occurring in up to 8% of TCP patients [66], raised the possibility of heredity as another potential contributory factor to the development of TCP. However, while there has been no further evidence to support this initial finding, the role played by genetic mutations in important regulators of pancreatic secretion as well as the innate protective mechanisms against premature zymogen activation have been extensively studied in patients with TCP. Table 46.1 provides a list of the most significantly proven mutations involved in the pathogenesis of TCP [34,67–74]. Mahurkar and colleagues [75] presented an interesting model called the "two-hit model" to hypothesize the pathogenesis of TCP. By this model, they believed that the first hit was the presence of persistent "super trypsin" within the acinar cell—the result of a loss of balance between activation events and degradation of active trypsin as a result of mutations in one or more of the aforementioned genes. This would lead to inflammation in the gland. A second hit in the form of another sequence of genetic mutations with/without environmental factors would then lead to the clinical disease entity of TCP.

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Table 46.1 Gene mutations involved in the pathogenesis of TCP.

Gene mutation	References
SPINK1	
pN34S variant	67, 69, 70, 84
Loss-of-function variant c.-142T>C	68
CTSB	
Polymorphism p.L26V	71, 85
Polymorphism p.S53G	85
CTRC	
c.217G>A (p.A73T) variant	34
c.703G>A (p.V235I) variant	34
Carboxypeptidase A1	
p.D32H, p.R169H, and p.Y308H variants	72
Glycoprotein 2	
c.1275A>G variant	73
Calcium-sensing receptor	
p.P163R, p.I427S, p.D433H, p.V477A variants	74

SPINK1: serine protease inhibitor Kazal type 1; *CTSB*: cathepsin B; *CTRC*: chymotrypsin C.

Natural History of the Disease

In the original reports of TCP, the disease was noted to afflict young individuals between the ages of 10 and 30 years who also demonstrated features of protein and calorie malnutrition, along with bilateral parotid enlargement and occasionally a cyanotic hue to the lips [5,76]. They suffered from recurrent severe upper abdominal pain radiating to the back that was relieved by bending forward. In the ensuing years, it was noted that while some patients developed features of pancreatic exocrine insufficiency such as maldigestion and steatorrhea, others did not do so because of their low-fat diet. They developed diabetes mellitus within 10–20 years from the onset of the initial symptoms of pain [31]. Mohan and colleagues [77] determined that the median time to development of diabetes mellitus in patients with TCP was 9.6 years from diagnosis and this was associated with an older age, higher body mass index, and lower fecal chymotrypsin level. The development of diabetes mellitus in TCP has been hypothesized to result from two mechanisms: the pathogenetic process of tissue fibrosis eliciting CP, and a selective pancreatic beta-cell impairment [78]. TCP is associated with an increased risk of pancreatic cancer development [79]. In a study from Chennai (India), the relative risk of pancreatic cancer in patients with TCP was estimated to be significantly high at 100 (95% CI: 37–218) [80].

In comparison to the initial reports of the dismal clinical course of TCP which resulted in death by early adulthood [22], a survival analysis of 370 patients in the mid-1990s determined that patients with TCP were living much longer than before [81] with 80% of patients still alive 35 years from the onset of the first episode of abdominal pain and a mean of 25 years from the diagnosis of diabetes mellitus. The causes of death in TCP include diabetes-related complications, pancreatic cancer [82], and severe infections [24].

Garg and Narayana [83] have recently questioned the need to consider TCP as a unique entity for multiple reasons, including its similarity to idiopathic CP down to the genetic level, in addition to a significant decline in the clinical picture that helped define this entity by the incorrect use of the term "tropical," which would normally be used for infectious diseases.

Conclusion

In conclusion, the incidence of TCP is on the decline even in developing countries. The disease is witnessing a paradigm shift in relation to a number of aspects including the reduced emphasis on macronutrient, protein calorie malnutrition, and cassava ingestion as etiological factors, in favor of micronutrient deficiency (including zinc) and oxidant stress, an increased appreciation of the role of gene mutations in the pathogenesis of the disease, and finally, significantly improved survival, possibly as a result of better management of the disease and its attendant complications. The mounting evidence calls for a unified, evidence-based approach by the pancreatology fraternity to clarify whether TCP should continue to remain a unique entity, or be included under the broad umbrella of idiopathic CP.

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47

CFTR-Associated Pancreatic Disease

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Introduction

There is a spectrum of pancreatic diseases associated with *CFTR* [1,2] mutations, namely classic cystic fibrosis (CF) (pancreatic insufficient or sufficient) and CFTR-associated pancreatitis. The pancreas pathology and damage are dependent on the amount of functional CFTR: the lower the function, the more prominent and earlier the sequelae. In addition, *CFTR* mutations may contribute to the development of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP).

Pathophysiology—Genotype and Phenotype Correlations

Although more than 2000 *CFTR* mutations have been identified, the functional importance is known only for a small number of mutations. *CFTR* mutations can be classified into six types of defects (class I–VI mutations) [3]: absence of protein synthesis (class I); protein misfolding and premature degradation (class II); disordered regulation (class III); defective chloride (Cl^-) conductance or channel gating (class IV); a reduced number of *CFTR* transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI) (Fig. 47.1) [4,5]. *CFTR* function is virtually absent with class I–III and VI mutations while class IV and V mutations allow some residual *CFTR* function. Pancreatic involvement correlates well with gene mutations at the *CFTR* locus and thus residual CFTR function, and less by other genetic modifiers or environmental factors [6]. Exocrine pancreatic insufficiency is seen almost exclusively in association with class I–III and VI mutations [5]. The absence of phenylalanine at position 508 (F508del, a class II mutation) constitutes two-thirds of *CFTR* mutations in northern European and North American populations. No other single mutation accounts for more than 5% of *CFTR* mutations worldwide [4]. Patients with at least one mutation belonging to classes IV or V generally present with milder disease, symptoms in late childhood or adulthood and they are pancreatic sufficient.

CFTR is expressed in epithelial cells of various organs including pancreatic ducts, and it functions as an apical membrane anion channel, involved primarily in anion secretion [7,8]. It is generally agreed that the lack of CFTR leads to acidic, dehydrated, and protein-rich secretions [9,10], which then plug the acinar and ductal lumen [11–13] and cause the destruction of the pancreas in CF. Among the various gastrointestinal organs affected by CF, the exocrine pancreas shows the strongest association between genotype and phenotype. In patients with the lowest CFTR function, considerable destruction of the pancreas starts *in utero* and functional loss of the exocrine pancreas develops at birth or in early infancy [14]. A group of patients with CF who have residual pancreatic exocrine function (pancreatic sufficient) are prone to recurrent attacks of pancreatitis and may become pancreatic insufficient over time [15,16]. The development of symptomatic episodes of CFTR-associated pancreatitis is dependent on the intricate balance between impaired ductal flow and alkalinization due to reduced CFTR function and the degree of preserved acinar reserve (Fig. 47.2).

Early studies suggested that *CFTR* mutations contributed to the development of CP alone or if additional risk factors were present [17–20]. Many of these studies were limited by relatively small number of patients, lack of control groups, and incomplete *CFTR* gene sequencing.

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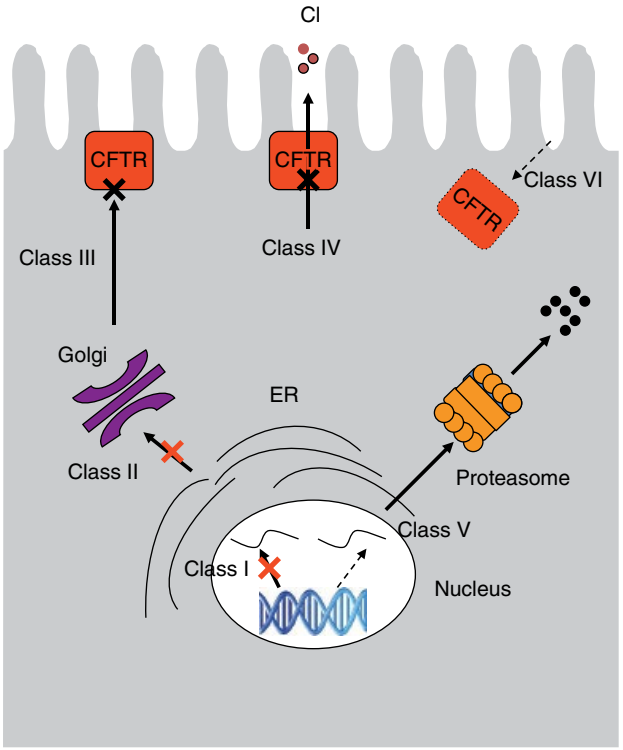


Figure 47.1 Classes of *CFTR* mutations. *CFTR* mutations are grouped into six functional classes. Class I mutations lead to protein synthesis defect, because premature stop codons or frameshifts for deletions or insertions preclude translation of full-length *CFTR*. Class II mutations lead to impaired protein trafficking, because CFTR is unable to complete its folding and ER machinery eliminates the protein. Class III mutants have defective channel gating, CFTR reaches the cell surface, but it is unable to perform channel gating due to diminished ATP binding and hydrolysis. Class IV mutants produce CFTR with reduced function. Class V mutants have reduced protein maturation caused by amino acid substitution or alternative splicing, the amount and therefore the function of CFTR that reaches the cell surface is reduced. Class VI mutants produce unstable protein, since CFTR at the plasma membrane is removed during the recycling and sent for lysosome degradation. CFTR: cystic fibrosis transmembrane conductance regulator; ER: endoplasmic reticulum.

Recent studies with larger German, French, and North American cohorts confirmed these earlier findings that *CFTR* variants play a role in idiopathic chronic pancreatitis [21–23], although the frequency of *CFTR* variants in CP was much lower than previously reported. The recent studies show no increased risk for CP with common polymorphic alleles T5 and TG12; the role of T5-TG12 complex allele remains to be determined [22].

Clinical Manifestations

The clinical manifestations of CFTR-associated pancreatic diseases correlate with the degree of pancreatic injury. Exocrine pancreatic damage in its severe form manifests as exocrine pancreatic insufficiency (EPI), which is present in 60–75% of infants at time of CF diagnosis [24,25]. Pancreatic lesions begin *in utero* and continue into early childhood when complete loss of pancreatic acinar tissue occurs [24]. Fat maldigestion with resultant steatorrhea happen only when pancreatic colipase/lipase secretion falls below 1–2% of normal levels [26], with risk of malnutrition and fat-soluble vitamin deficiencies. A causal relationship between early exocrine pancreatic disease in CF and the development of CF-related diabetes has also been reported [27].

Patients with sufficient pancreatic function who either have CF or CFTR-related disorder, are at risk of developing symptomatic acute and acute recurrent pancreatitis. Recurrent acute and chronic pancreatitis are known complications of CF, and they may occur in ~15–20% of patients with sufficient pancreatic function [28]. It is not known why a subgroup of patients with CF develops pancreatitis, but preservation of acinar cells seems to be a prerequisite for this complication. Recurrent pancreatic inflammation is a risk factor for further loss of residual function and progression to EPI [29].

The clinical landscape in relation to exocrine pancreatic function status and occurrences of symptomatic acute pancreatitis have changed in the era of CFTR modulator therapies. Two open-label, multicenter studies in young children aged 2–5 years [30] and 1–<2 years [31] have demonstrated, for the first time, the plausibility of a window of opportunity to rescue the exocrine pancreas if modulators are commenced early enough. In addition, there have been accumulating published and anecdotal reports of EPI patients presenting with symptomatic acute pancreatitis associated with a rise in fecal elastase levels [32,33]. Consequently, clinicians need to be vigilant of this potential effect. In contrast, among pancreatic sufficient patients with recurrent pancreatitis, there have been reports of resolution or reduction of subsequent attacks following the use of modulators [34,35].

With increasing survival of patients with CF, an increased risk of malignancy in the gastrointestinal and biliary tracts has been observed [36]. The risk of malignancy in the pancreas was reported, in a subanalysis, to be greater than the overall risk of cancer in the digestive tract (odds ratio [95% CI] of 31.5 [4.8–205] vs. 6.4 [2.9–14], respectively).

Despite treatment with pancreatic enzymes that prevent severe malnutrition, exocrine pancreatic involvement impairs growth and accelerates the progression of lung disease [37,38], the major cause of mortality in CF [39]. CF patients develop diabetes mellitus as they age: ~10% of patients have cystic fibrosis-related diabetes mellitus (CFRD) by 10 years of age, and ~50% of CF patients over 30 years of age have CFRD [40,41]. CFRD is associated with a rapid decline in pulmonary

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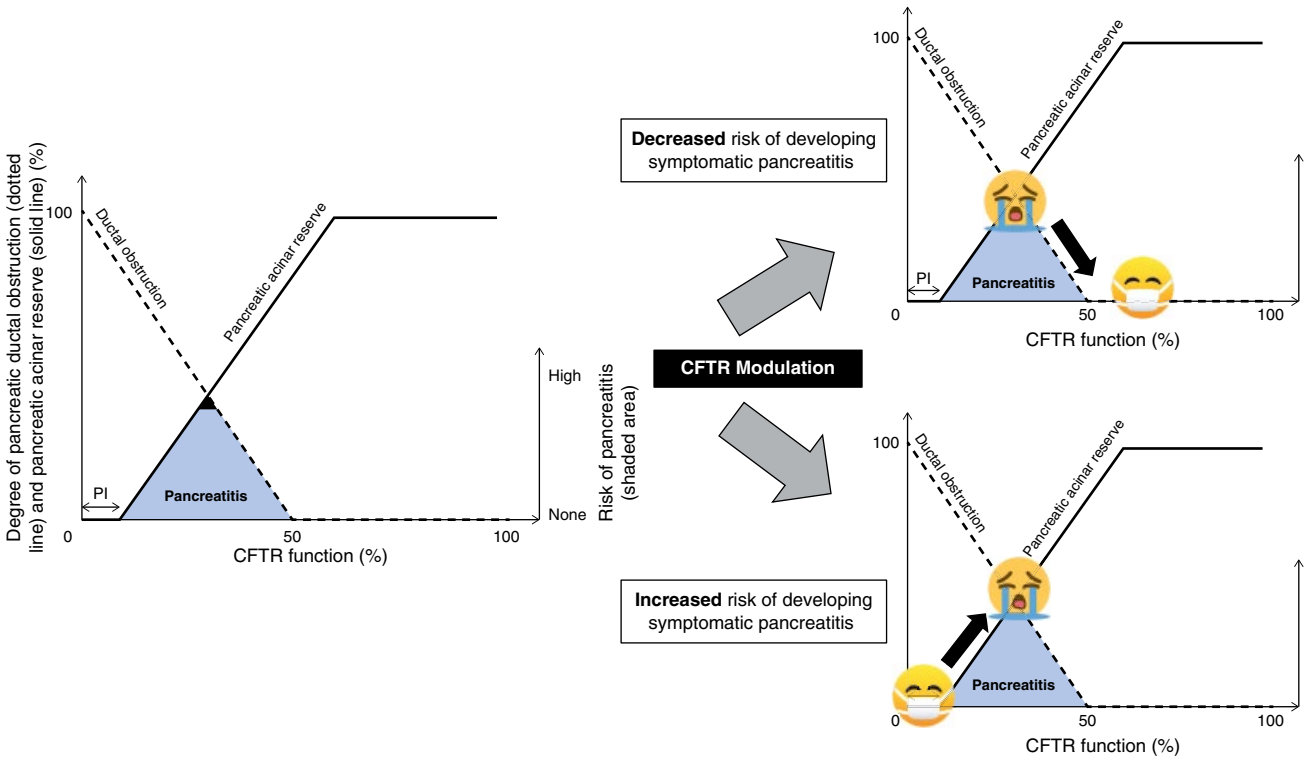


Figure 47.2 Proposed pathogenesis model explaining the effects of CFTR modulation on either reducing or increasing risk of development of symptomatic pancreatitis. The development of symptomatic episodes of CFTR-associated pancreatitis is associated with the opposing factors of severity of ductal obstruction and degree of preserved pancreatic acinar reserve. With CFTR modulation, there is a shift to the right along the x-axis toward greater CFTR function. In pancreatic sufficient individuals who are already experiencing symptomatic pancreatitis, there is reduction in risk of pancreatitis due to improved ductal flow. Among people with pancreatic insufficiency, there is no/minimal risk of pancreatitis despite severe ductal obstruction present due to lack of sufficient acinar tissue. However, with improved CFTR function, there is risk of developing pancreatitis if there is sufficient ductal obstruction in the presence of residual acinar tissue.

function, higher morbidity, and greater mortality [14,42]. The diagnosis of CFRD is preceded by a decline in body weight and lung function, along with insulin deficiency [41,43].

Diagnosis

The rationale for testing for CF is the risk of multiorgan involvement in CF-affected organs and available effective therapies. Several studies have shown that a large proportion of pediatric and adult patients with idiopathic acute recurrent and chronic pancreatitis carry mutations in the *CFTR* gene. In a study of children affected by pancreatitis, *CFTR* mutations were identified in 30 out of 89 (34%) and 24 out of 104 (23%) children with acute recurrent and chronic pancreatitis, respectively [44]. In a separate study of 42 children and adults with idiopathic acute recurrent and chronic pancreatitis, extensive *CFTR* genotyping identified 50% of patients with either one or two *CFTR* variants [45].

Currently, the diagnostic criteria for CF require the presence of characteristic symptom(s) of CF disease or a positive family history, *plus* an abnormal sweat chloride value (≥60 mmol/L) and/or two CF disease-causing mutations [46]. Consensus guidelines [46,47] recommend the diagnostic terminologies of: (i) "*CF disease*," to describe patients who fulfill the currently accepted diagnostic criteria; or (ii) "*CFTR-related disorder*" to describe individuals with the CF phenotype (e.g., pancreatitis), who have evidence of CFTR dysfunction but insufficient to fulfill the diagnostic criteria for CF disease (e.g., borderline sweat test [30–59 mmol/L] and/or one or two non-CF causing mutations).

As the majority of CFTR variants have unclear clinical significance, genotyping is the least sensitive diagnostic test for CF, compared to sweat testing and nasal potential difference (NPD) [20,45]. If performed, genotyping results should be interpreted with experts in CF genetics since nondiagnostic mutations for CF may be identified [48]. In a study comparing the yield of various diagnostic tests for CF, genotyping identified one or two *CFTR* mutations in 21 of 42 (50%) patients with idiopathic acute recurrent or chronic pancreatitis but was unable to establish or exclude the diagnosis of CF in any of them [45]. In contrast, sweat chloride and transepithelial NPD were able to diagnose

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CF in 5% and 29% of patients respectively [45]. While NPD is a sensitive and reproducible determinant of CFTR function [49], it has limitations. It is complex to perform, time- and labor-intensive, and operator-dependent. Access to NPD is also limited to specialized centers with NPD expertise. False positive results can occur with minor perturbations of the nasal epithelium, allergies, respiratory infections, and smoking.

As such, the sweat test remains the primary diagnostic test for CF [46,48]. Borderline (40–59 mmol/L) or abnormal (≥60 mmol/L) sweat chloride concentrations should lead to a referral to a CF clinic for further diagnostic evaluation, including for *CFTR* genotyping and alternative ion channel measurements (e.g., NPD or intestinal ion channel measurement), and various end-organ testing (e.g., lung function). Disease-specific counseling (e.g., fertility and smoking cessation) and genetic counseling are also important management considerations. Once the diagnosis of CF is made, the next step is to establish the exocrine pancreatic function and determine whether the patient requires pancreatic enzyme replacement therapy (PERT).

Because CF and CP share many pathological characteristics including pancreatic fibrosis, atrophy, and fatty infiltration [50], imaging studies proposed for the assessment of pancreatic involvement in CP may be applicable to CF pancreas. Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) can assess fibrosis (T1 mapping) [51], pancreas size [52], and ductal fluid secretion in response to secretin [53]. However, there are variations between studies and the ability of imaging studies to differentiate between pancreatic sufficient vs. pancreatic insufficient status in CF remains limited [54]. More data are needed before imaging studies can be used as diagnostic studies of CF pancreatic diseases to assess pancreatic structure and function.

Therapy

For patients with advanced pancreatic damage and EPI, the only treatment available currently is PERT [8]. Children <4 years of age require 1000 lipase units/kg per meal; 500 lipase units/kg per meal are used for those >4 years of age and 25,000–40,000 units/meal are used for adults [55]. For snacks half the dose is recommended. Infants may be given 2000–4000 units per 120 mL of infant formula or per breast feeding. The daily dose for most patients is less than 10,000 units of lipase/kg per day or 6000 units of lipase/kg per meal to prevent fibrosing colonopathy [56]. Aggressive nutritional management, fat-soluble vitamin supplementation is mandatory for all patients with EPI. Insulin is the treatment of choice for CFRD [57].

The ideal therapeutic strategy in CF should be repairing the underlying CFTR defect. Recent studies using CFTR modulators suggest that early initiation of ivacaftor may improve pancreatic function in infants and young children with gating mutations. In the ARRIVAL study, improvement in exocrine pancreatic function was observed in 4–24-month-old subjects after 24-week use of ivacaftor [31,58]. Similar improvements were observed in older children 2–5 years old by the use of ivacaftor for 24 weeks (KIWI study) [30] and results were sustained at week 84 (KLIMB study) [59]. These results were similar to the work done in the G551D CF ferret model, which showed protection from pancreatic disease if treated with ivacaftor *in utero*, but pancreatic destruction if withdrawn postnatally [60].

People with CF experiencing recurrent pancreatitis have observed a significant reduction in the number of attacks while on ivacaftor [34,35,61], suggesting that improving CFTR function can ameliorate pancreatitis. There are rare reports of pancreas transplantation reported in people with CFRD, which not only corrects the diabetes, but also eliminates the need for pancreatic enzyme use. Pancreas transplants are typically coordinated with other organ transplants (mostly liver), but combined liver, lung, and pancreas transplants have also been reported [62,63].

Future studies will examine the effects of highly effective CFTR modulators on the pancreas at various ages. Gene therapy remains an area of active research, targeting primarily lungs, as challenges exist to access the pancreas [64,65]. A minimally invasive method was successfully used to deliver gene therapy vectors to the newborn porcine pancreatic ducts [66], but there are no similar studies yet in humans.

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Alcohol and Smoking in Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) develops resulting from interactions of multiple environmental, metabolic, and genetic risk factors [1]. Alcohol is the leading cause for CP in many Western countries, and the association between alcohol misuse and CP has been recognized for a long time. As early as 1878, Friedreich [2] described "drunkard's pancreas": chronic interstitial inflammation in the pancreas which might result from alcohol misuse. In 1946, Comfort et al. [3] described the clinical presentation of chronic relapsing pancreatitis in subjects with alcohol misuse. Thereafter, it has been established that alcohol misuse is an important risk factor for CP. Of note, unlike the alcohol-induced liver injury, only 1–5 % of heavy drinkers develop pancreatitis [4], indicating that alcohol-related pancreatitis is not caused by alcohol misuse alone. Some individuals may develop alcohol-related pancreatitis with alcohol intake as low as 20 g/day, whereas most individuals do not develop pancreatitis no matter how much they drink or how long. In animals, ethanol feeding alone does not cause a pronounced pancreatic injury. Therefore, additional genetic and/or environmental predisposing factors are required for the development of clinical CP.

Conversely, the independent effects and risks associated with smoking have not been well recognized until recently. Because smoking is strongly associated with drinking alcohol [5,6], the independent effect of smoking can be difficult to assess. Smoking is now recognized to confer a strong, independent and dose-dependent risk of CP [5–7]. Importantly, smoking and alcohol interact and worsen acinar cell injury and pancreatitis synergistically [5,6]. In this chapter, we review the clinical observations and pathophysiology of alcohol-related and smoking-related CP.

Alcohol and Chronic Pancreatitis

Clinical Observations

Historically, alcohol misuse is the leading cause of CP and accounts for approximately 60–90% of CP cases in industrialized nations worldwide [6]. However, in recent years, the proportion of alcohol-related CP (ACP) cases might be smaller than expected. The North American Pancreatitis Study 2 (NAPS2) showed that the frequency of ACP at tertiary referral centers in the United States was 44.5% [6]. A report from Italy showed a shift in the etiologic profile of CP [8]. Alcohol misuse was the leading cause of CP (74%) between 1971 and 1995, but the proportion was decreased to 43% in patients evaluated between 2000 and 2006. These findings suggest that the contribution of alcohol misuse to the pathogenesis of CP might have been overestimated [6]. Referral bias might exist in tertiary referral centers and accurate assessment of alcohol exposure to determine the association with CP is challenging because self-reports about alcohol consumption are usually unreliable. Conversely, in Asia, ACP accounted for 72% of all CP cases in Japan in 2016 [9]. In India and China, the proportion of ACP was lower and idiopathic pancreatitis was the most common type, accounting for approximately 70% of the CP cases [10]. Importantly, alcohol consumption has been stable or decreasing in many North American and European countries as well as in Japan, whereas it has been increasing in India and China [10]. It would be of interest to see whether the trends in alcohol consumption affect the burden of ACP in India and China in the future.

There have been many studies that aimed to clarify the dose–response relationship between alcohol consumption and CP. The association between alcohol

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consumption and pancreatitis was evaluated in 540 cases and 695 controls in the NAPS2 [5]. Logistic regression analyses revealed a significant association between alcohol and CP only in very heavy drinkers who consumed ≥5 alcoholic drinks per day (odds ratio [OR] = 3.1). In another case-control study [11], among patients with onset of CP after the age of 35, alcohol intake, even less than 50 g/day, induced earlier disease characterized by more frequent severe pain, calcification, and complications such as pseudocysts. In a Japanese case-control study [12], compared with nondrinkers, the OR (95% confidence interval [CI]) for alcohol consumption of 20≤~<40 g/day, 40≤~<60 g/day, 60≤~<80 g/day, 80≤~<100 g/day, and ≥100 g/day were 2.6 (1.2–5.5), 3.2 (1.5–7.1), 9.2 (4.1–20.3), 13.0 (5.3–31.6), and 19.6 (8.2–46.8), respectively. A systematic review and meta-analysis of four studies (three case-control and one cohort studies) showed that the risk of CP increased monotonically according to the average alcohol consumption with no identifiable threshold in men [13]. The relative risks (RR) (95% CI) were 1.58 (1.32–1.90) at 25 g/day; 2.51 (1.74–3.61) at 50 g/day; 3.97 (2.30–6.85) at 75 g/day; and 6.29 (3.04–13.02) at 100 g/day.

It is well known that ACP is predominantly a disease of men [5,9]. However, alcohol misuse is an important health problem in women, too. It has been shown that susceptible women might develop ACP with shorter duration and lower cumulative amounts of alcohol consumption than men [14].

Ethanol Metabolism in the Pancreas

Ethanol can be metabolized in the pancreas, mainly in pancreatic acinar cells. Two pathways of ethanol metabolism have been described in pancreatic acinar cells: oxidative and nonoxidative pathways [15]. Ethanol oxidation involves the conversion of ethanol to acetaldehyde and acetate, a reaction catalyzed by ADH and cytochrome P450 2E1. The nonoxidative pathway of ethanol metabolism involves the esterification of ethanol with fatty acids to form fatty acid ethyl esters (FAEE) such as palmitic acid ethyl ester. This reaction is catalyzed by FAEE synthases. FAEE synthase activity in the pancreas is much greater than that in the liver, whereas pancreatic ADH and cytochrome P450 2E1 activities are low [15]. Therefore, the dominant nonoxidative metabolism is a characteristic feature of ethanol metabolism in the pancreas.

Pathophysiology

Several pathophysiological mechanisms linking alcohol consumption and pancreatitis have been suggested. At the cellular level, ethanol and its metabolites affect the cell functions and homeostasis of pancreatic cells including acinar cells, ductal cells, and stellate cells (Table 48.1) [16,17 and references therein]. Importantly, animal studies have suggested that ethanol alone does not induce pancreatitis unless additional pathogenic insults are present. One explanation would be that the pancreas can compensate harmful effects of alcohol through an adaptive stress response. Pancreatitis develops only when the compensatory mechanisms are disrupted/exhausted or if increased vulnerability due to other genetic and environmental cofactors are present. Findings in animal studies support the concept that alcohol misuse alone does not cause CP and additional cofactors are required for the development of CP in susceptible humans.

Table 48.1 Effects of ethanol on pancreatic cells [16,17].

1. induces mitochondrial damage
2. elevates intracellular calcium levels
3. disrupts expression and function of the CFTR
4. decreases bicarbonate secretion
5. increases pancreatic digestive enzyme content
6. redirects exocytosis to the basolateral surface
7. enhances pancreatitis responses elicited by hyperstimulation
8. induces endoplasmic reticulum stress
9. promotes oxidative stress
10. increases the fragility of lysosomes and zymogen granules
11. regulates transcription factors NF-κB and AP-1
12. activates stellate cells to promote fibrosis

CFTR: cystic fibrosis transmembrane conductance regulator; NF-κB: nuclear factor-κB; AP-1: activator protein-1.

Pancreatic Acinar Cells

Ethanol induces a sustained elevation of the intracellular calcium levels, which is central in promoting pathological events of pancreatitis. FAEE cause pancreatic calcium toxicity via inositol trisphosphate receptors and loss of adenosine triphosphate production [18]. Calcium overload reduces adenosine triphosphate production and subsequently causes dysfunction of endoplasmic reticulum (ER). Ethanol increases the fragility of zymogen granules and lysosomes, which sequester lysosomal enzymes such as cathepsin B within the cells. Oxidative alcohol metabolism induces mitochondrial dysfunction, which might play a role in ethanol-induced necrosis of the pancreatic acinar cells [19]. Mitochondrial dysfunction occurs due to membrane permeabilization mediated by persistent opening of the mitochondrial permeability transition pore, leading to loss of mitochondrial membrane potential and mitochondrial fragmentation.

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These changes might make the pancreas susceptible to necrotizing pancreatitis.

Chronic ethanol feeding in mice perturbs protein folding and induces ER stress, which in turn induces an unfolded protein response (UPR) involving the upregulation of spliced X box-binding protein 1 (sXBP1) in pancreatic acinar cells [20]. Ethanol administration to mice heterozygous for XBp1 ($XBP1^{+/-}$) resulted in dilated ER, loss of zymogen granules, accumulation of autophagic vacuoles, and acinar cells death, suggesting that these responses serve as a protective adaptive mechanism that prevents ethanol-induced damage.

Autophagy is impaired in pancreatitis and lysosome dysfunction might be involved. Autophagy comprises several intracellular pathways of lysosome-mediated degradation and recycling of organelles, long-lived proteins and lipids [21]. Fortunato et al. [22] reported that the combination of ethanol exposure and endotoxemia resulted in the depletion of several lysosomal proteins including lysosomal-associated membrane protein-2 (LAMP-2), a protein required for the proper fusion of autophagosomes with lysosomes. Cathepsin B-induced LAMP degradation and genetic LAMP-2 deletion caused pancreatitis through impaired autophagy in mice [23]. Human patients with alcoholic pancreatitis also exhibited local LAMP-2 depletion, indicating the crucial roles of LAMP-2 and autophagy in acinar cell death in humans.

Although numerous *in vitro* and *ex vivo* studies have shown the actions of ethanol and its metabolites on pancreatic cells, *in vivo* studies have shown that feeding ethanol to rats and mice even for a long time, with either liquid diet or continuous intragastric infusion, did not cause a prominent injury to the pancreas. Chronic ethanol feeding by the Lieber-DeCarli pair-feeding model [24] induces a number of metabolic changes in the acinar cells including an increase in the content of digestive enzymes and lysosomal enzyme and fragility of the zymogen granules and lysosomes. However, chronic pathological changes resembling CP will not develop. Conversely, chronic ethanol exposure sensitizes the pancreas to other insults. Pancreatitis developed in rats that had received an ethanol-containing diet in response to low doses of cholecystokinin octapeptide or its analogue caerulein, which do not cause pancreatitis by themselves [25]. The sensitization was accompanied by increased activation of nuclear factor-κB (NF-κB) and the upregulation of proinflammatory cytokines and chemokines in the pancreas [26]. Ethanol might regulate NF-κB and activator protein (AP)-1: the key transcription factors regulating the gene expression of inflammatory responses and cell survival. FAEE activate NF-κB and AP-1, whereas ethanol and acetaldehyde inhibit NF-κB activation [26]. Thus, ethanol may regulate the activation of NF-κB and AP-1 positively or negatively, depending on the predominance of which metabolic pathway's effects. These effects may play a role in the ethanol-induced toxicity in the pancreas. Of note, ethanol and its metabolites altered the cholecystokinin 8-induced activation of these transcription factors, which might be a mechanism by which ethanol sensitizes pancreatic acinar cells to pancreatitis.

Gukovsky et al. [27] reported that ethanol dramatically aggravated the pathological effects of the combination of cyclosporine A and caerulein. In ethanol-fed, but not control diet-fed, animals, the combined treatment of cyclosporine A and caerulein resulted in severe pancreatic injury that displayed three key responses of human ACP: loss of parenchyma, sustained inflammation, and fibrosis. Conversely, for the repair of the exocrine pancreas, acinar cells could act as progenitor cells; mature acinar cells undergo dedifferentiation and redifferentiation back to the differentiated phenotype [28]. Clemens et al. [29] reported that chronic ethanol administration delayed the structural and functional regeneration of the pancreas in mice. The delayed regeneration was associated with the decreased expression of pancreatic developmental factors including PDX-1. These findings suggest that ethanol might impair the recovery from acute pancreatic injury, thus facilitating the progression from acute pancreatic injury to CP.

Pancreatic Ductal Cells

Alcohol increases viscosity and precipitation of pancreatic juice and formation of protein plugs inside pancreatic ducts. Protein plugs lead to formation of calculi which damage ductal epithelium and cause obstruction of pancreatic ducts [30]. Several studies have highlighted the role of the pancreatic duct in the pathogenesis of alcohol-induced pancreatitis. Ethanol reduced the expression of cystic fibrosis transmembrane conductance regulator (CFTR), disrupted the folding of CFTR at the ER, and inhibited CFTR function in pancreatic ductal cells, all contributing to the increased viscosity of the pancreatic juice and small duct obstruction [31]. *CFTR* knockout mice given ethanol or fatty acids developed more severe pancreatitis than mice not given ethanol or fatty acids.

Pancreatic Stellate Cells

PSC play a pivotal role in pancreatic fibrosis in CP. Ethanol and its metabolites induced the activation, extracellular matrix production, and chemokine expression in PSC, leading to the perpetuated activation of PSC and pancreatic fibrosis [32]. A combination of short-term administration of caerulein and long-term intraperito-

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neal administration of ethanol led to the activation of PSC and fibro-inflammatory responses in the pancreas [33]. Chronic ethanol consumption accelerated pancreatic fibrosis in response to caerulein-induced pancreatitis in rats [34].

Animal studies have suggested that endotoxin in the microbiota might also be involved. Gut permeability is increased in alcoholics, allowing translocation of gram-negative bacteria across the mucosal barrier and allowing bacterial endotoxins to enter the circulation. A combination of Lieber-DeCarli ethanol-enriched diet and repeated injection of lipopolysaccharide (LPS) developed acute acinar cell injury, activation of PSC and fibrosis [35]. Repeated LPS injection caused pancreatic fibrosis in ethanol-fed rats, but not in rats fed the control diet. When ethanol administration was continued, the activation of PSC and fibrosis persisted, but resolved soon after ethanol was discontinued [36]. Conversely, continued alcohol intake perpetuates pancreatic injury by inhibiting apoptosis and promoting the activation of PSC. These findings indicate the importance of abstinence to prevent the progression of acute pancreatitis to CP.

Genetic Factors Predisposing for the Development of ACP

Recent studies have identified several risk loci in ACP. The serine protease inhibitor Kazal type 1 (SPINK1), also known as pancreatic secretory trypsin inhibitor, acts as the first line of defense against prematurely activated intracellular trypsinogen by inhibiting up to 20% of trypsin activity within the pancreas. A meta-analysis of 12 studies showed the association of the *SPINK1* c.101A>G (p.N34S) variant with ACP (OR = 5.28, 95% CI: 3.45–8.09) in a Caucasian population, which was smaller than that in idiopathic CP (OR = 13.64, 95% CI: 8.86–21.00) [37]. The loss-of-function *SPINK1* c.194+2T>C (IVS3+2T>C) variant is commonly found in CP patients in east Asia. The *SPINK1* c.194+2T>C variant is overrepresented in patients with ACP (OR = 30.59, 95% CI: 16.61–56.34) [38]. The association of the variants in the chymotrypsinogen C gene (*CTRC*) with ACP has been shown. LaRusch et al. [39] reported that the synonymous *CTRC* variant c.180C>T (p.G60=) was overrepresented in CP of all etiologies, but not in recurrent acute pancreatitis as compared with controls (16.8% in CP, 11.9% in recurrent acute pancreatitis, 10.8% in controls). The *CTRC* c.180T allele was overrepresented in ACP patients (20.8%) compared to NACP patients (12.4%) (OR = 1.9, 95% CI: 1.30–2.79). A meta-analysis of four studies showed that the *CTRC* c.180T allele was overrepresented in CP (OR = 1.99, 95% CI: 1.49–2.67) [40].

A genome-wide or exome-wide approach overcomes the limitations of a candidate gene approach, enabling the discovery of new and unsuspected pancreatitis susceptibility genes. A genome-wide study from North America identified the association of common variants in the *CLDN2-MORC4* (rs7057398 and rs12688220) and *PRSS1-PRSS2* loci (rs10273639) conferred an increased risk of ACP, but not with alcohol-associated cirrhosis or alcohol dependence [41]. A meta-analysis of five studies from worldwide countries has confirmed the association of *PRSS1* rs10273639 with ACP (pooled OR = 1.67, 95% CI: 1.56–1.78) [42]. Functional studies indicated that the rs10273639 or rs4726576, which is in perfect linkage disequilibrium with rs10273639, altered the intrapancreatic trypsinogen levels [43]. Importantly, although the degree of association varies, most of the variants associated with ACP have associations with NACP, suggesting common mechanisms for alcohol-related and non-ACP. Another genome-wide study from Europe replicated previously reported risk loci *CLDN2-MORC4*, *CTRC* (c.180C>T, p.G60=), *PRSS1-PRSS2*, and *SPINK1* (c.101A>G, p.N34S) in ACP patients [44]. In addition, this study identified *CTRB1-CTRB2* (chymotrypsin B1 and B2) as a new risk locus for ACP and NACP. The association within the *CTRB1-CTRB2* locus was linked to a 16.6 kb inversion that altered CTRB1/CTRB2 expression, thereby affecting protective trypsinogen degradation. Importantly, the association of the previously reported and new risk loci was observed when compared with chronic alcoholics, suggesting that these loci are associated with the pancreas-specific injury among alcoholics.

Smoking and Chronic Pancreatitis

Recent clinical studies have shown that smoking is another important risk factor for CP, and the underlying mechanisms linking smoking and CP are being elucidated. Importantly, ethanol and smoking synergically affect the development and course of CP.

Clinical Observations

There is accumulating clinical evidence that smoking is a dose-dependent risk factor, independent of alcohol, for CP. Smoking is a risk factor for the progression from AP to recurrent AP and CP [45]. Compared to the never smoker or former smoker, current smoker had a risk of recurrent AP (OR = 2.77, 95% CI: 1.69–4.53) and CP (OR = 3.62, 95% CI: 1.98–6.60). There have been several meta-analyses that assessed the risk of CP among smokers. A meta-analysis of 12 studies showed that, compared to lifetime nonsmokers, pooled risk estimates (95% CI)

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for current smokers were 2.8 (1.8–4.2) overall and 2.5 (1.3–4.6) [46]. The risk diminished significantly after smoking cessation, as the RR estimate for former smokers dropped to a value of 1.4 (1.1–1.9). A recent systematic review and meta-analysis of 22 studies revealed the summary relative risks (RR) (95% CI) for CP compared to never smokers were 3.00 (1.46–6.17) in ever, 2.72 (1.74–4.24) in current, and 1.27 (1.00–1.62) in former smokers [47]. Another meta-analysis of 10 prospective studies revealed that RR (95% CI) for CP were 1.93 (1.60–2.32) in current smokers, 1.30 (1.08–1.57) in former smokers, and 1.59 (1.39–1.82) in ever smokers compared to never smokers [48]. Dose–response analysis revealed that the summary RR per 10 pack-years was 1.22 (1.11–1.33) for CP.

Smoking accelerates the progression of CP. Smoking is independently associated with earlier onset, recurrence, appearance of calcifications, and diabetes mellitus [49]. Smoking was associated with approximately 5-year-earlier diagnosis of ACP, and with the appearance of pancreatic calcifications (hazard ratio [HR] = 4.9, 95% CI: 2.3–10.5) and diabetes (HR = 2.3, 95% CI: 1.2–4.2), independent of alcohol consumption [50]. The lower risks for CP development and progression in former smoker than those in current smoker suggest that smoking cessation decreases the risk and progression of CP. Smoking cessation would be an important strategy for primary as well as secondary prevention of pancreatitis. In addition to alcohol, physicians should routinely counsel patients for the benefits of smoking cessation. Widespread recognition of the association between smoking and CP could potentially curtail smoking rates in subjects with CP and those at risk of CP [51].

Pathophysiology

Among the more than 4000 compounds in cigarette smoke, effects of cigarette smoke, nicotine, and the tobacco-specific most abundant nitrosamine known as nicotine-derived nitrosamine ketone (NNK) have been studied alone or in combination with ethanol with regard to pancreatic diseases [52]. Major cellular components of the pancreas including pancreatic acinar cells, ductal cells, and PSC express nicotinic acetylcholine receptors, which bind to nicotine and NNK, suggesting that cigarette smoke and its major components directly affect pancreatic cells.

Cigarette smoke and its components affect cell functions and homeostasis in pancreatic cells [7, 52 and references therein] (Table 48.2). Cigarette smoke reduced pancreatic bicarbonate secretion in part by disrupting CFTR. NNK caused premature activation of trypsinogen and chymotrypsinogen in isolated pancreatic acinar cells. Nicotine activates multiple signal transduction pathways resulting in high levels of intracellular calcium release and cell injury. Clinically relevant concentrations of cigarette smoke component NKK could activate PSC, suggesting a potential mechanism for smoking-induced CP progression [53].

Table 48.2 Effects of cigarette smoke and its components on pancreatic cells [7,52].

1. induces mitochondrial damage
2. elevates intracellular calcium levels
3. disrupts expression and function of the CFTR in ductal cells
4. decreases fluid and bicarbonate secretion
5. induces endoplasmic reticulum stress
6. promotes oxidative stress
7. activates pancreatic stellate cells to promote fibrosis

CFTR: cystic fibrosis transmembrane conductance regulator.

In animal studies, rats exposed to high-dose cigarette smoke for up to 12 weeks developed a chronic inflammation resulting in pancreatic fibrosis and scarring of pancreatic acinar cell structure [54]. The ratio of trypsinogen to its endogenous trypsin inhibitor was elevated after chronic cigarette smoke exposure for 3 months, suggesting an increased vulnerability to self-digestion of the pancreas [55]. Exposure to nicotine caused the production of reactive oxygen species in pancreatic acinar cells [56]. Both nicotine and NNK have been shown to induce morphological changes in the pancreas consistent with those seen in pancreatitis. Furthermore, nicotine affects pancreatic secretion and NNK induces premature zymogen activation, two well-known features of pancreatitis. These cigarette toxins may mediate both pro- and anti-inflammatory pathways and can induce changes in pancreatic acinar cell function at the level of transcription, leading to conditions such as thiamin deficiency and mitochondrial dysfunction. Such circumstances could leave the pancreas prone to the development of pancreatitis.

Cigarette smoke might contribute to CP development through the modulation of immune cells. Xue et al. reported a role of aryl hydrocarbon receptor agonists, such as dioxin and benzo[a]pyrene, in smoking-associated CP [57]. Aryl hydrocarbon receptor ligands in cigarette smoke induces IL-22 production in $CD4^+$ T cells through aryl hydrocarbon receptors during the pancreatic damage. IL-22 interacts with IL-22 receptor on PSC and upregulates production of extracellular matrix, leading to the development of pancreatic fibrosis. The role of IL-22 was further supported by the higher serum IL-22 levels in current smokers with CP. AhR ligands did not induce fibrosis in the absence of

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caerulein, suggesting that AhR activation by cigarette smoke alone is not sufficient, and additional pancreatic insults are required to induce CP.

Because most drinkers smoke, it is interesting to see the interaction between alcohol and smoking in CP. Lugea et al. [58] reported that smoking disrupts the protective adaptive mechanism that prevents ethanol-induced damage. Cigarette smoke extracts reduced spliced XBP1 levels, and increased ethanol-induced oxidative and ER stresses, leading to cell death in pancreatic acinar cells. These might be mechanisms by which alcohol and smoking interact and worsen acinar cell injury and pancreatitis.

In summary, cigarette smoke and its components affect cell functions and homeostasis in a similar manner to ethanol and its metabolites. As in the case of ethanol, cigarette smoke or its components alone did not induce CP and additional insults are required for CP. Mechanisms of synergy between alcohol and cigarette smoke have been identified. Because only a small portion of smokers develop pancreatitis, it is reasonable to assume that there might exist some genetic background of smoking-associated CP. Further studies are warranted to clarify this issue.

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Idiopathic and Rare Causes of Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is now recognized as a heterogeneous inflammatory disease that can develop in individuals with multiple risk factors, including environmental and genetic factors [1,2]. Many risk factors have been described in the TIGAR-O and M-ANNHEIM classifications, which include alcoholic, smoking, genetic, autoimmune, obstructive, nutritional, and rare metabolic factors [3,4]. However, recent international consensus guidelines strongly agree that alcohol, smoking, and certain genetic alterations are risk factors for CP [5].

Idiopathic CP (ICP) is identified after ruling out other potential causes, including rare ones [2,6]. It has been proposed that ICP can be further classified into three types, primarily based on clinical features: early-onset ICP (EO-ICP), late-onset ICP (LO-ICP), and tropical pancreatitis (TP) [3]. This chapter mainly focuses on the clinical features of ICP, including EO-ICP and LO-ICP described in recent reports. Moreover, we discuss the background risk factors for ICP, which include environmental risk factors, such as smoking and consuming small amounts of alcohol, and genetic risk factors (7–11]. In addition, rare causes of CP are also described.

Idiopathic Chronic Pancreatitis

Definition

To date, heavy alcohol drinkers (usually 50–80 g or more per day) with CP have been defined as having alcoholic CP (ACP). In others, CP has been defined as ICP after excluding all known rare causes such as obstructive, hereditary, and autoimmune diseases. Therefore, patients with ICP may include moderate or social drinkers [6]. Originally, ICP in patients with absolute abstinence from alcohol has been classified as EO-ICP or LO-ICP [12,13]. Thus, it is necessary to strictly distinguish between two categories of ICP, one that excludes all drinkers and one that includes people who drink small amounts of alcohol (light drinkers).

Classification

Early-Onset and Late-Onset

Patients with ICP who abstain from alcohol and were diagnosed at the Mayo Clinic had a bimodal age distribution. Their ICP has been classified into two types: EO-ICP or LO-ICP [6,12]. Age 35 is used as a cutoff for distinguishing between these two types of ICP [12]. A bimodal age distribution among patients with ICP has also been reported in Italy and among patients of European ancestry in the United States [13,14]. Although the peaks occurred at higher ages in a report from Japan, ICP showed a bimodal age distribution [15]. However, a bimodal distribution was not found in Chinese patients with ICP [16]. Since the latter two reports included light drinkers with ICP, light alcohol consumption might have affected the distribution of onset age [9,13]. Smoking and racial differences are other potential factors that should be studied in the future [6,17].

Tropical Pancreatitis

TP is a type of ICP seen in tropical countries. It is characterized by large pancreatic calculi and ductal dilatation in a young malnourished patient who presents with abdominal pain, diabetes, or both [18]. It has been reported in many parts of tropical Asia and Africa, but mostly in India, especially in the states of Kerala and Tamil Nadu [19]. Although malnutrition and cassava

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intake were previously thought to be causally associated with TP, they are no longer implicated as causative factors [17].

Prevalence

Table 49.1 shows the etiologies of CP from recently published epidemiologic analyses in population-based, multicenter, or nationwide cross-sectional studies [20–28]. In most studies, alcoholic was the most common etiology of CP, accounting for 33.6% to 72.0% of cases. The proportion of ICP cases was between 12.9% and 28.6% in the presented studies except for a nationwide study from India. The study showed the most common etiology was idiopathic, accounting for 60.2% of cases [25]. ICP was prominent in India. This finding was confirmed by three observational studies from single-centers in both northern and southern India [29–31].

Table 49.1 Etiology of CP in epidemiologic studies.

Author [ref]	Nation or region	Study period	Study design	Number of patients	Etiology
Lankisch et al. [20]	Germany / Lüneburg County	1988–1995	Population-based study	74	ACP 71.6% ICP 28.4%
Wang et al. [21]	China	1994–2004	Retrospective multicenter study	2008	ACP 35.1% Biliary 34.4% Hereditary 7.2% ICP 12.9%
Frulloni et al. [22]	Italia	2000–2005	Prospective multicenter study	893	ACP 33.6% Obstruction 26.7% Alcohol + obstruction 9.2% Autoimmunity 3.8% Dystrophy 6.2% Hereditary 4.0% ICP 16.6%
Coté et al. [23]	United States	2000–2006	Prospective multicenter study	539	ACP 44.5% Genetic 8.7% Autoimmune 2.2% Obstructive 8.7% Other 7.2% ICP 28.6%
Ryu et al. [24]	Korea	2001–2004	Retrospective multicenter study	814	ACP 64.3% Obstructive 8.6% Autoimmune 2.0% Other 4.4% ICP 20.8%
Balakrishnan et al. [25]	India	2005–2007	Prospective multicenter study	1033	ACP 38.7% Other 1.1% ICP 60.2%
Hirota et al. [26]	Japan	2007	Cross-sectional study	1236	ACP 69.7% Obstructive 1.1% Hereditary 0.9% Other 7.3% ICP 21.0%
Conwell et al. [27]	United States	2008–2012	Prospective multicenter study	521	ACP 45.7% Genetic 9.8% Obstructive 6.9% Autoimmune 1.5% Other 11.9% ICP 24.2%
Masamune et al. [28]	Japan	2016	Cross-sectional study	2102	ACP 72.0% Hereditary 1.6% Obstructive 0.4% Autoimmune 0.4% Other 1.9% ICP 23.7%

Ref: reference; ACP: alcoholic chronic pancreatitis; ICP: idiopathic chronic pancreatitis.

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Tropical Pancreatitis

It has been reported that the prevalence of TP has significantly decreased. Previously, it was reported that TP accounted for more than 50% of CP cases in India [18]. However, a nationwide study conducted from 2005 to 2007 in India demonstrated TP made up only 3.8% of CP cases [25]. This finding was supported by a single-center observational study that demonstrated the proportion of typical TP was 5.8% [30]. Malnutrition, a typical feature of TP, has been rarely observed among patients with ICP in India. The prevalence of diabetes has decreased from 90% to 50% of ICP cases [17,30]. Furthermore, it has been pointed out that the number of drinkers is increasing due to lifestyle changes. The prevalence of ACP has been increasing in India [25]. The spectrum of clinical features in ICP has been changing in India and possibly other places.

Clinical Characteristics

Idiopathic vs. Alcoholic

ACP is generally recognized to cause severe symptoms [32]. To clarify the clinical characteristics of patients with ICP, seven reports comparing ICP and ACP from the United States, East Asia, and India were reviewed (Table 49.2). In these studies, ICP included light drinkers. Since the three studies were single-center observational studies, selection bias was possible [29,30,33]. The background of patients might be different between multicenter studies at specialty hospitals [23,24] and nationwide cross-sectional surveys [15,28] that included general hospitals because young symptomatic patients are expected to concentrate in specialty hospitals. The two studies from Japan are nationwide surveys conducted in different years [15,28]. Therefore, many of the participants in these studies might be duplicated.

Table 49.2 Comparison of clinical features between ACP and ICP.

Author [ref]	Coté et al. [23]	Hao et al. [33]	Ryu et al. [24]	Hirota et al. [15]	Masamune et al. [28]	Bashin et al. [29]	Midha et al. [30]
Country	United States	China	Korea	Japan	Japan	India	India
Study period	2000–2006	2000–2013	2001–2004	2011	2016	1999–2004	2004–2008
Number of patients (ACP/ICP)	240 / 154	404 / 1633	523 / 169	1171 / 347	1513 / 498	59 / 64	157 / 242
Males, % (ACP/ICP)	70.0 / 41.6[a]	98.3 / 63.1[a]	96.0 / 66.7[a]	92.2 / 54.6[a]	91.0 / 60.0[a]	100 / 65.6[a]	99.4 / 63.6[a]
Age at onset, years (ACP/ICP)	–	38.1 / 41.6[a]	–	51.5 / 57.2[a]	–	–	37.9 / 24.7[a]
Age at study, years (ACP/ICP)	50.9 / 50.0	42.6 / 47.0[a]	50.7 / 50.4	60.4 / 67.2[a]	–	41.5 / 33.0[a]	40.2 / 27.5[a]
Ever smoker, % (ACP/ICP)	92.9 / 58.6[a]	80.7 / 22.8[a]	–	85.0 / 39.8[a]	79.8 / 41.5[a]		70.7 / 12.8[a]
Pain, % (ACP/ICP)	–	94.6 / 91.8[b]	–	68.1 / 54.8[a]	–	91.5 / 96.9	–
Calcification, % (ACP/ICP)	66.2 / 53.9[a]	83.9 / 73.0[a]	72.3 / 64.5	71.7 / 63.4[a]	70.3 / 59.7[a]	35.6 / 46.9	68.8 / 82.6[a]
Diabetes, % (ACP/ICP)	29.2 / 26.4	38.9 / 26.3[a]	35.0 / 26.0[a]	40.1 / 30.5[a]	43.1 / 40.3	22.0 / 23.4	36.3 / 35.5
Exocrine insufficiency, % (ACP/ICP)	30.8 / 28.6	29.7 / 20.8[a]	–	–	33.6 / 30.5	28.0 / 12.0	6.3 / 16.9[a]
Pseudocyst, % (ACP/ICP)	38.3 / 13.0[a]	23.3 / 14.7[a]	33.5 / 21.9[a]	–	29.6 / 11.2[a]	47.4 / 34.3	40.1 / 14.5[a]
Biliary stricture, % (ACP/ICP)	21.7 / 8.4[a]	17.8 / 15.9	13.6 / 14.8	–	16.8 / 7.0[a]	–	29.3 / 10.7[a]
Surgery %, (ACP/ICP)	–	16.6 / 20.7	No difference[c]	–	17.8 / 12.1[a]	–	–

[a] $P < 0.05$.
[b] Type of pain was different ($P < 0.001$).
[c] No specific numbers were given.
Ref: reference; ACP: alcoholic chronic pancreatitis; ICP: idiopathic chronic pancreatitis.

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Taking these potential biases into account, some characteristic features were demonstrated. First, compared to ACP, which has a male predominance, the proportion of male patients with ICP was relatively low. The majority of patients with ACP were smokers. Second, there were likely regional differences in the age of patients with ICP. In the United States and East Asia, age at onset was in the 40s and 50s, and age at the time of the study was approximately in the 40s to 60s. In India, age at onset was in the 20s and age at time of the study was approximately in the 20s and 30s. Patients with ICP in India were shown to be approximately 20 years younger than those in other countries. Conversely, patients with ICP in Japan were 10 years older than those in other East Asia countries and the United States. Third, in the United States and East Asia, patients with ACP tended to have a higher incidence of calcification and diabetes than patients with ICP. However, patients with ICP in India had more calcification than those with ACP. There were no significant differences between the proportion of patients with ICP and patients with ACP who have diabetes in India. Finally, a higher proportion of patients with ACP had pseudocyst formation. This finding was seen in almost all reports.

In summary, patients with ACP were predominantly male and smokers in all countries. They tended to have more severe clinical features than patients with ICP. Compared with ACP, a higher proportion of patients with ICP are women. In the United States and East Asia, patients with ICP are as old as or slightly older than patients with ACP, except for patients in India, who developed ICP at a very young age. However, patients with ICP in India tended to have a high rate of pancreatic calcification and diabetes as complications, even though they were very young.

Early-Onset and Late-Onset

Comparisons of clinical features between EO-ICP and LO-ICP were reported in five papers, two from the United States and three from India (Table 49.3). Layer et al. reported the results of a single-center observational study from the Mayo Clinic [12]. Lewis et al. reported a multicenter study with 26 participating institutions in the United States [13]. These studies defined patients with ICP as strictly abstinent from alcohol, which excluded even social and light drinkers. The latter study only included patients of European ancestry. Conversely, three studies from India, which were all single-center observational studies, did not define patients with ICP as strictly abstinent from alcohol [29–31].

According to Table 49.3, which shows a comparison of clinical features between EO- and LO-ICP, regional

Table 49.3 Comparison of clinical features between EO-ICP and LO-ICP.

Author [ref]	Layer et al. [12]	Lewis et al. [13]	Bashin et al. [29]	Midha et al. [30][c]	Rajesh et al. [31][d]
Country	United States	United States	India (North)	India (North 61%, Other 39%)	India (South)
Study period	1976–1985	2000–2014	1999–2004	2004–2008	2004–2010
Number of patients (EO/LO)	25 / 41	61 / 69	41 / 23	171 / 71	111 / 94
Males, % (EO/LO)	44.0 / 56.1	37.7 / 18.8[a]	75 / 48	63.2 / 64.8	61.3 / 50.0
Age at onset, years (EO/LO)	19.2 / 56.2[a]	20 / 58[a]	23 / 44[b]	18.7 / 39.1[a]	15.0 / 38.1[a]
Age at study, years (EO/LO)	–	30.1 / 64.3[a]	–	–	28.2 / 42.5[a]
Ever smoker, % (EO/LO)	–	33.3 / 43.5	–	9.9 / 19.7	8.1 / 12.1
Pain, % (EO/LO)	100 / 75.6[a]	96.1 / 69.2[a]	95.1 / 100	88.3 / 84.5	No difference[e]
Calcification, % (EO/LO)	56.0 / 36.6	45.9 / 50.7	46.3 / 47.8	–	95.5 / 97.9
Diabetes, % (EO/LO)	32.0 / 41.5	29.5 / 27.5	17.1 / 34.8	33.3 / 40.8	41.4 / 69.1[a]
Exocrine insufficiency, % (EO/LO)	44.0 / 46.3	29.5 / 36.2	7.3 / 0	16.4 / 18.3	34.4 /53.2[a]
Pseudocyst, % (EO/LO)	16.0 / 14.6	11.5 / 27.5[a]	–	11.7 / 21.1	7.4 / 10.6
Biliary stricture,% (EO/LO)	0 / 7.3	–	–	8.2 / 16.9[a]	–
Surgery %, (EO/LO)	60.0 / 31.7[a]	23.0 / 29.0	–		–

[a] $P < 0.05$.
[b] No statistical results were shown.
[c] EO-ICP was defined based on age at diagnosis <30 years. LO-ICP was defined based on age at diagnosis >30 years.
[d] EO-ICP was defined based on age at onset <30 years. LO-ICP was defined based on age at onset ≥30 years.
[e] No specific numbers were given.
Ref: reference; EO: early-onset idiopathic chronic pancreatitis; LO: late-onset idiopathic chronic pancreatitis; ICP: idiopathic chronic pancreatitis.

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differences between the United States and India are remarkable. First of all, the patient composition was different. More patients in the United States had LO-ICP while more patients in India had EO-ICP. Compared with EO-ICP patients in the United States, EO-ICP patients in India were predominantly male. Age at EO-ICP onset was approximately 20 years in both the United States and India. Patients with EO-ICP in the two countries had generally similar clinical features with predominantly complaints of pain and similar complication rates to LO-ICP even though they were younger. Second, the clinical characteristics of patients with LO-ICP were different between the two countries. The age at LO-ICP onset was in the late 50s in the reports from the United States, while it was approximately 40 years in the reports from India. In the US studies, significantly fewer patients with LO-ICP complained of pain compared to patients with EO-ICP. Conversely, most patients with LO-ICP in India complained of pain. Patients with LO-ICP in India had similar rates of pancreatic calcification and diabetes as patients in the United States, even though they were on average more than 10 years younger. Finally, in particular, patients with LO-ICP in southern India had high rates of pancreatic calcification, diabetes, and exocrine insufficiency [31]. In this report, although patients with EO-ICP were very young, almost all of them had pancreatic calcification [31]. One reason for these differences might be explained by differences in patient background such as a small amount of alcohol intake and smoking, but further research including genetic analysis would be required.

Background Risk Factors

Smoking

Cigarette smoking has been identified as an independent risk factor for the development of CP [7,8]. Smoking facilitates the development of pancreatic calcification and diabetes in patients with CP [15,34]. As shown in Table 49.2, the association between ACP and smoking is strong. The combination of alcohol abuse and smoking produces a higher cumulative risk for CP [35]. An association between ICP and smoking has also been reported. Among patients in Italy, smoking increased the risk of pancreatic calcification and heavy smoking (>20 cigarettes per day) was associated with diabetes [36]. A report from the Mayo Clinic showed that smoking increases the risk of pancreatic calcification in LO-ICP but not in EO-ICP. However, smoking did not affect development of exocrine or endocrine insufficiency [37]. In patients with EO-ICP in southern India, smoking was an independent significant risk factor for diabetes according to a multivariate analysis [31].

Small Amount of Alcohol Intake

As mentioned above, in general ICP includes patients who drink small amounts of alcohol (<50 g per day). Lankisch et al. reported the effect of a small amount of alcohol intake on the clinical course of ICP. Patients with LO-ICP drinking less than 50 g of alcohol per day were younger at disease onset and reported more frequent and severe pain than patients with LO-ICP who did not drink any alcohol [9]. A systematic review and meta-analysis demonstrated a linear dose–response relationship between alcohol consumption and development of CP, which was monotonically increasing with no identifiable threshold [10]. This indicates that even intake of a small amount of alcohol is a risk factor for CP.

Genetic Factors

Associations have been identified between several gene variants and ICP risk. In idiopathic disease, full sequence analysis of the following genes has been recommended in international consensus guidelines: cationic trypsinogen (*PRSS1*), carboxypeptidese A1 (*CPA1*), serine protease inhibitor Kazal type 1 (*SPINK1*), chymotrypsinogen C (*CTRC*), carboxyl ester lipase (*CEL*), and cystic fibrosis transmembrane conductance regulator (*CFTR*) [5]. Variants of these genes are classified into three categories according to mechanisms in the pathogenesis of CP. Variants of *PRSS1*, *SPINK1*, and *CTRC* are involved in the trypsin-dependent pathway. Variants of *CPA1* and *CEL* are involved in the misfolding-dependent pathway, which is associated with protein misfolding and endoplasmic reticulum stress. Variants of *CFTR* are involved in the ductal pathway, which is related to disruption of chloride-bicarbonate channel activity in pancreatic duct cells [2,11]. Mutations in *PRSS1* and *CPA1* are associated with >300-fold and 25-fold higher risk of CP, respectively; thus, they are occasionally referred to as hereditary CP. The other gene variants have relatively low risk effects and are associated with sporadic CP with no family history [5].

A US multicenter study reported that 49% of patients with EO-ICP carried a pathologic variant associated with one or more of the following genes: *CFTR*, *SPINK1*, and *CTRC*. A *SPINK1* mutation significantly accelerated the onset of symptoms in the EO-ICP group, from age 22 to age 12 [13]. A study from India reported that the *SPINK1* N34S mutation was present in 42% of patients with ICP, which was significantly higher than the percentage in patients with ACP (17%) and controls (4%). This study also reported that 50% of patients with ICP and 10% of controls had *CFTR* variants [30]. Heterozygous *SPINK1* mutations reportedly do not cause pancreatitis. It appears that patients with heterozygous *SPINK1* mutations must also have a mutation in other susceptibility genes (e.g., *PRSS1* or *CFTR*) in order to develop recurrent acute pancreatitis (RAP) or CP [38].

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Other Rare Causes

Pancreatic divisum

Pancreatic divisum (PD) is the most common congenital malformation of the pancreas. It involves a congenital disconnection between the main pancreatic duct and the major papilla. PD is classified as an obstructive cause of CP [3]. Although increased pressure in the dorsal pancreatic duct and minor papilla have been reported in PD, the majority of patients with PD are asymptomatic. Therefore, there is considerable debate as to whether it is causally associated with pancreatitis or abdominal pain [39]. Some reports indicate that the existence of a genetic cofactor plus PD leads to the development of CP. Garg et al. reported *SPINK1* mutations in 41.7% of patients with PD and ICP, which was significantly higher than 2% in healthy controls. They also reported that 41.7% of patients carried *CFTR* gene polymorphisms [40]. Bertin et al. reported the frequency of PD in patients with RAP or CP is significantly associated with *CFTR* mutations or polymorphisms [41].

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a distinct form of pancreatitis. Therapeutically, AIP has a dramatic response to steroids. AIP is classified into type 1, which is a type of IgG4-related systemic disease, and type 2, which frequently accompanies inflammatory bowel disease [42]. Currently, the long-term prognosis of AIP is not well understood. However, an international study group reported pancreatic duct stones in 7% of patients with type 1 AIP, but not in patients with type 2 AIP [43]. According to a report from Japan, among 52 patients with type 1 AIP who had no pancreatic stones at diagnosis, 20 (38.5%) of them developed *de novo* pancreatic stones after 3 or more years of follow-up [44]. The relationship between AIP and classic CP will become clearer in the future.

Hyperparathyroidism

The causal relationship between primary hyperparathyroidism (hypercalcemia) and RAP or CP is debatable. A systematic review demonstrated AP or CP occurred in 1.5% to 15.3% of patients with primary hyperparathyroidism, but the included studies had confounding factors, biases, and a lack of appropriate controls. In addition, the authors suggested the pancreatitis in this setting is likely the result of additional genetic and environmental factors [45]. Aslam et al. reported that hyperparathyroidism accounted for 1.94% of RAP or CP cases. In patients with CP associated with hyperparathyroidism, severe pain was a predominant symptom. After parathyroidectomy and subsequent decreases in serum calcium levels, there was a reduction in their symptoms [46].

Hyperlipidemia

Hypertriglyceridemia is a well-established but underestimated cause of AP and RAP. However, whether hypertriglyceridemia can cause CP has not been well studied [47]. Vipperla et al. performed a retrospective study that reviewed the medical records of 121 patients with serum triglyceride levels of ≥500 mg/dL who experienced 225 attacks of AP between 2001 to 2013 at their institute in the United States. They found 20 (16.5%) of 121 patients were diagnosed with CP (9 with preexisting CP, 11 with new-onset CP during follow-up) [48]. Their relatively small single-center retrospective study needs to be validated in future prospective or large multicenter studies with simultaneous analysis of confounding factors such as alcohol intake and smoking.

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Early Chronic Pancreatitis

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Concept/Definition

The concept of chronic pancreatitis was established by Comfort et al. in 1946 [1,2]. They proposed that chronic pancreatitis was characterized by the progressive destruction of the pancreas. In the subsequently defined classification systems such as the Marseille classification [3], Cambridge classification [4], and Marseille-Roma classification [5], irreversible pancreatic changes associated with chronic pancreatitis were considered to cause permanent loss of pancreatic exocrine and endocrine functions. The conventional diagnostic criteria for chronic pancreatitis only enable us to detect the disease at the end stage, which ought to be irreversible. To improve the prognosis of chronic pancreatitis patients, it is indispensable to diagnose chronic pancreatitis in the early stage and prevent its progression through early interventions.

In 1996, the term "early-stage alcoholic chronic pancreatitis" was used to define a clinical stage linking alcoholic acute pancreatitis and alcoholic chronic pancreatitis by Ammann et al. [6]. They emphasized that the diagnosis "early-stage alcoholic chronic pancreatitis" was confirmed by criteria independent from histology, i.e., the long-term follow-up that eventually revealed the typical clinical features of chronic pancreatitis. It could only be diagnosed in a retrospective manner.

The category of early chronic pancreatitis was the first to be introduced into the diagnostic criteria proposed by the Japan Pancreas Society in 2009 [7]. Early chronic pancreatitis corresponds to the stage at which chronic pancreatitis has already started with clinical symptoms and signs of pancreatic injury; however, characteristic morphological changes of the pancreas have still not been detected clearly on conventional imaging modalities. Theoretically early chronic pancreatitis is considered to be a reversible pathological condition [8].

A new mechanistic definition of chronic pancreatitis was proposed by Whitcomb et al. in 2016 [9]. A conceptual model of chronic pancreatitis was derived, recognizing that subjects may exist in: (A) "at-risk" state of chronic pancreatitis, or in four active states; (B) acute pancreatitis-recurrent acute pancreatitis; (C) early chronic pancreatitis; (D) established chronic pancreatitis; and (E) end-stage chronic pancreatitis (Fig. 50.1). Early chronic pancreatitis may overlap conceptually with "minimal change chronic pancreatitis" or "pre-chronic pancreatitis," depending on eventual diagnostic criteria and distinctions from other states. The transition from "B" to "C" involves detection of biomarkers of chronic pancreatitis pathogenesis or pathology, but does not reach a state of "D." Biomarkers may be biochemical, structural or functional. The transition from "C" to "D" involves progression of disease to a persistent state of pathology or dysfunction. This new definition of chronic pancreatitis may allow for a rational approach to early diagnosis.

However, there still has not been international consensus on the definition of early chronic pancreatitis. In 2018, international consensus statements on early chronic pancreatitis were developed by a working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group, and European Pancreatic Club [10]: morphology-based diagnosis of early chronic pancreatitis is not possible without additional information; new approaches to the accurate diagnosis of early chronic pancreatitis will require a mechanistic definition; such a definition will require prospective validation.

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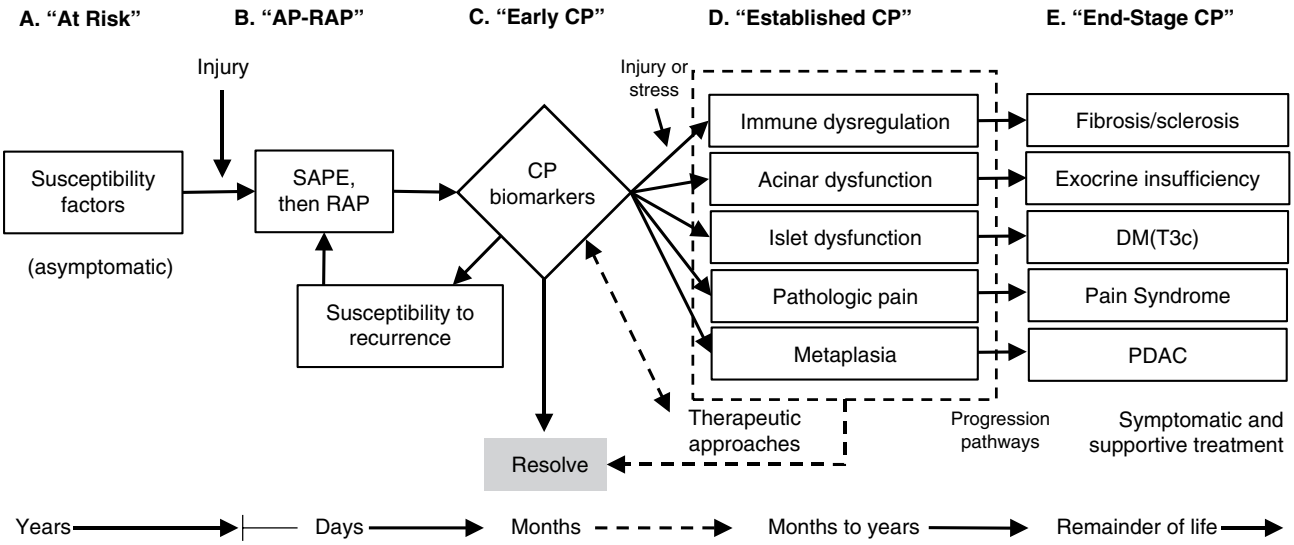


Figure 50.1 A conceptual model of chronic pancreatitis used for definition development [9]. AP: acute pancreatitis; RAP: recurrent acute pancreatitis; CP: chronic pancreatitis; SAPE: sentinel acute pancreatitis event; DM: diabetes mellitus; PDAC: pancreatic ductal adenocarcinoma. *Source:* Whitcomb et al. 2016 [9]. With permission of Elsevier.

Risk Factors/Etiology

Based on the new mechanistic definition of chronic pancreatitis [9], the risk factors of early chronic pancreatitis can be considered similar to those of recurrent acute pancreatitis and chronic pancreatitis. International classification systems such as TIGAR-O [11] and the M-ANNHEIM classification system [12] incorporate common etiological risks including alcohol and nicotine consumption, genetic mutations and polymorphisms, metabolic disorders, ductal obstruction, immunological factors, and idiopathic pancreatitis.

Epidemiology

A nationwide epidemiological survey of early chronic pancreatitis was conducted in Japan [13]. Patients with early chronic pancreatitis who were diagnosed according to the Japanese diagnostic criteria 2009 [7] and had visited the selected hospitals in 2011 were surveyed. The estimated prevalence and the annual incidence of early chronic pancreatitis were 4.2 and 1.0 per 100,000 persons, respectively. The male-to-female sex ratio was 1.32:1. The mean age was 60.4 and the mean age at disease onset was 55.4. The common etiologies were idiopathic (47.7%) and alcoholic (45.0%).

Clinical Presentation

A history of acute pancreatitis, especially recurrent acute pancreatitis, is a significant risk factor for early chronic pancreatitis [9,10,14,15]. However, some patients with chronic pancreatitis are asymptomatic during the early stage, and incidental imaging findings, steatorrhea, or diabetes may be the first clinical manifestation of chronic pancreatitis. According to a nationwide epidemiological survey conducted in Japan, 91.4% of patients with early chronic pancreatitis had recurrent upper abdominal pain, and 81.5% had abnormal pancreatic enzyme levels in the serum or urine. Only 13.9% were positive for abnormal pancreatic exocrine function [13].

Diagnosis

There still has not been international consensus on the diagnostic criteria for early chronic pancreatitis.

In 2009, the Japan Pancreas Society proposed the world's first diagnostic criteria for early chronic pancreatitis in the Japanese clinical diagnostic criteria for chronic pancreatitis 2009 (DC2009) [7]. In 2019, the Japan Pancreas Society proposed the revised DC2009, namely, "clinical diagnostic criteria for chronic pancreatitis 2019 (DC2019)" (Table 50.1) [17]. Early chronic pancreatitis is diagnosed using a combination of five clinical signs: (i) repeated upper abdominal or back pain; (ii) abnormal pancreatic enzyme levels in the serum or urine; (iii) abnormal pancreatic exocrine function; (iv) continuous heavy drinking of alcohol equivalent to or more than 60 g/day of pure ethanol or mutation in the pancreatitis-associated gene such as *PRSS1* and *SPINK1*; (v) past history of acute pancreatitis; and imaging findings on EUS, MRCP, or ERCP. Imaging findings on EUS were

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Table 50.1 Japanese clinical diagnostic criteria for chronic pancreatitis 2019 *Source:* [16]/Springer Nature.

Diagnostic items for chronic pancreatitis
① Characteristic imaging findings
② Characteristic histological findings
③ Repeated upper abdominal or back pain
④ Abnormal pancreatic enzyme levels in the serum or urine
⑤ Abnormal pancreatic exocrine function
⑥ Continuous heavy drinking of alcohol equivalent to ≧60 g/day of pure ethanol or mutation in the pancreatitis-associated gene
⑦ Past history of acute pancreatitis
Imaging findings of early chronic pancreatitis
Either (a) or (b)
a) More than two features among the following four EUS findings including (1) or (2)
1) Hyperechoic foci (non-shadowing) or strands
2) Lobularity
3) Hyperechoic MPD margin
4) Dilated side branches
b) Irregular dilatation of more than three side branches on MRCP or ERCP
Definite chronic pancreatitis: either (a) or (b)
a) Definite findings of ① or ②
b) Probable findings of ① or ②, plus more than two items among ③, ④, and ⑤
Probable chronic pancreatitis
Probable findings of ① or ②
Early chronic pancreatitis
More than three items among ③~⑦ plus imaging findings of early chronic pancreatitis

Note 1: Differential diagnosis from other pancreatic diseases especially pancreatic cancer and intraductal papillary mucinous neoplasm is important.
Note 2: If imaging findings of early chronic pancreatitis were absent, a diagnosis of possible chronic pancreatitis could be made in the patients without ① and ②, but with more than three items among ③~⑦ after ruling out other diseases. Imaging examinations including EUS are recommended for the patients with possible chronic pancreatitis.
Note 3: Patients with only two items among ③~⑦ and imaging findings of early chronic pancreatitis are regarded as possible early chronic pancreatitis after ruling out other diseases, and require careful follow-up. Footnote: Long-term prognosis should be clarified in patients with early chronic pancreatitis.

consolidated from seven items in DC2009 to four items: hyperechoic foci (non-shadowing) or strands; lobularity; hyperechoic MPD margin; dilated side branches. Early chronic pancreatitis can be diagnosed if a patient does not justify a diagnosis of definite or probable chronic pancreatitis, but satisfies at least three of five clinical signs and imaging findings of early chronic pancreatitis. The approach by the Japan Pancreas Society still has not been fully accepted internationally, while it provides a potentially useful definition of early chronic pancreatitis.

It has also been reported that three or more attacks of acute pancreatitis with no morphological changes to the pancreas can be an improved diagnostic criterion for early chronic pancreatitis [16].

Diagnostic Modalities for Early Chronic Pancreatitis

Transabdominal Ultrasonography (US)

Transabdominal US is recommended as the first-line noninvasive imaging approach for evaluating patients with suspected chronic pancreatitis. However, the ability of transabdominal US to diagnose early chronic pancreatitis has not been fully validated. HaPanEU/UEG working group indicated that abdominal US can only be used to diagnose chronic pancreatitis at an advanced stage [17].

Computed Tomography (CT)

The ability of CT to diagnose early chronic pancreatitis has not been fully validated as well as transabdominal US.

Magnetic Resonance Imaging (MRI)

Japanese clinical diagnostic criteria for chronic pancreatitis 2019 incorporated a finding of irregular dilation of more than three side branches on MRCP into diagnostic criteria for early chronic pancreatitis [16]. This MRCP finding has been defined in accordance with image grading "mild" of ERP defined in the Cambridge classification [4]. The ability of MRCP to diagnose early chronic pancreatitis needs to be prospectively verified.

T1-weighted MR signal of the pancreas, which was associated with pancreatic exocrine dysfunction [18] and the grade of ductal changes under the Cambridge classification [19], may be helpful in the evaluation of suspected early chronic pancreatitis. Main pancreatic duct irregularity, T1-weighted MR signal, and duodenal filling after secretin injection may be predictors of pancreatic fibrosis [20].

Endoscopic Ultrasonography (EUS)

EUS is considered the most sensitive modality for detecting early chronic pancreatitis, although early chronic pancreatitis may not be diagnosed by current imaging techniques [10]. So far, there is no consensus cutoff of EUS findings for establishing a diagnosis of early chronic pancreatitis.

In 2009, Japanese clinical diagnostic criteria incorporated EUS findings into diagnostic criteria for early chronic pancreatitis [7]. Considering the diagnosis of

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indeterminate for chronic pancreatitis based on the Rosemont classification [21], five features of pancreatic parenchymal factors (lobularity with honeycombing; lobularity without honeycombing; hyperechoic foci without shadowing; stranding; cysts) and two features of pancreatic ductal factors (dilated side branches; hyperechoic MPD margin) were adopted for the EUS findings of early chronic pancreatitis. In the 2019 revision of diagnostic criteria, EUS findings were consolidated from seven items to four items: lobularities with and without honeycombing were consolidated to lobularity; hyperechoic foci without shadowing and stranding were consolidated to hyperechoic foci (nonshadowing) or strands; and cysts were removed from the diagnostic items (Table 50.1) [16]. The interobserver reliability of EUS criteria of diagnostic criteria 2019 was higher than that of diagnostic criteria 2009 [22].

Elastography

EUS-elastography has recently allowed the evaluation of the elasticity of deep organs, such as the pancreas [23,24]. The usefulness of EUS-elastography for the diagnosis of early chronic pancreatitis has yet to be established [25], although there has been a single arm study that patients with suspected early chronic pancreatitis had an abnormally high strain ratio at EUS-elastography [26].

ERCP

The Japanese clinical diagnostic criteria incorporated a finding of irregular dilation of more than three side branches on ERP into diagnostic criteria for early chronic pancreatitis [7,16]. This ERP finding has been defined in accordance with image grading "mild" defined in the Cambridge classification [4]. The ability of ERP to diagnose early chronic pancreatitis needs to be prospectively verified.

Pancreatic Function Testing

Exocrine pancreatic insufficiency is a common complication of chronic pancreatitis. Conversely, early chronic pancreatitis is considered to be a stage of chronic pancreatitis with preserved pancreatic function and potentially reversible features [10]. The usefulness of pancreatic function testing for the diagnosis of early chronic pancreatitis still has not been established, although it is considered that early chronic pancreatitis can be diagnosed by a combination of factors including pancreatic function testing [10].

Direct hormone-stimulated tests, using cholecystokinin or secretin, are considered the most sensitive and specific tests for pancreatic insufficiency. The positive predictive value of the secretin pancreatic function testing for the subsequent development of chronic pancreatitis has been reported to be 45% with a negative predictive value of 97% [27].

The Japanese clinical diagnostic criteria incorporated a finding of abnormal results in BT-PABA test into diagnostic criteria for early chronic pancreatitis [7,16]. Based on this criteria, only 13.9% of early chronic pancreatitis was positive for abnormal pancreatic exocrine function [13].

Fecal elastase-1 is considered to be inappropriate for the diagnosis of early chronic pancreatitis because the correlation of fetal elastase-1 with mild ductal changes is not strong [28,29].

Histological Evaluation

While conventional chronic pancreatitis has been diagnosed mainly on the basis of structural changes related to fibrosis, histological findings for the diagnosis of early chronic pancreatitis have not yet been established.

Furthermore, direct acquisition of pancreatic tissue for the diagnosis of early chronic pancreatitis is limited. It has been reported that EUS-guided fine-needle biopsy provided inadequate material for the histological diagnosis of early chronic pancreatitis [30].

Biomarkers

So far, there are no widely accepted biomarkers for the diagnosis of early chronic pancreatitis [10]. There is a report that indicated the usefulness of blood-based microRNA biomarker panel for the diagnosis of early chronic pancreatitis [31].

Genetic Markers

Genetic variants are important risk factors for early chronic pancreatitis and can add specificity to the likely etiology, but they are neither necessary nor sufficient to make a diagnosis of early chronic pancreatitis [10]. The Japanese clinical diagnostic criteria has incorporated mutations in the pancreatitis-associated genes such as *PRSS1* and *SPINK1* for the diagnosis of early chronic pancreatitis [16].

Management/Treatment

Evidence for the management of early chronic pancreatitis is insufficient.

In patients with acute pancreatitis or recurrent acute pancreatitis, it is important to evaluate risk factors in

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order to prevent disease progression [11]. It is expected that precision medicine will be established according to risk factors in the future. Alcohol abstinence and smoking cessation can be the mainstays for preventing the progression of early chronic pancreatitis.

It has been reported that a combination treatment of proton pump inhibitor, camostat mesilate, and pancrelipase improved epigastric pain [32] and EUS findings [33] in patients with early chronic pancreatitis.

Prognosis

Prospective study of early chronic pancreatitis diagnosed based on the Japanese diagnostic criteria 2009 was conducted in Japan [14]. Among the 83 patients who completed the 2-year follow-up period, four (4.8%) patients progressed to definite chronic pancreatitis. The diagnosis of 48 (57.8%) patients was unchanged, and that of 31 (37.3%) patients was downgraded.

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51

Chronic Pancreatitis with Inflammatory Mass in the Pancreatic Head

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Definition

Chronic pancreatitis can present with enlargement and mass-formation of the pancreatic head, mimicking virtually all symptoms of a malignant pancreatic head tumor and confronting the clinician with significant diagnostic and therapeutic challenges. This phenomenon has been termed the "inflammatory (pseudo) tumor" [1], "tumor-forming chronic pancreatitis" [2], and other. For the purpose of this article, we will use the term inflammatory pancreatic head mass (IPHM).

From a pathophysiological point of view, IPHM is thought to result from recurrent acute and chronic inflammation of the pancreatic parenchyma, but at the same time to perpetuate disease progression as a "pacemaker" by causing main pancreatic duct (MPD) obstruction leading to chronic ductal hypertension [3]. There is no generally accepted definition of IPHM, but the following criteria may be applied: presence of an abnormally enlarged pancreatic head, often accompanied by pancreatic calcifications, MPD dilatation, and irregularities and atrophy of the pancreatic parenchyma to the left of the mesentericoportal axis [4–6] (Figs 51.1 and 51.2).

Incidence

The concept of the IPHM as a pacemaker of chronic pancreatitis has been established by Beger et al. [3] and followed mainly by European surgeons. The incidence of IPHM in surgical patients is in the range of 85%; however, exact figures have rarely been reported in detail [5,7]. The average size of the pancreatic head has been shown to be significantly larger in a study comparing German (median 4.5 cm) and North American (median 2.6 cm) patients undergoing surgery for chronic pancreatitis [5]. The significance of this finding lies in the fact that it explains regional differences in operative procedures used to treat chronic pancreatitis; however, the underlying cause is not clear. Reasons might be a pattern of clinical transfer of the patient from the gastroenterologist to the surgeon, genetic differences, or different risk factors for the development of chronic pancreatitis.

Symptoms, Pathophysiology, and Clinical Problems

An IPHM can cause many clinical symptoms and complications, which in principle constitute the classical complications of chronic pancreatitis. Differential diagnosis and decision-making may be complicated as virtually all of these symptoms can also be caused by pancreatic head cancer.

One of the most frequently reported symptoms is pain [4,7]. Typically, the pain maximum is located to the epigastric area and may radiate to the flanks and back. In some cases, however, back pain may be the primary complaint. The pain can be episodic or continuous, with sudden exacerbations of variable frequency from daily to once in several months, often triggered by alcohol or food intake. Signs of acute pancreatitis like elevation of serum amylase or lipase and edematous swelling of the pancreatic head are often found associated with severe acute pain attacks, but may as well be missing, especially with longer duration of disease. In line with this, there is good evidence from histopathological and experimental studies that pancreatic pain is not only caused by acute inflammation but also from chronic neuropathy of visceral nerves in the pancreas [8]. Importantly about 50–90% of patients will not become pain-free even 10 years after disease onset [9].

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Figure 51.1 Inflammatory pancreatic head mass. Computed tomography showing a large inflammatory pancreatic head mass in a patient with chronic pancreatitis, with typical diffuse pancreatic calcifications and a large pseudocyst in the pancreatic head.

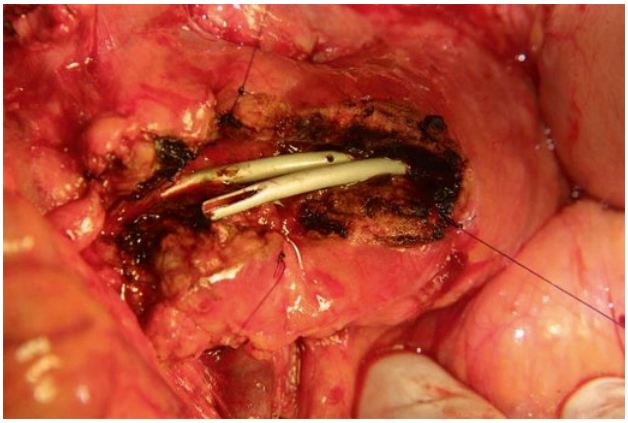


Figure 51.2 Impacted stent in the irregular and scarified main pancreatic duct. Prolonged interventional treatment leading to nonremovable stents in the pancreatic duct with marked pancreatic duct irregularities and narrowing.

Episodes of acute pancreatitis can lead to the development of pancreatic pseudocysts or walled-off necrosis (WON, Fig. 51.3) [10], with secondary complications like superinfection, pseudoaneurysm, hemorrhage, compression of the duodenum or bile duct, internal pancreatic fistula, and pancreatic ascites.

Biliary stricture is reported in up to 35% of patients [6], leading to jaundice and recurrent cholangitis. Of note, subclinical common bile duct (CBD) narrowing can be aggravated to frank obstruction by acute edematous swelling of the pancreatic head during episodes of acute

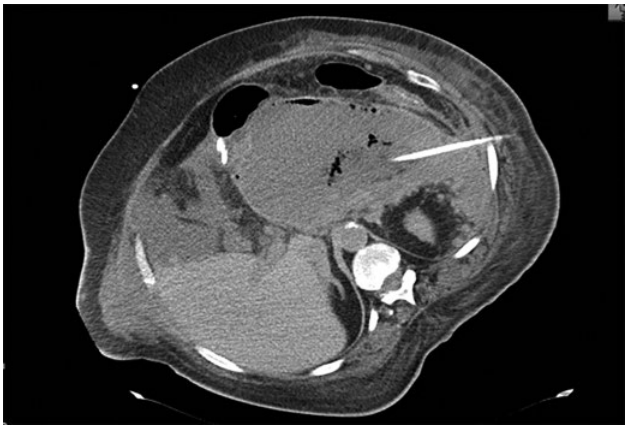


Figure 51.3 Walled-off necrosis. Magnetic resonance imaging depicting an inflammatory pancreatic head mass with walled-off necrosis which developed after an episode of acute pancreatitis in a patient with chronic pancreatitis. External interventional drainage.

pancreatitis. Maldigestion and absorption with steatorrhea, coagulopathy, and malnutrition occurs as a result of persistent cholestasis. Duodenal stenosis is found in about 10% of patients [6], resulting in gastric dilatation, postprandial bloating and vomiting, anorexia and malnutrition. Malnutrition may be exaggerated by pancreatic exocrine insufficiency. Loss of endocrine function typically occurs later and will affect around 80% of patients [9]. Stenosis and finally thrombotic occlusion of the mesentericoportal vessels is usually a late complication. Occlusion of the splenic vein results in left-sided portal hypertension with development of gastric fundal varices and splenomegaly. As complete occlusion of the portal vein usually develops gradually, extensive collaterals develop around the pancreatic head, a phenomenon called cavernous transformation [6]. Patients suffering from chronic pancreatitis have a 10-fold elevated risk of about 3% to develop pancreatic cancer [9].

Clinical Workup and Differential Diagnosis

The most important differential diagnoses are pancreatic head cancer and autoimmune pancreatitis. Careful clinical history-taking can yield important hints. Longstanding complaints or recurrent attacks over a period of years rather than months, accompanied by signs of chronic malnutrition points toward benign IPHM, whereas clinical deterioration over weeks to months with weight loss or new-onset diabetes mellitus are suggestive of malignancy. Jaundice can occur with IPHM but should always prompt efforts to rule out malignancy. Associated autoimmune disease points to autoimmune

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pancreatitis [11]. Laboratory workup should include serum amylase and lipase activity and carbohydrate antigen 19-9 (CA19-9), as elevated serum enzyme activity indicates an episode of acute pancreatitis, whereas marked elevation of the tumor marker in absence of acute pancreatitis is suggestive of malignancy. Sensitivity and specificity of CA19-9 for discrimination of chronic pancreatitis from PDAC were reported as 84% and 75% [12]. Serum immunoglobulin G4 (IgG4) can be increased in autoimmune pancreatitis [13]. Because of the risk of tumor spillage and lack of therapeutic consequences, tissue biopsy is not recommended when resectable malignancy is suspected.

Cross-sectional imaging by contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) is mandatory. In IPHM, the pancreatic head is enlarged with loss of the lobular parenchymal architecture, calcifications, and narrowing of the pancreatic duct (Fig. 51.1). There can be mass-forming lesions in the pancreatic head virtually indistinguishable from pancreatic cancer. Upstream MPD dilatation is often absent in autoimmune pancreatitis [11]. Accuracy of modern cross-sectional imaging for differentiation of IPHM and pancreatic cancer has been reported in the range of 90% [14]. Magnetic resonance cholangiopancreatography can be a valid substitute for invasive endoscopic retrograde cholangiopancreatography (ERCP) to assess configuration of the biliary tree and MPD (Fig. 51.2). In view of eventual surgical intervention, it is of paramount importance to assess mesentericoportal vein status and signs of portal hypertension.

Treatment

Asymptomatic IPHM virtually does not exist; however, symptom-free periods of weeks to months are common. Indications for invasive treatment are persistent pain or dependence on analgesics, recurrent acute pancreatitis, obstructive cholestasis, gastric outlet obstruction, development of persistent large or symptomatic pancreatic pseudocysts or walled-off pancreatic necrosis (WON), and suspicion of malignancy. Conservative management is chosen in case of inoperability or as a strategy to avoid operative treatment during a period of recovery, either after an episode of acute pancreatitis or as a bridge to operation.

Medical therapy consists of pain control and eventual substitution of pancreatic enzymes and insulin. It must be stressed that clinical remission of symptoms can be achieved by cessation of alcohol consumption in alcohol-induced chronic pancreatitis. Furthermore, the role of tobacco smoke as a causal agent has recently been recognized [15]. At least initially, surveillance of a pancreatic head mass by cross-sectional imaging should be performed every 3 to 6 months to rule out malignancy.

Endoscopic stenting of the MPD can be effective to induce remission of pancreatic cysts, pancreatic fistula as well as pain by decompression of the MPD. However, randomized trials have shown that surgical treatment provides more effective and durable pain control [16–18] and has been included in international guidelines [19,20]. For example, patients with obstructive chronic pancreatitis, who recently started opioid treatment (no longer than 6 months) were randomized to either early surgical drainage (by a lateral pancreaticojejunostomy or duodenum-preserving pancreatic head resection) or endoscopic drainage (stent, lithotripsy) within 6 weeks of randomization. Izbicki pain score [21] was significantly lower in patients treated with surgery than with endoscopic intervention [18]. In addition, the Izbicki pain score was found to be able to identify those patients who benefit most from surgery [21]. Another disadvantage of endoscopic therapy is the necessity of regular stent exchange every 3 to 6 months to prevent cholangitis and tissue overgrowth; however, while efficacy is similar between plastic stents and metal stents, reintervention is lower in fully covered self-expanding metal stents as shown in a recent randomized controlled trial for benign biliary strictures due to chronic pancreatitis [22]. When a stent cannot be removed due to incrustation or migration, surgical intervention is needed (Fig. 51.1). Stenting of the CBD for obstructive jaundice is only a short-term option as remission of CBD obstruction can only be expected in cases of acute edematous swelling of the IPHM in acute pancreatitis.

Operative therapy can be divided into drainage procedures and those procedures that involve resecting a part of the pancreas. While drainage procedures aim at decompression of the MPD by pancreatojejunostomy, removal of the IPHM is the goal of resectional procedures, which can be combined with MPD drainage. On surgical exploration, the IPHM is usually found to be heavily indurated, and the inflammatory fibrotic process may extend into the peripancreatic tissues causing heavy adhesions to the organs in vicinity, like the retropancreatic blood vessels, duodenum, and hepatoduodenal ligament. These conditions render operative procedures involving the pancreatic head very challenging and in rare cases even technically impossible, especially when associated mesentericoportal hypertension leads to diffuse bleeding.

Radical pancreatoduodenectomy (PD) with (Longmire-Traverso [23]) or without (Kausch-Whipple [24,25]) preservation of the pylorus is the procedure of choice when malignancy is suspected and offers very good long-term pain control in chronic pancreatitis. For the IPHM, duodenum-preserving pancreatic head resection (DPPHR) was developed by Beger and colleagues [3]. In the Frey modification [26], pancreatic parenchyma is spared by

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excoriation of the IPHM without transsection at the pancreatic neck, and laterolateral pancreatojejunostomy ensures adequate MPD decompression. In the Hamburg modification of DPPHR [6], drainage of the MPD is further optimized by a V-shaped excision along the MPD. Randomized trials have shown reduced perioperative and short-term morbidity in DPPHR compared to PD with comparable long-term results [6]; however, long-term quality of life and serious adverse events after 24 months were equal between PD and DPPHR [27]. Equality in this context clearly speaks for duodenum-preserving procedures as organ preservation should be in the focus of every surgeon whenever possible. Equality was also reported for Beger versus Frey procedures [28,29] and so far no randomized trial has involved other DPPHR modifications.

Pure MPD drainage procedures like the Puestow-Gillesby [30] (pancreatic left resection with splenectomy and laterolateral pancreatojejunostomy), Partington-Rochelle [31] (laterolateral pancreatojejunostomy) or Izbicki [32] (longitudinal V-shaped excision and laterolateral pancreatojejunostomy) operations do not remove the IPHM. MPD drainage in unselected patients only achieved 50–65% permanent pain control [6], which is inferior to that of pancreatic head resection with 75–95% [33–45]. Although no randomized trial has compared drainage versus resection procedures, drainage procedures are therefore reserved for patients without IPHM.

However, in case of mesentericoportal vein occlusion with portal hypertension and cavernous transformation, pancreatic head resection becomes impossible and therapy is limited to operative or endoscopic MPD drainage. Preoperative recanalization of the portal vein can be performed in selected patients with short-segment portal vein occlusion [46]. Gastroenterostomy and hepaticojejunostomy are measures of last choice for biliary or duodenal obstruction.

Adequate timing is an important aspect in the management of patients with IPHM. Maximum duration of a trial of nonoperative management of IPHM should be 6 months, as optimal operative treatment usually becomes impossible in an advanced stage. In the presence of mesentericoportal vein narrowing or partial thrombosis, elective surgery should be performed as soon as possible, and prophylactic anticoagulation is advocated until surgery.

Certain contraindications impede early surgery. Cachexia should be treated by high-caloric nutrition with adequate simultaneous supplementation of pancreatic enzymes and vitamins, and in case of gastric outlet obstruction by jejunal tube feeding, to achieve adequate nutritional status for operation. Elective surgery is also not indicated before at least 3 months have passed since the last episode of acute pancreatitis. Serum pancreatic enzyme activity can be used to monitor acute pancreatitis activity.

On histopathological workup, IPHM is characterized by fibrotic atrophy of exocrine acinar epithelium, the remaining ductal and islet epithelia becoming "skeletonized" in fibrous connective tissue. Strong inflammatory granulocytic or lymphocytic infiltration is uncommon. In contrast, autoimmune pancreatitis typically shows duct-centric inflammation, with IgG4 positive plasma cells or granulocytic epithelial lesions [11]. As overall tissue organization is heavily disturbed and chronic pancreatitis can be associated with pancreatic intraepithelial neoplasia (PANIN), distinction from PDAC can be difficult even for experienced pathologists. Intraoperative frozen section examination at least of the surgical resection margins is mandatory and in case of any doubt, radical oncologic resection is warranted.

Summary

Chronic pancreatitis with inflammatory pancreatic head mass is a domain of surgical therapy. The main differential diagnoses are pancreatic head cancer and autoimmune pancreatitis. Best results are achieved by resection of the pancreatic head mass with adequate drainage of the pancreatic duct, but pancreatic head resection may become impossible in advanced stages of the disease. Adequate workup and timing of conservative and surgical therapy is of paramount importance for successful management.

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Structural Complications: Strictures, Stones, Pseudocysts, and Vascular Complications

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Introduction

Chronic pancreatitis (CP) is a chronic inflammatory process in the pancreas, during which the pancreatic parenchyma is pathologically replaced by fibrous connective tissue, resulting in a series of structural complications and progressive insufficiency of exocrine and endocrine function [1]. Morphologic changes of the pancreas are one of the important features during CP, though they are usually not apparent in the early phase. The typical structural complications include, but are not limited to, strictures of pancreatic duct and/or biliary tract, intraductal stones, development of pseudocysts, and peripancreatic vascular complications. These structural changes will lead to dilation of the pancreatic duct, intraductal high pressure, and parenchyma atrophy of the pancreas. The corresponding clinical manifestations are malnutrition and pain syndromes.

A comprehensive understanding of the natural history of CP is also important, since the evolution of changes in morphology and function may take years to manifest.

Pathophysiologic Basis and Morphological Features of the Pancreas

The pathogenic mechanism of CP remains elusive and controversial. Several theories have been proposed in the past several decades: toxic-metabolic, oxidative stress, stone and duct obstruction, necrosis-fibrosis, primary duct hypothesis, and sentinel acute pancreatitis event hypothesis [2]. Each of these models is compelling and provides a certain mechanism to explain the diverse etiologies of CP, providing rationale for the cardinal pathologic changes of fibrosis, loss of acinar tissue (atrophy), stones, and duct changes. Grossly, the pancreas becomes firm and shrunken, with an irregular contour. Dilated pancreatic duct is usually presented due to the obstruction of main pancreatic duct caused by either inflammatory fibrosis around the duct or intraductal stones. Fibrous scarring may result in the distortion or disappear of the normal macroscopic lobulation. Parenchyma calcifications and pseudocysts formation may be related to specific etiologies.

Strictures of Pancreatic Duct, Biliary Tract or Duodenum

Pancreatic parenchyma is replaced by fibrosis in advanced CP patients, and the recurrent inflammatory episodes might develop periductal fibrotic strictures, leading eventually to pancreatic duct stricture. The most common reasons for pancreatic duct strictures are inflammation, fibrosis, and previous stone [6]. However, Kalady et al. [7] had reported that nearly 12% of the CP patients with isolated pancreatic duct strictures were associated with malignancy, especially for those without pancreatitis history or irregular pancreatic duct side branches, as well as those with stricture located only in the head or neck. Therefore, all newly developed pancreatic duct strictures should be further evaluated by EUS or CT/MRI before treatment. The endoscopic management (ERCP or EUS-guided pancreatic drainage) is suited for CP patients with localized strictures, and surgical approaches remain the key choice for selected patients [8,9].

Stricture of common bile duct (CBD) is reported to be usually caused by fibrosis of the pancreatic head, which

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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exerts extrinsic pressure on the intrapancreatic CBD. Moreover, inflammation caused by either pancreatic calculi or pseudocysts in the pancreatic head was also reported to contribute to significant biliary stricture during the acute phase [10]. The incidence of CBD stricture in CP patients ranges from 3% to 46%, and approximately 17% present as asymptomatic cholestasis [6]. Treatment of CBD stricture depends on the patients' manifestation and morphologic changes of the pancreas. The indications for biliary decompression include cholangitis, severe and persistent jaundice, and occurrence of CBD stones. The drainage of bile duct can be accomplished either endoscopically or surgically. Despite the minimally invasive advantages of endoscopic therapy, there is still no evidence on which is the better strategy for CP-associated biliary stricture, while surgical interventions showed superior results in terms of long-term pain relief [11]. In a multicenter randomized study of multiple plastic stents versus covered self-expandable metallic stent (cSEMS) in the treatment of biliary stricture in CP patients, Haapamäki and colleagues found that a 6-month treatment with either multiple plastic stents or cSEMS produced good long-term relief of biliary stricture [12]. Surgical treatment should also be considered if bile duct obstruction recurs after long-term endoscopic therapy. Moreover, surgery must be undertaken if malignancy cannot be excluded.

Around 5% of CP patients developed duodenal stenosis due to paraduodenal pancreatic inflammation, named groove pancreatitis (GP), which is characterized by scarring between the duodenum and pancreatic head, accompanied by blood vessels compression, CBD stricture, duodenal wall rigidity, and luminal narrowing (Fig. 52.1) [13,14]. Patients with GP usually complain of upper abdominal pain, nausea, recurrent vomiting with weight loss for weeks to years. The characteristic manifestation is duodenal stenosis resulting in gastric outlet obstruction. Although tubular stricture of CBD is frequent, obstructive jaundice is rarely presented, and the main pancreatic duct is normal in most patients, which helps differentiate it from pancreatic adenocarcinoma. However, differentiating GP from pancreatic cancer is difficult because both of these two diseases are associated with similar clinical presentation, radiologic findings, as well as gross pathologic features [14]. Conservative and endoscopic treatments are helpful in many cases, while surgical intervention may be necessary in cases either with diagnostic uncertainty or severe obstructive symptoms.

Pancreatic Ductal Stones

Pancreatic ductal stones are a direct consequence of CP and occur in approximately 50% of cases, with the prevalence increasing over time to reach 50% at 5 years and nearly 100% after 14 years of the disease onset [16]. Pancreatic stones can cause outflow obstruction and produce upstream ductal hypertension and subsequent parenchymal hypertension, thus result in pseudocysts or fistula formation, recurrent exacerbations or contribution to the pathogenesis of pain.

Long-term alcohol consumption has been identified to be a major cause of calcium stone formation, which is possibly through disturbing the cholinergic regulation of pancreatic secretions and aggravating the loss of endocrine and exocrine functions [17]. Noticeably, pancreatic ductal stones are also common in nonalcoholic CP

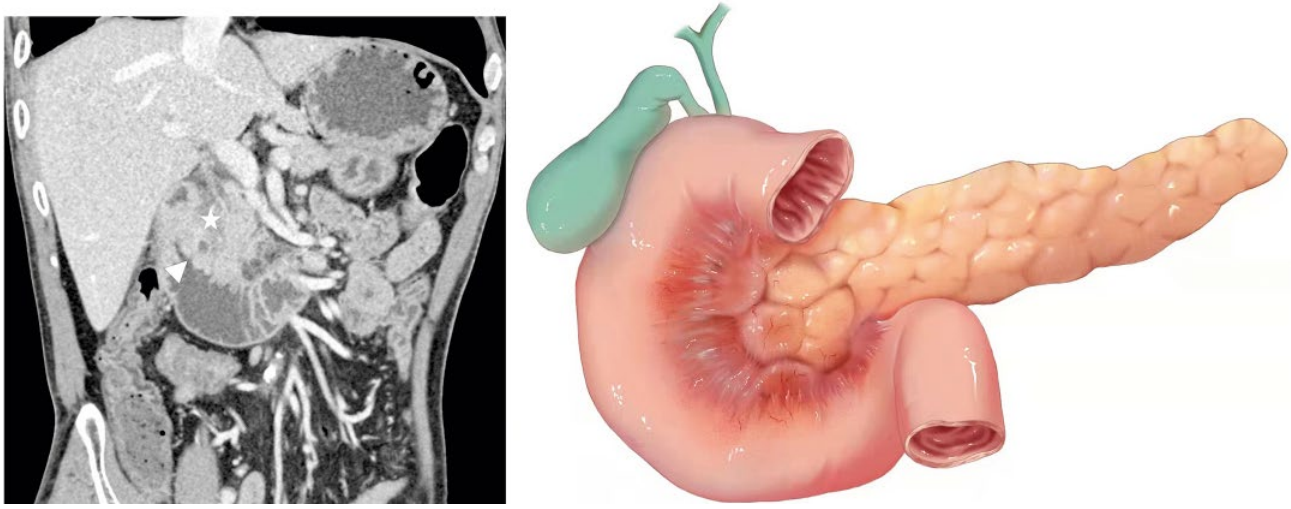


Figure 52.1 Groove pancreatitis. Left: coronal reconstruction image of contrast-enhanced CT. "Sheet-like" hypodense and "patchy" enhanced soft tissue are shown in the pancreatic-duodenal groove (asterisk). Medial duodenal wall is thickened with intramural cyst (arrowhead). Right: schematic diagram of groove pancreatitis. *Source:* Yinmo Yang.

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patients. Maruyama reported that pancreatic stone formation in autoimmune pancreatitis was associated with narrowing of both Wirsung and Santorini ducts, which may subsequently result in pancreatic juice stasis and stone formation [18]. Pancreatic duct stenosis promotes the formation of intraductal stones, while the stones lead to intraductal ulcers and scars, which aggravate the pancreatic duct narrowing and cause more stone formation, resulting in CP progression and even increasing risk of cancer [19]. In a retrospective analysis of risk factors for pancreatic duct stones formation, both the main pancreatic duct narrowing and chronic alcohol consumption were identified as significant independent risk factors, and the period between diagnosis of CP and pancreatic stones formation seemed significantly shorter in alcoholic CP patients than in nonalcoholic patients [20]. Hao and colleagues [21] constructed a pancreatic stone-predicting nomogram for CP patients, and found that the age at onset of CP, body mass index, smoking, diabetes mellitus, pancreatic pseudocyst, biliary stricture, severe acute pancreatitis, and type of pain were significantly associated with intraductal stone development.

Symptomatic CP patients and those with duct obstruction caused by the pancreatic ductal stones were eligible for endoscopic or surgical treatments [22]. To remove the intraductal stones, endoscopic therapy should be the first choice, especially for patients without other complications. While for patients with multiple strictures, calculi in the body/tail region, concerns of associated solid mass, or failure of endoscopic therapy, surgery should be considered.

Pseudocyst in CP

Pancreatic pseudocyst is a fluid accumulation with high concentration of amylase that is surrounded by a fibrous capsule (Fig. 52.2). Pseudocyst usually arises from the disruption of the main pancreatic duct or major duct branches. In contrast to real cyst, it has no internal epithelial cell lining and the patients might have a history of clinical manifestations related to acute or chronic pancreatitis. Pseudocyst is considered to be one of the most common complications of both AP and CP with the prevalence of 20–40% in CP patients [23]. It is more commonly presented in patients with alcoholic CP.

The symptoms of a pseudocyst are usually nonspecific, most patients only complain about vague abdominal pain, nausea, or vomiting [24]. In up to 40% of CP patients, the pseudocysts will spontaneously resolve after 6 weeks, and only conservative supportive care is needed. However, large cysts are more likely to become symptomatic or cause complications. When the pseudocyst persists for longer than 12 weeks, there will be rare possibility for it to disappear spontaneously, and the additional complications include infection, hemorrhage, pseudocyst rupture, and disruptions of the pancreatic duct system [24,25]. In cases where symptoms worsen or complications occur, multiple modalities of treatments including percutaneous drainage, endoscopic procedures, and surgical drainage can be offered depending on the individual patient profile.

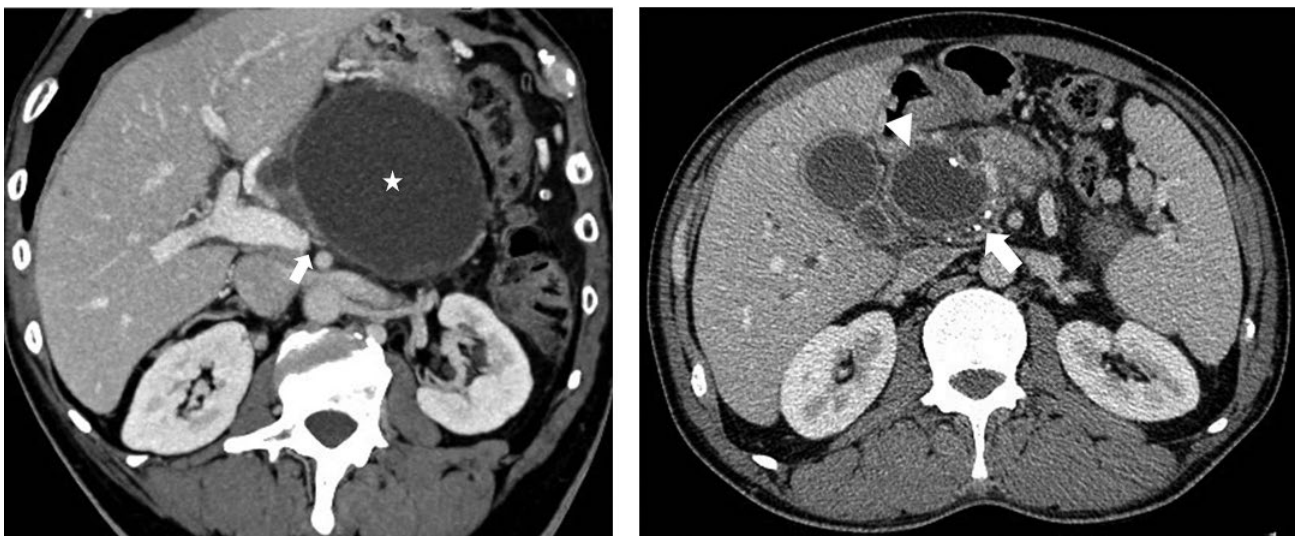


Figure 52.2 Pseudocysts in CP patients (contrast-enhanced CT). Left: pseudocysts (asterisks) can be seen in the pancreatic area, and splenic vein is occluded (white arrow). Right: pseudocyst (white triangle) is shown in the pancreatic head, with calcifications of the cystic wall and surrounding tissues (white arrow). *Source:* Yinmo Yang.

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Vascular complications of CP

Peripancreatic inflammation may affect the vessels in closest proximity to the pancreas, resulting in venous thrombosis most commonly involving the splenic vein, or pseudoaneurysm most commonly involving the splenic artery. Vascular complications occur in about 8.4–12.2% of CP patients, with the incidence of venous thrombosis and pseudoaneurysm approximately 7.6~10.9% and 0.8~2.5%, respectively [26,27]. Vascular complications were more commonly shown in males and alcoholic CP, while less commonly in patients with pancreatic atrophy and calcification [26]. Pseudocysts and alcoholic CP have been found to be risk factors for vascular complications in CP cases [27,28]. In a retrospective analysis of the database of 1363 patients with CP, alcoholic CP, presence of pseudocyst and inflammatory head mass were shown to be independent risk factors for venous thrombosis, whereas alcoholic CP and pseudocyst were identified as independent risk factors for pseudoaneurysm [26].

Consequences of pancreatitis-associated splenic vein thrombosis include gastroesophageal varices, venous collaterals, splenomegaly, and gastrointestinal bleed, with prevalences of 28.9%, 44.3%, 18.1%, and 14.1%, respectively [26]. Patients with pseudoaneurysm usually present with gastrointestinal bleeding, or are incidentally detected on contrast-enhanced CT done for other indications.

Sinistral portal hypertension (SPH), also known as regional, segmental, splenoportal, localized or left-sided portal hypertension, is a pathological condition of splenic vein hypertension localized in the left-sided gastrosplenic region, presents in less than 5% of all patients with portal hypertension (Fig. 52.3) [29]. In contrast to cirrhosis-related portal hypertension, SPH is characterized by normal hepatic function, isolated gastric varices, and splenomegaly. The CP-related SPH accounts for 31.8–53.8% of all cases, and the main etiology is splenic vein occlusion caused by venous thrombosis, extrinsic splenic vein compression by pseudocysts, inflammatory changes in the vascular endothelium, or relatively low perfusion associated with pancreatic fibrosis [30–31]. The incidence of SPH in patients with CP ranges from 9.7% to 22%, among which 4–17% develop severe gastrointestinal bleeding [26,31–35]. Splenomegaly is frequently observed in patients with SPH, while the incidence of hypersplenism is not as common as in portal hypertension. The site of gastrointestinal bleeding in patients with SPH is mainly located in the proximal stomach due to gastric varices, which is different from the lower esophageal hemorrhage in portal hypertension. Generally, CP-related SPH patients without history of gastrointestinal bleeding do not require surgical intervention [35]. Splenectomy is the most common therapeutic choice for SPH patients who experience gastrointestinal bleeding. Endoscopic therapy and splenic artery embolization could be the choices for patients

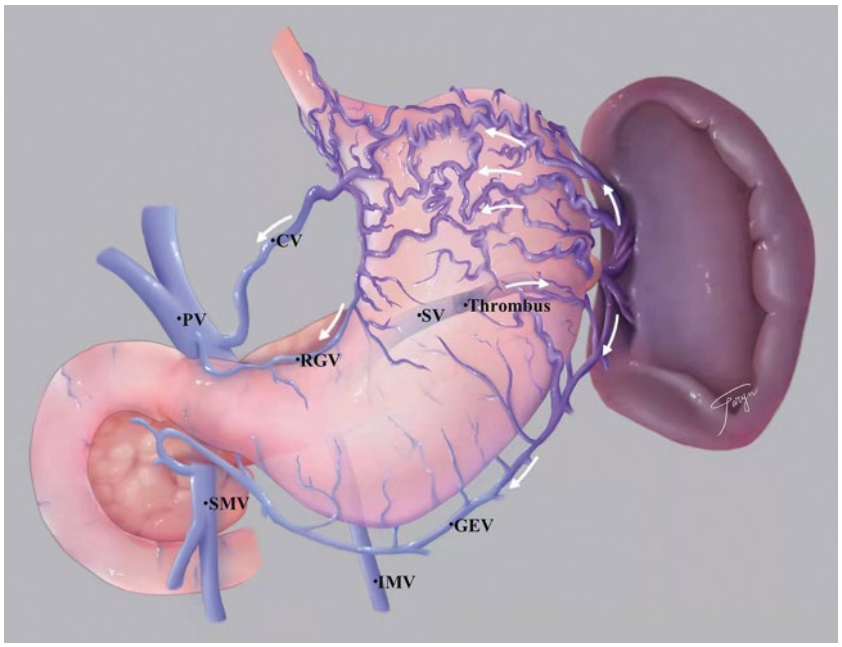


Figure 52.3 Schematic diagram of sinistral portal hypertension (SPH) caused by CP-related splenic vein thrombosis. PV: portal vein; CV: gastric coronary vein; RGV: right gastric vein; SV: splenic vein; SMV: superior mesenteric vein; IMV: inferior mesenteric vein; GEV: gastroepiploic vein. *Source:* Yinmo Yang.

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who are not suitable for surgery. However, for patients with SPH as the initial manifestation, the possibility of pancreatic cancer should be considered, because the involvement of splenic vein by pancreatic cancer is another important etiology of SPH.

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Nutritional Evaluation and Support: An Overview

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Introduction

Nutrition in chronic pancreatitis has been described as a problem area [1]. There is a high risk of undernutrition, and the etiology is multifactorial. Exocrine pancreatic insufficiency (EPI) results in the malabsorption of macro- and micronutrients. Moreover, pancreatic enzyme replacement therapy (PERT) is often underused and underprescribed [2], and may not fully restore normal digestive function [3]. Poor dietary intake is common due to abdominal symptoms, pain, heavy smoking, fear of eating (due to distressing synptoms), and (for some) alcohol abuse. However, not all patients with chronic pancreatitis are classically underweight (particularly in the earlier stages of diease), and some may be overweight or obese.

Undernutrition

The mean body mass index (BMI) of patients with chronic pancreatitis varies considerably between different countries, reflecting the general nutritional status of the country. Examples of BMI values reported for patients with chronic pancreatitis include: 19.3 kg/m^2 in India, 21.9 kg/m^2 in Italy, 22.1 kg/m^2 in Poland, 23 kg/m^2 in Denmark, 24 kg/m^2 in the Netherlands, and 25.9 kg/m^2/25.5 kg/m^2 in males/females in Ireland. Patients with chronic pancreatitis have consistently lower BMIs, lower muscle mass, and handgrip strength than matched controls. The clinical impact of overweight and obesity among patients with chronic pancreatitis is uncertain, but obesity may mask micronutrient deficiencies and sarcopenia. Those who abuse alcohol have an increased risk of undernutrition. High alcohol users tend to have poor nutrient intakes, either due to effects on appetite or due to displacement of food [4]. High alcohol intake also independently increases the risk of osteoporosis, and may be associated with diarrhea and malabsorption [5]. Sarcopenia, a disorder associated with loss of muscle mass, strength and function [6], may develop in patients with chronic pancreatitis, particularly if there is EPI [7].

Nutrient Deficiency

Specific nutrient deficiencies may arise in chronic pancreatitis as a result of steatorrhea (loss of fat-soluble vitamins), alcoholism (increased requirement or loss of water-soluble vitamins), or poor/imbalanced dietary intake. The prevalence of specific nutrient deficiencies varies between studies and countries [8]. They reported that the rate of vitamin A, D, and E deficiency were 16.8%, 57.6%, and 29.2% respectively, with considerable heterogeneity. Another systematic review found that while vitamin D insufficiency and deficiency were highly prevalent in patients with chronic pancreatitits, there was no significant difference between patients and healthy controls [9]. Only one study has investigated the prevalence of vitamin K deficiency, reporting that 63% of chronic pancreatitis patients had low serum levels of vitamin K [10], but vitamin K deficiency is more correctly measured by undercarboxylated osteocalcin or by measurement of proteins of vitamin K absence, and not by measurement of serum vitamin K or prothrombin time, both of which are inaccurate [12]. There have been few studies on other micronutrients, but isolated studies identified low magnesium [13] and zinc levels [14] among chronic pancreatitis patients. In a study from India, folate and vitamin B12 were reportedly lower in

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patients with tropical and alcohol-related chronic pancreatitis than in controls, and low levels correlated with increased oxidative stress. Smoking was associated with much higher risk of folate deficiency [15].

Despite the ostensibly common occurrence of biochemical vitamin deficiency, there are few published reports on the clinical manifestation of such deficiencies in chronic pancreatitis. The exception is vitamin D, which contributes (among other factors) to the well-documented high prevalence of osteoporosis [16]. Overt vitamin D deficiency resulting in osteomalacia (adult rickets) has also been reported [17]. Neurologic abnormalities associated with vitamin E deficiency have also been rarely reported. One patient out of 13 with biochemical vitamin E deficiency had typical neurologic manifestations along with poorly controlled diabetes [18]. A condition known as brown bowel syndrome (associated with vitamin E deficiency) has also been reported in a deficient patient with chronic pancreatitis, celiac disease, and adenocarcinoma of the colon [19].

Clinical manifestations of vitamin A deficiency tend to manifest as visual defects. One case report [20] described a 45-year-old male with chronic pancreatitis, chronic alcoholism, diabetes, and a history of cholecystectomy. The patient presented with steatorrhea, cachexia, low BMI, and severe weight loss, along with ocular pain, photophobia, and decreased visual acuity. A second report [21] described a patient with chronic pancreatitis, malnutrition, and vitamin A deficiency who developed ulcerative keratitis in one eye and necrotizing stromal ulceration with hyphema in the other eye. In general, clinical deficiencies appear to take years to develop, and occur when there is an additional comorbidity, such as celiac disease or diabetes, or post surgery.

Micronutrient Supplementation

There is a notable research gap regarding the management of nutrient deficiency in chronic pancreatitis, excepting vitamin D. In a study comparing oral vitamin D supplementation to ultraviolet B (UVB) radiation in chronic pancreatitis, oral supplementation (1520 IU/day) was significantly more effective in increasing serum 25(OH)D, achieving an increase of 32.3 nmol/L (95% 15–50 nmol/L) over 10 weeks [22]. High-dose, single-dose supplementation also appears to be safe and effective in increasing serum 25(OH)D. One study compared 600,000 IU or 300,000 IU single intramuscular injections or intramuscular saline, and found that the higher dose was more effective at increasing serum 25(OH)D, with no reports of hypervitaminosis or hypercalcemia [23].

There are few studies, if any, examining the effectiveness or safety of supplementing vitamins A, E, or K in patients with chronic pancreatitis and biochemical deficiencies. One study documented unexplained excess levels of vitamin A in patients with chronic pancreatitis who were not being supplemented [24]. Therefore, mass supplementation of patients is not recommended, nor is it possible to recommended dosage, administration methods, or specific patient types that warrant supplementation. A precision medicine approach is warranted, with measurement of serum vitamins and attention given to optimizing dietary intake and PERT.

Dietary Intervention

Nutritional status can be improved in chronic pancreatitis with the use of PERT when EPI exists, and by individualized dietary intervention and dietary counseling by an experienced dietitian who specializes in pancreatic disease and works within a multidisciplinary team [25]. In general, interventional studies investigating the effect of various treatments on nutritional status in chronic pancreatitis are scarce, representing a clear research gap. Nevertheless, active treatment works for those who receive it. A systematic review identified eight studies on the long-term nutritional effects of clinical interventions (including input by specialist dietitians, PERT dose escalation, supplementation, or tube feeding) [26]. All studies included in the review demonstrated improved weight gain and pain control compared to a deterioration of nutritional status in patients who were not treated.

Nutritional requirements are up to 35 kcal/kg per day [5,27], and 1.2–1.5 g protein/kg per day [5,27,28]. Particularly in the early stages, very low-fat diets (or fat-free diets) are not recommended as they decrease energy intake and make food less palatable [5,29]. Rather, PERT should be optimized to allow for a moderate fat intake. In the later stages of disease, or where gastrointestinal symptoms are difficult to manage, fat restriction may be necessary. In this case, care must still be taken to optimize PERT along with acid-suppression medications and to exclude other causes of malabsorption (such as small intestinal bacterial overgrowth and giardiasis). There is no evidence that vegetable fat is better tolerated than animal fat as no studies have investigated this [5]. Clinicians must also ensure that patients are compliant with PERT, that they understand how to take it appropriately, and that PERT capsules are suitably stored. For example, high temperatures may denature PERT, reducing their effectiveness. PERT should therefore not be stored in the pockets of tight-fitting clothing, on sunny windowsills, or in hot car

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glove compartments [30]. If PERT cannot be swallowed, the capsules may be opened and the microspheres placed in an acidic puree (such as apple sauce), and swallowed at intervals throughout the meal. The mouth should be rinsed well with cool water to prevent ulceration. They should not be allowed to touch, or remain in, the mouth [30].

Where malabsorption continues with apparently adequate PERT, a restriction in dietary fiber might improve absorption, as dietary fiber may reduce enzyme availability [5,27]. However, long-term fiber restriction should be avoided as a diet rich in fruit and vegetables should be recommended. For most patients, particularly in the later stages of disease or for those with intractable malabosprtion and distressing symptoms, a frequent, low-volume meal pattern should be advised with the avoidance of large meals at any sitting. A trial-and-error approach might be required as tolerance to food may be patient-specific. Some patients will require oral nutritional supplements if dietary intake alone is not adequate, and whole-protein types could be tried first before progressing to peptide-based or medium-chain triglyceride (MCT)-enriched supplements. Antioxidant supplementation for the treatment of chronic pancreatic pain was considered a promising treatment option [31], but subsequent studies cast doubt on its effectiveness [32]. A systematic review on the effect of antioxidants in pain reduction, adverse events, and quality of life found 12 studies, 4 of which were included in a meta-analysis [33]. The review found no effects on pain or improvement in quality of life for those taking antioxidants versus placebo, nor were there increased adverse events.

Enteral and Parenteral Nutrition

The vast majority of patients with chronic pancreatitis will be maintained on an oral diet, with or without supplementation. Enteral nutrition is indicated for malnourished patients who are unable to meet their requirements orally [28,34,35,36]. Enteral feeding via the jejunal route should be performed in the case of delayed gastric emptying, chronic subacute obstruction of the upper gastrointestinal tract by pancreatic cysts [37], and persistent nausea or vomiting, or pain [28]. Nasojejunal feeding is associated with a reduction in pain, pseudocysts, and inflammation, as well as improvements in nutritional status [38,39]. Where jejunal feeding is required for a prolonged period, a surgical jejunostomy could be considered [28,40]. With regard to the composition of enteral feeds, peptide-based, MCT-based formulas may be trialled where standard feeds are not tolerated [36].

Some patients may require the administration of PERT along with enteral feeds. Enzymes may be flushed via the feeding tube every 2 hours or added to the feed itself [30]. Parenteral nutrition should be avoided, if possible, as complication rates are higher in chronic pancreatitis due to pancreatic endocrine insufficiency (hyperglycemia) and immuno-incompetence (catheter sepsis). The use of transnasal endoscopic placement of distal jejunal feeding tubes in chronic pancreatitis usually avoids the need for commonly cited indications of parenteral nutrition, including gastric outlet obstruction secondary to duodenal stenosis, complex fistulating disease, and severe malnutrition prior to pancreatic surgery [34,36,41].

Combined Pancreatic Exocrine and Endocrine Deficiency

With end-stage calcific chronic pancreatitis, pancreatic endocrine deficiency exacerbates malnutrition and makes nutritional management even more challenging. Type 3c diabetes (also termed diabetes of the exocrine pancreas [42]) is known as "brittle diabetes" and carries a high risk of hypoglycemia and neuroglycopenia, due to insulin therapy, glycogen deficiency, enhanced peripheral insulin sensitivity, malabsorption, poor dietary intake, and, for some, persistent excess alcohol intake [43]. Rapid swings in blood glucose between hypoglycemia and hyperglycemia are common, the former due to impaired pancreatic glucagon and polypeptide responses, the latter exacerbated by unsuppressed hepatic glucose production [44]. Due to its volatile nature, patients may be wrongly assumed to be noncompliant with guidelines. Attempts to increase dietary intake and the addition of PERT to manage PEI may aggravate hyperglycemia further and have to be carefully covered by increased insulin therapy. Continous glucose monitors may be useful. Patients must be jointly managed with an endocrinologist, and careful dietary monitoring by a specialist diabetes dietitian is essential [29,44].

Structured Nutritional Assessment

Once diagnosed with chronic pancreatitis, patients should undergo thorough and regular nutritional assessment by an experienced, specialist dietitian, working in conjunction with the multidisciplinary team. Figure 53.1 summarizes the nutritional assessment of patients with chronic pancreatitis and includes eight key elements:

1) There should be an anthropometric assessment (including BMI, mid-upper arm circumference, triceps skinfold). Formal measures of sarcopenia may be useful.
2) A detailed assessment of current and habitual dietary intake should be undertaken.

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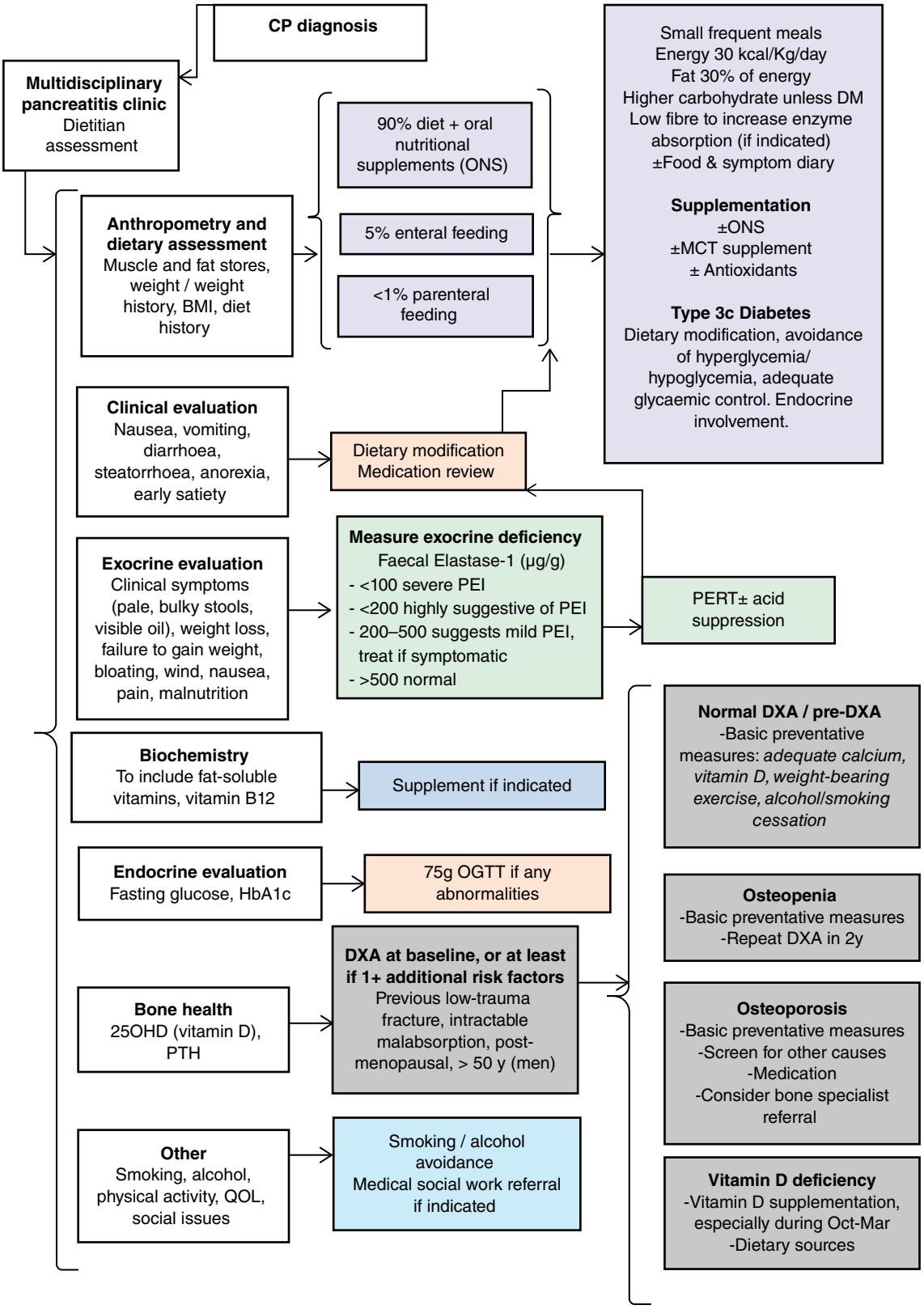


Figure 53.1 Structured nutritional assessment and intervention for patients with chronic pancreatitis (CP). DM, diabetes mellitus; ONS, oral nutritional supplement; MCT, medium-chain triglyceride; PEI, pancreatic exocrine insufficiency; OGTT, oral glucose tolerance test; DXA, dual X-ray absorptiometry; PTH, parathyroid hormone; QOL, quality of life; PERT, pancreatic enzyme replacement therapy. *Source:* Modified from Duggan et al. 2010 [5].

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3) Clinical evaluation should include the presence of nausea/vomiting, diarrhea, malabsorption, bloating, wind, anorexia, early satiety, and pain.
4) An assessment of exocrine function should be performed, including the clinical symptoms and signs of malabsorption, as well as an objective measure of EPI.
5) A biochemical assessment of nutritional status should include measurement of fat-soluble vitamin levels, as well as measurement of fasting glucose and glycated hemoglobin (HbA_{1c}).
6) Endocrine evaluation: A 75 g oral glucose tolerance test may be required, as some early cases may not be identifiable by fasting glucose and HbA_{1c} alone [45].
7) Bone health should be evaluated by measurement of serum 25(OH)D and a baseline bone density scan. All patients with chronic pancreatitis should be counseled regarding basic preventative measures.
8) The patient should be counseled regarding smoking and alcohol status, physical activity, relevant social/financial issues, and an assessment of quality of life should be performed.

Routine assessment will inform nutritional management, which should include optimization of dietary intake, appropriate and adequate PERT, and, for some, oral nutritional supplements and micronutrient supplementation. Routine nutritional assessment by a specialist registered dietitian working within a multidisciplinary team is vital.

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54

Exocrine Pancreatic Insufficiency

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Introduction

Pancreatic exocrine insufficiency (EPI) is defined by the presence of inadequate pancreatic digestive enzymes in the intestinal lumen to allow normal digestion of fat, carbohydrates, and protein [1]. These digestive enzymes account for the majority of enzymatic digestion in humans under normal circumstances, but there are alternative salvage pathways for starches and complex carbohydrates (salivary amylase), protein (pepsin and brush border peptidases), and fat (gastric lipase), and the colon can absorb up to 500 kcal/day due to bacterial fermentation of soluble fiber to short chain fatty acids, which are then absorbed. The pancreas secretes approximately 10-fold the amount of enzymes required for digestion with each meal, likely an evolutionary advantage when food was scarce and only intermittently available. Whether a reduction in pancreatic enzyme secretion reaches a threshold of being "insufficient" is often difficult to precisely determine, and depends on residual pancreatic secretory capacity, the contents of the meal being digested, intestinal structure and function, and the efficiency of compensatory or salvage mechanisms of digestion [1,2]. EPI most commonly occurs due to acinar cell damage and loss, pancreatic ductal obstruction preventing enzymes reaching the duodenum, and asynchronous or delayed mixing of the meal and enzymes. A number of other conditions are associated with EPI, such as acid-induced inactivation of enzymes, inadequate hormonal signaling for pancreatic secretion, and some rare genetic syndromes. Many other clinical conditions have been postulated to be associated with EPI, including long-standing type 1 and 2 diabetes, the extremes of age, renal failure, irritable bowel syndrome, smokers, and even otherwise unexplained bloating and gas symptoms.

Digestion and absorption of dietary nutrients is a complex process, with many overlapping mechanisms in addition to pancreatic enzyme secretion [1]. Complex carbohydrates are well absorbed in the absence of pancreatic amylase, due to a combination of salivary amylase and brush border enzymes. Similarly, protein digestion and absorption is relatively well preserved in the absence of pancreatic proteases, due to the actions of pepsin and brush border peptidases. Fat digestion and absorption is most dependent on pancreatic lipase and colipase, but gastric lipase can be upregulated and allows nearly 50% of normal fat absorption in the absence of pancreatic lipases. These alternative mechanisms of digestion and absorption, and the physiologic pancreatic enzyme reserve capacity, explain why some individuals with diseases causing EPI seem to suffer no nutritional consequences. A second term, exocrine pancreatic dysfunction (EPD), has been proposed to describe these individuals with diminished pancreatic enzyme secretion that is not sufficient to lead to nutritional consequences [3].

Disease States Associated with EPI (Table 54.1)

The most common cause of EPI is chronic pancreatitis (CP). Prevalence estimates for EPI in patients with CP range from 30–50% [4–6]. EPI is typically a late consequence of CP, with a mean time to onset of 10–15 years. The risk of EPI is greater and onset is earlier with CP due to alcohol, smoking, and certain genetic causes (e.g., *PRSS1* mutation), compared to other etiologies. Cystic fibrosis patients almost universally have EPI, usually detected at birth.

Pancreatic cancer is another common cause of EPI [7–11]. Around 70% of pancreatic cancer occurs in

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Table 54.1 Some disease states associated with EPI.

Disease state	Prevalence of EPI	Comments
Chronic pancreatitis	30–50%	Longer duration of disease and specific etiologies (alcohol, smoking, certain genetic causes) increase risk
Cystic fibrosis	>90%	Most are pancreas insufficient at birth
Pancreatic cancer, ampullary cancer, main duct IPMN	35–75%	Depending on location of cancer (head>body>tail) and degree of main pancreatic duct obstruction. Risk increases after any pancreatic resection
Pancreatic surgery	Variable, 30–50%	Depending on amount of resection, and presence of Roux reconstruction limiting mixing of enzymes and meal
Nonpancreatic intestinal surgery	Very common depending on surgery	Risk highest after gastrectomy or gastric bypass
Acute pancreatitis	Variable, 20–45%	Depending on degree of necrosis, but can occur in absence of significant necrosis
Diabetes	Unknown	Long-standing diabetes associated with reduced fecal elastase. Reduced pancreatic volume and serum levels of trypsin in type 1 DM
Aging	Unknown	Fecal elastase levels drop in advanced age (>70)
Celiac disease	Unknown	Possibly due to small bowel injury leading to diminished CCK release, can improve on gluten-free diet
Genetic syndromes	Schwachman–Diamond or Johanson–Blizzard	Isolated deficiency of pancreatic enzymes

IPMN: intraductal papillary mucinous neoplasm.

the head of the pancreas, with ductal obstruction and upstream dilation and atrophy of the pancreatic body and tail. In those with unresectable pancreatic cancer, EPI occurs in the majority (50–90%). In those with resectable disease, EPI is present prior to resection in 40–50%, and increases to ≈75% after resection. Pancreatic surgery, for benign or malignant indications, is also commonly associated with postoperative EPI. EPI after pancreaticoduodenectomy, for example, is common (40–90%) and most patients require pancreatic enzyme replacement therapy after surgery [11]. Other surgical procedures may also cause EPI by interfering with mixing of enzymes and the meal. Examples include bariatric surgery [12], or Roux-type operations after gastric resections.

Necrotizing pancreatitis can cause EPI in one-third to half of patients, depending on location and extent of necrosis [13–15]. Recent studies document that EPI can also occur acutely in those with milder forms of acute pancreatitis, and can persist in approximately 20% [16].

A number of other conditions have been suggested to cause EPI [17]. The most data are in patients with diabetes. Pancreatic weight and volume are markedly reduced in patients with type 1 DM [18], and even in first-degree relatives of patients with type 1 DM [19]. Autopsy studies in these patients show interacinar fibrosis, and fecal elastase and serum trypsinogen are often reduced. Of note, symptomatic EPI is quite rare in these patients, leading to a proposal to define this as an exocrine pancreatopathy rather than exocrine insufficiency [18]. These findings point to a complex interplay between the exocrine and endocrine pancreas. A few studies have also documented apparent EPI at the extremes of age (<1 or >80), in those with chronic renal failure, in those who are malnourished or critically ill, and in those with otherwise unexplained osteoporosis [17]. Data supporting these etiologies of EPI are meager. Two additional conditions merit mentioning, celiac disease and gastrinoma. In the first, duodenal damage is postulated to cause defective signaling of CCK from the duodenum, and in the second excess acid can denature pancreatic digestive enzymes.

There are also now multiple direct-to-patient offerings on the internet regarding EPI, describing bloating and loose stools and excess flatulence as being consistent with EPI and suggesting patients contact their physician to discuss these symptoms and whether treatment with PERT should be considered. In parallel, many enzyme products of low or unknown potency are available over the counter to treat these symptoms of purported EPI. Of course, with very few exceptions, these patients do not have EPI.

Diagnosis and Staging of EPI

It can be difficult to determine with confidence if EPI is present. While the potential disease associations are known (Table 54.1), the lack of an accurate diagnostic test limits diagnostic confidence. EPI is a clinically defined syndrome, which is suspected based on the presence of steatorrhea, weight or muscle mass loss,

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fat-soluble or other vitamin deficiency, or other clinical features in a patient at risk for EPI [1,20]. The confirmation of maldigestion may be achieved by directly measuring inadequate digestion of fat or protein (e.g., 72-hour fecal fat). This type of test requires a diet of precisely known fat content, so that the amount of dietary fat that is digested and absorbed can be calculated (the CFA - coefficient of fat absorption = [dietary fat-stool fat]/dietary fat; with a normal of ≥93%). By convention, these tests use a high-fat diet (usually 100 gm of fat/day) to gauge maximum pancreatic secretory capacity, but this does not provide insight into the efficiency of fat absorption with routinely consumed or low-fat meals. The presence of an abnormal CFA does not in and of itself prove that EPI is responsible, merely that maldigestion or malabsorption is present. These 72-hour stool collections are challenging, and are rarely done outside of clinical research.

Pancreatic function can also be measured directly, with a tube or endoscope in the duodenum collecting pancreatic secretions after a supraphysiologic stimulus with either secretin (producing ductal secretin of bicarbonate and fluid) or cholecystokinin (CCK; producing acinar secretion of enzymes). It is noteworthy that the results of these direct pancreatic function tests often do not correlate with fecal fat output. As an example, there is no correlation with abnormal bicarbonate output and fecal fat in a secretin-pancreatozymin (CCK) direct pancreatic function test [3]. This discordance may be related to the fact that these tests do not measure the extrapancreatic sources of lipolysis, hence, there is no way to define a cutoff in a pancreatic function test below which EPI (as opposed to EPD) is likely to occur. These direct pancreatic function tests are complex and invasive, and therefore rarely utilized in clinical settings.

Several tests are being developed which measure digestion that is specifically dependent on pancreatic digestive enzymes. These include a ^{13}C- mixed triglyceride breath test, which measures triglyceride maldigestion by collecting $^{13}CO_2$ in expired air after ingestion of a test meal [21,22]. The lipids in the meal require pancreatic lipase and colipase for digestion. Another uses measurement of metabolites in blood of lipids digested by pancreatic lipase [1]. Both tests are not currently available to clinicians. An ideal test would measure specific pancreatic enzyme-dependent digestion, be widely available, not require complex collection of stool, and be precise and repeatable. Unfortunately, no such test is currently available to clinicians.

Instead, the most commonly utilized test is the fecal elastase-1 (FE-1) [1,20,23,24]. This is actually a misnomer, as elastase-1 is not expressed in the human pancreas due to transcriptional silencing. The commercial assay actually detects chymotrypsin-like elastases (CELA3A and CELA3B isoforms) [25]. Nonetheless, the test is conventionally referred to as fecal elastase-1. Levels of FE-1 < 100 μg/gm of stool are considered abnormal, and levels of 100–200 μg/gm of stool are considered indeterminate. The test can be measured while patients are taking PERT. Several caveats apply: (i) the stool sample must be solid or semi-solid as watery stool dilutes the elastase; (ii) the results can be variable, so testing more than once is often useful; and (iii) a low elastase alone does not prove EPI is present (it needs to be in the correct clinical setting). In a systematic review and meta-analysis of FE-1, the sensitivity is 0.96 (95% CI: 0.79–0.99) and specificity 0.88 (95% CI: 0.59–0.97) compared to fecal fat measurement [26]. The wide confidence intervals are noteworthy, and in a low prevalence population (EPI is present in <5% of the population) the test has a substantial false positive rate. A number of clinical conditions have been associated with low levels of FE-1. In particular, as mentioned above, long-standing diabetes is associated with reduction in pancreatic weight and volume and a decreased FE-1, but interestingly not often with abnormal fat digestion and EPI [18,19].

There have been proposals to define stages of increasing severity of EPI [3,23]. In one proposal [23], mild EPI is defined as the reduction in secretion of one digestive enzyme without steatorrhea, moderate EPI as a reduction in both digestive enzymes and bicarbonate without steatorrhea, and severe EPI as the presence of steatorrhea. This categorization requires measurement of pancreatic digestive enzyme and bicarbonate output, which is not feasible for clinical use. A second proposal [3] suggests four stages, based on FE-1 levels, the presence of symptoms, fat-soluble vitamin levels, and the CFA. In this proposal, only those with a CFA < 85% would receive PERT therapy. As in the first proposal, CFA is only very rarely available and so these staging systems are helpful as frameworks but do not have much current utility to clinicians.

Accurate diagnosis of EPI can be challenging, but begins with a clinical assessment of symptoms that might be consistent with the syndrome, such as weight or muscle mass loss, diarrhea, steatorrhea, or increased bloating and flatulence in a patient at risk of possible EPI. Measurement of baseline nutritional markers in these patients (see Chapter 53) is also appropriate, and low levels of fat-soluble vitamins can support the diagnosis of EPI. Fecal elastase testing is the next step, with the caveats noted above. Ultimately, a presumptive diagnosis of EPI is made by the clinician, taking into account the clinical setting and ancillary tests, but without a gold-standard test to confirm the clinical impression. A final diagnostic approach merits mention—a therapeutic trial of PERT. There is no standardized approach to determine the degree of clinical symptom improvement needed for a therapeutic trial, and the specificity of these improvements, hence it is not usually helpful in deciding on the presence of EPI.

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Management with PERT

When enzyme replacement therapy is initiated, a number of important principles must be followed. The normal pancreas produces around 900,000 USP units of lipase with each meal (more than 12,000 units/kg/meal in an average-sized adult). As noted above, a rule of thumb is that approximately 10% of normal pancreatic enzyme secretion can avoid steatorrhea (and presumably the associated nutritional consequences). That would suggest that a typical-sized adult would need 90,000 USP units per meal. Also as noted above, there are alternative and compensatory mechanisms for nutrient absorption, and the pancreas may still be producing some enzymes. In many practice guidelines, a starting dose of 40,000–50,000 USP units of lipase per meal is suggested [1,2,20,23,24]. Typically, half this amount is taken with snacks. It is entirely appropriate to allow the patient to titrate the dose to the relative fat content of the meal. The enzymes need to be delivered during the meal, to achieve maximal mixing. The enzyme products can also be prescribed in a weight-based algorithm, which is particularly appropriate for infants and children [27].

The enzymes should be taken during the meal or snack, for maximal mixing with the meal. In practice, taking some of the pills during the meal and some with the last bite is often suggested. Many patients do not receive clear instructions on how to take the PERT.

In the United States, five products are currently available (Table 54.2). These are of variable potency, and by convention the products are identified by their lipase content. All are of porcine origin. With the exception of one, all are enteric coated and release their enzyme contents at approximately pH 5.5 or greater. In patients with chronic pancreatitis, diminished bicarbonate secretion may acidify the duodenum and proximal jejunum, and delay the release of these enzymes. Some studies, but not all, have noted increased proximal release of enzymes when acid-suppressing medications (proton pump inhibitor, or H2 receptor antagonist) are also utilized. These are not routinely required when using these enteric-coated formulations, but can be added when response is less than optimal [23]. When using a non-enteric coated product, an acid-reducing medication is required to prevent acid denaturation of the enzymes.

In systematic reviews and meta-analyses of PERT therapy [28,29] in chronic pancreatitis, it is noteworthy that PERT improves but does not normalize fat digestion. The CFA improves from a baseline of 63–67%, to around 83%. Simply put, the current PERT products are not as effective as a normal pancreas. PERT therapy does improve symptoms such as steatorrhea, weight loss, and postprandial bloating and gas. PERT improves quality of life and various nutritional parameters in patients with chronic pancreatitis [1,23,30]. Similar improvements are seen in those with EPI due to pancreatic cancer [30,31]. Limited data support some modest reduction in mortality with the use of PERT as well. These benefits are substantial, but a number of barriers exist preventing the appropriate use of PERT therapy. First and foremost, the lack of a widely available and accurate diagnostic test hampers the ability to identify patients who would benefit.

Table 54.2 Enzyme products currently available in the United States.

Product	Formulation	Lipase content/ capsule or pill
Creon®	Enteric-coated porcine	3000, 6000, 12000, 24000, 36000
Pancreaze®	Enteric-coated porcine	2600, 4200, 10500, 16800, 21000
Zenpep®	Enteric-coated porcine	3000, 5000, 10000, 15000, 20000, 25000, 40000
Pertzye®	Enteric-coated porcine with bicarbonate	4000, 8000, 16000, 24000
Viokace®	Non-enteric coated porcine	10440, 20880

Many patients with diseases causing EPI are not identified, and many are not treated with adequate dosage. In one survey of 91 European patients with previous pancreatic surgery, the median dosage of lipase was 50,000 U/meal, but many were on half this dose and the majority had ongoing steatorrhea despite therapy [32]. In a second survey of patients with EPI due to chronic pancreatitis, the median starting dose was 25,000 U/meal, and the majority of patients had ongoing steatorrhea or weight loss [33]. In a large US administrative database [34], only 6.5% of patients with chronic pancreatitis were tested for EPI and only 10% received a PERT prescription of a minimally effective dosage. Only 2% of pancreatic cancer patients had testing for EPI, and only 5% received a prescription for a minimally effective dosage. Taken together, these studies demonstrate that even those at high risk of EPI are infrequently tested and infrequently treated for EPI. An additional impediment to appropriate use of PERT, at least in some countries, is the cost. In the USA, no generic products are available, and the cost without insurance may approach $2000/monthly. In the USA, at least one-third of PERT prescriptions are never filled, likely due to cost.

There are a variety of dietary recommendations [1,2,20,24], but limited science to support these. It is generally recommended to follow a relatively low-fat diet, but very low-fat diets put the patient at risk of fat-soluble vitamin deficiency. Many pancreatologists do

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not restrict lipids. Smaller, more frequent meals are also often recommended. A diet rich in complex carbohydrates, low in insoluble fiber, and containing at least 1.5 gm/kg of protein daily is commonly recommended.

Failure to Respond to PERT Therapy

Effective therapy with PERT should stop steatorrhea, allow gain of weight and muscle mass, and correct deficiencies of vitamins and trace elements. EPI is associated with a number of common nutritional consequences, including sarcopenia, weight loss, fat-soluble vitamin deficiency, and osteopenia and osteoporosis, to name just a few. These are discussed in Chapters 53 and 55. Adequate PERT therapy is defined by improvement, and hopefully normalization, in these clinical and laboratory features and nutritional consequences. Although measuring the improvement in digestion on PERT with a fecal fat analysis or breath test would be useful to gauge the adequacy of PERT therapy, this is rarely possible. Measuring fecal elastase provides no information on the effectiveness of therapy. The most common reason for failure of PERT is an inadequate dose. As noted above [32–34], this is an exceedingly common problem, likely due to a lack of knowledge in medical professionals writing the prescription. Providing an appropriate dosage, and reinforcing the timing of the PERT is the first step in patients who do not seem to be responding as expected to PERT. In patients who are not responding, increasing the dosage to 90,000 U/meal (or sometimes higher) is appropriate as an initial step [23]. In some patients, lipase may be inactivated by gastric acid (a common issue with the uncoated tablets). Some data demonstrate that acid-reducing medications might allow more proximal release of digestive enzymes from enteric-coated preparations as well, and this is recommended for nonresponders in some guidelines [23].

In those who do not respond despite appropriate dosage and timing, consideration should be given to alternative diagnoses. The most common is small intestinal bacterial overgrowth (SIBO), with symptoms and features that are indistinguishable from EPI. In one systematic review, SIBO can be found in 36% of patients with chronic pancreatitis [35]. This is even more common in those with EPI after gastrointestinal surgery [36]. The reason that SIBO is so common is not known, but could reflect a reduction in bactericidal effect of pancreatic digestive enzymes, side effect of opioid therapy, or associated diabetes with enteral neuropathy. Breath testing for SIBO, or empiric antibiotic treatment, can be considered in those who do not respond as anticipated to PERT. In those who do not respond to PERT and have significant weight loss, consideration can also be given to a secondary pancreatic or extrapancreatic malignancy, or to other causes of malabsorption or maldigestion unrelated to the pancreatic disease (e.g., celiac disease).

EPI is common in patients with benign and malignant pancreatic diseases, and in those with previous pancreatic surgery. Appropriate management requires an understanding of compensatory mechanisms that allow digestion and absorption despite EPI, the lack of an accurate diagnostic test, the appropriate dosage and timing of PERT, and the ongoing management of the variety of nutritional consequences of EPI.

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Bone Disease in Chronic Pancreatitis

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Introduction

Patients with chronic pancreatitis have a higher-than-normal risk of developing low bone mineral density (BMD) and osteoporosis [1]. Osteoporosis is characterized by compromised bone strength cause by bone mass loss and bone quality deterioration, resulting in increased fracture risk [2]. In patients with chronic pancreatitis, the high prevalence of osteoporosis translates into a higher prevalence of low-trauma (fragility) fractures compared to healthy controls [3,4]. The etiology of osteoporosis in chronic pancreatitis is multifactorial; low serum 25(OH)D, suboptimal dietary intake, heavy smoking, low physical activity, chronic inflammation, and malabsorption are all likely to contribute [5,6]. Patients with chronic pancreatitis develop osteoporosis despite the absence of additional risk factors (such as long-term steroid use or hypogonadism) that drive bone demineralization in other gastrointestinal conditions [7]. The economic cost of osteoporosis and fracture is considerable. Hip fractures are associated with an 8–36% increase in mortality within 1 year, and approximately a fifth of patients with hip fracture require long-term nursing care [2,8]. By 2025, in the United States, it is projected that there will be greater than three million fractures annually costing more than $25 billion per year [2].

Measures of Bone Density and Bone Metabolism

DXA is considered the clinical gold standard for the measurement of bone mass [9]. DXA works by generating an image of bone mineral content (BMC, g calcium) when the X-ray tube is scanned over the area of interest. Software uses an algorithm to yield BMD (g/cm^2) from BMC and bone area (cm^2) [10]. Absolute measurements of BMD are of little value, as they are determined by the site of measurement, the calibration used by the manufacturer and the particular instrument [10]. BMD deteriorates with age; therefore, age-related changes need to be considered. Because of machine and skeletal site differences, BMD results are noted by a derived statistical value, the T-score. Bone density measurements follow a Gaussian distribution, and therefore are described as the number of standard deviations (SD) [11] from the mean for normal controls. Therefore, the T-score is not an absolute value, but the number of SD above or below the BMD average value in young healthy adults [11] (representing "peak bone mass"). For example, a T-score of -2.5 indicates that an individual's BMD is 2.5 SD below (young adult) average. Bone density is divided into several categories: normal (T-score >-1), osteopenia (T-score -1 to -2.5), and osteoporosis (T-score <-2.5).

Although DXA is the primary diagnostic tool for bone health assessment [12], it is limited by the fact that bone mineral density changes so slowly that DXA is not always suitable for monitoring the effects of treatment. Bone remodeling in the adult skeleton is a dynamic and continuous process with a tightly coupled balance between resorption of old micro-damaged bone and formation of new bone. The bone remodeling cycle is a coordinated action between osteoclasts (bone resorption cells) and osteoblasts (bone formation cells), and an imbalance of either formation or resorption can lead to substantial deterioration in bone strength over time. Biochemical markers of bone metabolism (bone turnover markers, BTM) can provide an accurate, noninvasive assessment of bone formation, resorption, and turnover. BTM include serum carboxy-terminal telopeptide of type I collagen (CTX-I) for bone resorption and serum procollagen 1 amino-terminal propeptide

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(P1NP) and osteocalcin for bone formation [5,13]. In chronic pancreatitis, the chronic inflammatory state (characterized by high levels of proinflammatory cytokines) is associated with higher bone turnover [7]. Therefore, in addition to DXA, these measures of bone activity may have a role in the overall management of bone health in chronic pancreatitis.

The Risk of Developing Osteoporosis and Fracture in Chronic Pancreatitis

In the only meta-analysis on this topic to date (published in 2014), two-thirds (65%) of 513 patients who had undergone dual X-ray absorptiometry (DXA) had osteoporosis or osteopenia [1]. Only two of the included studies were controlled, with osteoporosis prevalence among healthy controls of 8.6–10.2% [14,15]. These findings have been largely corroborated by more recent reports confirming that most patients with chronic pancreatitis have either osteoporosis or osteopenia [16–18], although in the first report from China, just over a third of those with chronic pancreatitis had low BMD [19]. Importantly, low BMD translates into a real risk of low-trauma fracture. A US study [4] reported that the risk of fracture in chronic pancreatitis (4.8%) was similar (or higher), than in other gastrointestinal disorders such as celiac disease (5%), Crohn's disease (3%), post-gastrectomy (5.4%) or cirrhosis (4.8%). The rate among healthy controls was 1.1%. Similarly, a European study [3] reported a higher fracture rate among chronic pancreatitis compared to controls (adjusted hazard ratio of 1.7 [95% CI: 1.6, 1.8]).

Management

Given that osteoporosis is costly and largely preventable—coupled with the lack of clinical trials investigating treatments for osteoporosis in chronic pancreatitis—clinicians must focus on prevention [6,20]. The high risk of developing osteoporosis dictates that basic preventative measures should be advised for *all* chronic pancreatitis patients. Although some risk factors are nonmodifiable (increasing age, female sex, history of previous low-trauma fracture, and family history of osteoporosis), the modifiable risk factors should be addressed [5]. This includes correcting poor diet (particularly adequate calcium and vitamin D intake), recognizing and treating malabsorption with adequate pancreatic enzyme replacement therapy, preventing/treating underweight body mass index, ensuring regular weight-bearing exercise, and emphasizing the importance of smoking and alcohol avoidance for bone health. Vitamin D supplementation may be required to optimize levels of serum 25(OH)D, and safe sunshine exposure should also be encouraged. According to the HaPanEU guidelines [20], all patients with chronic pancreatitis should undergo regular serum 25(OH)D assessment and a baseline DXA at diagnosis, with a follow-up DXA every 2 years. Particular attention should be given to those at higher risk including post-menopausal women, those who have had previous low-trauma fractures, men >50 years, and those with malabsorption.

For those with confirmed osteoporosis (or who have vertebral fractures), appropriate osteoporosis medication such as bisphosphonates should be prescribed (although the lack of published interventional studies on therapeutic agents for osteoporosis in chronic pancreatitis constitutes a critical research gap). As well as ensuring that the basic measures for bone health (described above) are implemented, referral to a bone specialist is highly recommended. In the United States, there is evidence that pancreas specialists are more likely than primary care physicians or gastroenterologists to address bone health [21], therefore ongoing education, awareness campaigns, and promotion of bone health for chronic pancreatitis is vital.

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Diabetes from Exocrine Pancreatic Disease

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Introduction

Pancreatic diseases frequently induce not only pancreatic exocrine insufficiency (PEI) but also endocrine impairment, which result in the development of diabetes mellitus. Diabetes from exocrine pancreatic disease, namely, pancreatic diabetes or type 3c diabetes, is categorized as secondary diabetes that is associated with various pancreatic diseases, such as acute or chronic pancreatitis and pancreatic cancer, as well as pancreatic resection [1–9]. Although type 1 diabetes and type 2 diabetes are well studied, research on pancreatic diabetes is limited, and its characteristics remain unclear. Sustained inflammation and fibrotic change due to pancreatic diseases lead to β-cell loss and reduced insulin secretion, and this is the most common pathogenesis of pancreatic diabetes. In addition, the levels of pancreatic counterregulatory hormones, such as glucagon, are decreased in these patients. Malnutrition resulting from PEI should also be monitored. Therefore, recognizing the differences between pancreatic diabetes and other types of diabetes is very important to achieve good glycemic control and ensure an appropriate quality of life in patients with pancreatic diabetes.

Definition, Prevalence, and Etiology of Pancreatic Diabetes

The American Diabetes Association (ADA) categorizes pancreatic diabetes as a "specific type of diabetes due to other causes" and distinct from type 1, type 2, and gestational diabetes. Pancreatic diabetes includes both structural and functional loss of glucose-normalizing insulin secretion due to pancreatic exocrine dysfunction [1]. It has been called "type 3c diabetes" that is derived from diverse etiologies including pancreatitis (acute, chronic, or hereditary), pancreatic trauma, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, and fibrocalculous pancreatopathy. However, the most common cause of pancreatic diabetes is chronic pancreatitis. In routine clinical practice, patients with pancreatic diabetes have been misdiagnosed as having type 2 diabetes.

The prevalence of pancreatic diabetes among all types of diabetes in Western populations has been reported to be 5–10% [4,6]. Ewald et al. [10] studied 1868 patients diagnosed as having diabetes over a 2-year period and reported that 172 of these patients (9.2%) could be classified as having pancreatic diabetes. In contrast, a nationwide survey in Japan revealed that patients with true pancreatic diabetes (newly developed diabetes associated with pancreatic disease) who received treatment in 2005 accounted for only 0.8% of all patients with diabetes [11]. A more recent large retrospective cohort study from England revealed 559 out of 31,789 new diagnoses of adult-onset diabetes were cases of diabetes following pancreatic disease (1.8%) [12]. Although the prevalence of pancreatic diabetes differs among studies, clinicians should always consider the possibility of pancreatic diabetes when they first make a diagnosis of diabetes. If the accurate diagnosis of pancreatic diabetes and prognosis of pancreatic disease improve, the prevalence of pancreatic diabetes may increase in the future.

Chronic pancreatitis has been well recognized as a major cause of pancreatic diabetes, but a cohort study in New Zealand found that acute pancreatitis is the most frequent preceding disease. In that study, acute pancreatitis

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accounted for 61% of the overall prevalence of diseases of the exocrine pancreas [13]. In another study by Ewald et al. [10], the underlying pancreatic diseases included chronic pancreatitis (78.5%), pancreatic cancer (8.1%), hereditary hemochromatosis (7.0%), and cystic fibrosis (4.1%), as well as pancreatic resection (2.3%). Ito et al. [11] reported that the causal factors of pancreatic diabetes were chronic pancreatitis (40.0%), pancreatic cancer (24.6%), pancreatectomy (10.2%), acute pancreatitis (7.5%), and autoimmune pancreatitis (6.1%).

Patients with chronic pancreatitis frequently have diabetes as a comorbidity, even though its occurrence varies widely from 5% to >80% [2,14–16]. In a study conducted in the United States, 383 out of 1171 patients (32.7%) with chronic pancreatitis had diabetes [17]. A multicenter Italian survey also reported endocrine insufficiency in 31% of patients with chronic pancreatitis [18]. The duration of chronic pancreatitis is a well-known and significant risk factor for the development of diabetes. A large-scale study from China that included 1633 patients revealed a cumulative rate of diabetes mellitus of 21.7% at 10 years after the diagnosis of chronic pancreatitis [19]. In a follow-up survey of patients with chronic pancreatitis without diabetes, 121 of 418 patients (28.9%) were newly diagnosed as having diabetes over a period of 8 years [20]. A recent nationwide epidemiological survey of chronic pancreatitis in Japan also showed that patients with advanced-stage chronic pancreatitis (definite/probable cases) had a higher proportion of diabetes than did those with early-stage chronic pancreatitis (42.3% vs. 19.3%) [21]. A systematic review and meta-analysis involving 8970 patients from 15 studies reported that the incidence of new-onset diabetes after chronic pancreatitis diagnosis was 30%. The prevalence of newly diagnosed diabetes was 15% within 36 months, and it increased to 33% after 60 months from the diagnosis of chronic pancreatitis [22]. Therefore, the prevalence of pancreatic diabetes and chronic pancreatitis as an underlying disease seems far underestimated because many patients with diabetes do not undergo any evaluation of pancreatic exocrine diseases and many patients with chronic pancreatitis do not undergo any evaluation of diabetes.

Risk Factors for the Development of Diabetes in Chronic Pancreatitis

The risk factors for diabetes in patients with chronic pancreatitis include alcohol consumption, smoking, and pancreatic calcification, which are also the risk factors for the progression of chronic pancreatitis [11,21,23,24]. Alcohol consumption was the most common cause of chronic pancreatitis, and it accounted for 72.0% of cases in a recent nationwide survey in Japan [21]. Ito et al. also reported that alcohol consumption was the main causal factor for chronic pancreatitis in patients with pancreatic diabetes (77.3%, 231/299) [11]. In a long-term study of 2037 patients with chronic pancreatitis, 28.8% (587/2037) developed diabetes during a median follow-up period of 7.6 years [24]. Furthermore, the development of diabetes was significantly earlier and more common in alcoholic chronic pancreatitis than in idiopathic chronic pancreatitis. The cumulative rates of diabetes development at 10 years after the onset of chronic pancreatitis was 29.7% and 21.7% in patients with alcoholic and idiopathic chronic pancreatitis, respectively.

Smoking is another important factor associated with the development of diabetes in chronic pancreatitis. Many reports have documented a relationship between smoking and the progression of chronic pancreatitis [21,25–29], which is inevitably associated with the development of diabetes. Maisonneuve et al. reported that smoking was associated with a significant increase in the risk of developing diabetes (hazard ratio, 2.3) after the diagnosis of pancreatitis [26]. Therefore, patients with chronic pancreatitis and diabetes should take steps to improve their lifestyle via abstinence from alcohol and smoking cessation.

Pancreatic calcification is a key finding in the diagnosis of chronic pancreatitis and is involved in disease progression. Several studies have revealed a correlation between pancreatic calcification and the development of diabetes [7,20,23,30]. The risk of diabetes increased 1.32-fold after the onset of pancreatic calcification [20]. A study from China also revealed pancreatic calcification as a risk factor for the development of diabetes mellitus (hazard ratio, 2.326) [30]. Therefore, it is important to recognize pancreatic calcification not only as an indicator of advanced chronic pancreatitis (exocrine insufficiency) but also as an indicator of impaired pancreatic endocrine function.

Clinical Characteristics of Pancreatic Diabetes

Pancreatic diabetes is characterized by the impaired synthesis and secretion of insulin from β cells and glucagon from α cells because of primary pancreatic diseases [20]. Furthermore, PEI resulting from the decreased secretion or outflow obstruction of pancreatic juice induces the impaired absorption of glucose. Since the degree of impairment in pancreatic endocrine and exocrine functions differs in each patient,

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the pathophysiology and treatment of pancreatic diabetes are complicated. Pancreatic diabetes is also known as "brittle diabetes" because the fluctuations in blood glucose levels result in unstable glycemic control.

Recently, Fukuda et al. reported that the incidence of diabetes was significantly higher in patients who underwent distal pancreatectomy than in those who underwent pancreatoduodenectomy despite no significant difference in the volume of the resected pancreas between the two groups [31]. They also revealed significant alterations in the gut microbiome and increased secretion of glucagon-like peptide-1 (GLP-1) in patients who underwent pancreatoduodenectomy, which possibly protected against the development of diabetes. This study shed light on the pathogenic mechanism of pancreatic diabetes, but further validation studies are warranted in the future.

Evaluation and Diagnosis of Pancreatic Diabetes

PEI

Patients with pancreatic diabetes, especially those with chronic pancreatitis, frequently have accompanying PEI, which results in some degree of fat malabsorption and malnutrition [16]. Severe PEI can lead to overt steatorrhea and weight loss that may decrease the quality of life of patients with pancreatic diabetes. Therefore, the evaluation of pancreatic exocrine function and appropriate pancreatic enzyme replacement therapy (PERT) are mandatory for these patients. Although accurate evaluation of PEI is difficult, diagnostic tests including the fecal elastase-1 or *N*-benzoyl-L-tyrosyl-p-aminobenzoic acid test are recommended if available [16]. Evaluating the patient's symptoms, including abdominal bloating or discomfort, diarrhea, and weight loss, at each follow-up visit and performing blood tests, including those for hemoglobin, total protein, albumin, and total cholesterol levels, are important for the evaluation of PEI.

Diagnosis of Pancreatic Diabetes

As in other type of diabetes, pancreatic diabetes is diagnosed on the basis of plasma glucose (PG) levels and hemoglobin A_{1c} (HbA_{1c}) analysis. A fasting PG level ≥126 mg/dL, 2-h PG level ≥200 mg/dL during a 75-g oral glucose tolerance test (OGTT), random PG level ≥200 mg/dL, or HbA_{1c} level ≥6.5% may indicate the presence of diabetes [1]. In patients with symptoms related to diabetes or those with significantly high PG levels, the OGTT should be avoided because of the increased risk of hyperglycemia. The evaluation of insulin secretory capacity, such as by using the insulinogenic index (30 min) calculated from a 75-g OGTT test, fasting C-peptide immunoreactivity (CPR), 24-h urinary CPR, or ΔCPR after glucagon injection, is also important in pancreatic diabetes, as it could help differentiate "insulin-dependent" and "noninsulin-dependent" diabetes. Determining insulin dependence is essential for choosing the appropriate medical treatment.

Pancreatic diabetes is more common than expected, and patients with pancreatic diabetes are mostly misclassified as having type 2 diabetes owing to poor awareness of this type of diabetes [4]. Moreover, no specific diagnostic criteria are available for pancreatic diabetes. Hart et al. proposed conceptual diagnostic criteria for pancreatic diabetes, which included three components: fulfillment of the diagnostic criteria for diabetes, presence of a pancreatic exocrine disease, and diabetes that is reasonably certain to be secondary to pancreatic exocrine disease [2]. Ewald and Hardt [4] also proposed diagnostic criteria for pancreatic diabetes (type 3c diabetes mellitus) (Table 56.1). The major criteria included the presence of exocrine pancreatic insufficiency, pathological pancreatic imaging findings, and absence of autoimmune markers associated with type 1 diabetes mellitus. However, distinguishing pancreatic diabetes from other types of diabetes is sometimes difficult because patients with long-standing type 1 and type 2 diabetes frequently have accompanying PEI. Therefore, clinicians should always consider the possibility of diabetes when treating pancreatic exocrine diseases, such as chronic pancreatitis and pancreatic cancer, as well as the possibility of pancreatic exocrine diseases when treating diabetes.

Table 56.1 Proposed diagnostic criteria for type 3c diabetes mellitus [4].

Major criteria (must be present)
• Presence of exocrine pancreatic insufficiency (monoclonal fecal elastase-1 test or direct function tests)
• Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
• Absence of type 1 diabetes mellitus associated autoimmune markers
Minor criteria
• Absent pancreatic polypeptide secretion
• Impaired incretin secretion (e.g., GLP-1)
• No excessive insulin resistance (e.g., HOMA-IR)
• Impaired beta cell function (e.g., HOMA-B, C-Peptide/glucose-ratio)
• Low serum levels of lipid soluble vitamins (A, D, E and K)

Source: Ewald and Hardt 2013 [4], table 2.

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Treatment of Pancreatic Diabetes

Lifestyle Improvement and Management of PEI

In patients with pancreatic diabetes, lifestyle correction through weight control in overweight patients, abstinence from alcohol, and smoking cessation should be considered as an initial treatment, as in patients with other types of diabetes. When chronic pancreatitis is the underlying cause of pancreatic diabetes, abstinence from alcohol and smoking cessation are especially important to prevent the progression of pancreatitis and achieve better glycemic control. Regarding dietary therapy, stereotypic energy restriction to improve glycemic control is not recommended as it exacerbates nutritional disorders due to PEI, which is frequently present in patients with pancreatic diabetes. The presence of PEI is of great importance, as this feature differentiates pancreatic diabetes from other types of diabetes. Patients with PEI diagnosed on the basis of symptoms, blood tests, and pancreatic exocrine function tests require adequate PERT and sufficient energy intake. The PG level is sometimes elevated after PERT; nevertheless, oral hypoglycemic agents or insulin therapies for patients with pancreatic diabetes should be considered together with appropriate PERT.

Insulin Therapy

Insulin therapy should be considered as the first-line treatment for patients with pancreatic diabetes and advanced stages of pancreatic exocrine diseases, such as chronic pancreatitis or pancreatic cancer, as well as for those who have undergone pancreatectomy [14], because these patients generally develop "insulin-dependent" diabetes. Intensive insulin therapy with long-acting insulin as a basal requirement and preprandial short- or ultra-short-acting insulin for postprandial hyperglycemia are recommended for pancreatic diabetes because these mimic physiological insulin secretion and are helpful in preventing hypoglycemia [7,9,32]. Insulin dependence in pancreatic diabetes is similar to that in type 1 diabetes mellitus, and both conditions meet the absolute indication for insulin therapy. However, compared to type 1 diabetes, pancreatic diabetes shows more impaired secretion of counterregulatory hormones for hypoglycemia, including glucagon and pancreatic polypeptide. Therefore, fluctuations in blood glucose levels are frequently observed after the injection of small doses of insulin, and this makes it difficult to achieve good glycemic control in these patients. Niwano et al. recently compared the insulin requirement between patients undergoing total pancreatectomy (pancreatic diabetes) and those with type 1 diabetes [33]. They found that the total daily insulin and basal insulin levels were significantly lower in patients undergoing total pancreatectomy than in those with type 1 diabetes. Even in the same "insulin-dependent" condition, we should pay attention to hypoglycemia more carefully in patients with pancreatic diabetes than in those with type 1 or type 2 diabetes. When good glycemic control is difficult to achieve in pancreatic diabetes, an insulin pump (continuous subcutaneous insulin infusion) could be a treatment option [33]. Moreover, adjusting the insulin dose after the evaluation of pancreatic exocrine function and adequate PERT are very important.

Therapy with Other Hypoglycemic Agents

The degree of insulin deficiency and insulin resistance varies with disease severity and duration [34]. Therefore, as in patients with type 2 diabetes, those with pancreatic diabetes who have not undergone total pancreatectomy and are not "insulin-dependent" can be administered oral hypoglycemic agents. Metformin, which is widely used in patients with type 2 diabetes and insulin resistance, is associated with a decreased risk of various cancers, including pancreatic cancer [35]. Therefore, some studies preferred metformin as the first-line treatment for pancreatic diabetes [2,16,34]; nevertheless, further validation of the effect of metformin is required. Insulin secretory agents, such as sulfonylureas and glinides, are also treatment options in patients with preserved insulin secretory capacity. However, the efficacy of incretin-based therapy using dipeptidyl peptidase-4 inhibitors and GLP-1 analogs, which also enhance insulin secretion, for pancreatic diabetes has been controversial [9,14,36]. Moreover, the tendency has been to refrain from these drugs owing to a possibility of pancreatitis [34], but several recent reports have demonstrated no relationship between incretin-based therapy and pancreatitis or pancreatic cancer [37–39]. Nevertheless, GLP-1 analogs have been associated with a high frequency of gastrointestinal symptoms as side effects [34]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which inhibit renal glucose reabsorption and increase urinary glucose excretion [40], have recently been widely used in patients with diabetes. SGLT2 inhibitors may be a treatment option because of their insulin-independent action; however, their side effects include weight loss, which should be considered in patients with pancreatic diabetes. A recent study showed no significantly increased risk of acute pancreatitis associated with the use of SGLT2 inhibitors [41]. Although evidence regarding oral hypoglycemic agents for pancreatic diabetes is scarce, clinicians should select

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appropriate drugs after evaluating the insulin secretory capacity, insulin resistance, and nutritional status, including pancreatic exocrine function, in each case.

Complications and Glycemic Target of Pancreatic Diabetes

Good glycemic control reduces the risk of microvascular and macrovascular complications in patients with diabetes [11,36]. A Japanese nationwide survey revealed that the incidence of retinopathy was lower in pancreatic diabetes than in type 1 and type 2 diabetes, but the incidence of neuropathy and nephropathy was comparable [11]. The prevalence of diabetic complications, including cerebrovascular and cardiovascular disorders, also increases with the duration of diabetes [11,14,36]. Therefore, as in other types of diabetes, achieving good glycemic control could improve the quality of life of patients with pancreatic diabetes. Conversely, rapid fluctuations in glucose levels, namely "brittle diabetes," are frequently observed in patients with pancreatic diabetes and result in poor glycemic control. Avoiding severe hypoglycemia is very important in these patients with "brittle diabetes." A large retrospective cohort study from England revealed that patients with pancreatic diabetes had worse glycemic control than did those with type 2 diabetes. The odds ratio for poor glycemic control (defined as HbA_{1c} ≥7%) at 5 years after the diagnosis was 1.7 in patients with pancreatic diabetes than in those with type 2 diabetes [12]. According to the recommendations of the ADA, less stringent targets (HbA_{1c} up to 8%) may be appropriate if the risks and burdens outweigh the potential benefits [42]. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic targets. Although this recommendation is mainly for patients with type 1 or type 2 diabetes, the same situation is frequently observed in those with pancreatic diabetes and unstable glycemic control. Therefore, less stringent glycemic control may be recommended for patients with pancreatic diabetes. Accordingly, the Japanese guidelines for chronic pancreatitis proposed that an HbA_{1c} level of 7.5% could be used as a target; nevertheless, further research is warranted to set an optimal glycemic target for this condition.

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Oxidative Stress and Antioxidants in Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas characterized by repeated episodes of pancreatic inflammation and injury which result in pancreatic exocrine and/or endocrine insufficiency. Morphologically, it is characterized by parenchymal loss leading to atrophy, fibrosis, and ductal stricture and/or calcification causing ductal dilatation [1]. The pathophysiological mechanisms of CP are not well understood. Over the past few decades, oxidative stress has emerged as an important mechanism contributing to pancreatic inflammation and the role of antioxidants has been evaluated in patients with CP.

Free-radical production is an integral part of cellular physiology. These free radicals are neutralized by specific cellular enzymes and other small molecules called scavengers and antioxidants. In health, intricate balance exists between free radicals and antioxidants. However, excessive production of free radicals by activation of oxidative pathways or deficiency of antioxidants tilts the balance leading to "oxidative stress." It is formally defined as "an imbalance between oxidants and antioxidants in favor of oxidants leading to disruption of redox signaling and control, and/or molecular damage" [2]. This review focuses on oxidative stress and the role of antioxidants in mitigating oxidative stress, inflammation, and relieving pain in patients with CP.

Pro-Oxidants

Pro-oxidants are the molecules that favor formation of free radicals. Free radicals have one or more free electrons and usually are reactive oxygen species (ROS) or reactive nitrogen species (RNS) in the cellular environment. Free radicals and their reaction products are a part of normal cell physiology by acting as second messengers and they play an important role in cellular signaling [3]. Mitochondria are the site of physiological oxidative stress. Excessive production of ROS and RNS may damage biomolecules such as lipids, DNA, and proteins (Fig. 57.1).

Detoxification of xenobiotics is another source of production of free radicals. Xenobiotics are toxic substances that enter the body and undergo detoxification in two phases to a hydrophilic substance thus facilitating their excretion in the urine. In phase I metabolism, cytochrome P450 (CYP 450) oxidase system and hydrolyzing enzymes either cleave the parent molecule or result in oxidation or hydroxylation. In phase II metabolism, they are conjugated to a hydrophilic group (glucuronidation, acetylation, methylation, sulfation, or conjugation with glutathione) to form a polar water-soluble inactive compound that can be excreted by the body. Induction of phase I enzymes can itself result in generation of free radicals through the CYP450 system.

Various exogenous substances such as alcohol, tobacco, environmental pollutants, heavy metals, certain drugs, dietary toxins, and fumes lead to free radical generation. Alcohol metabolism can result in production of free radicals. Alcohol is converted to acetaldehyde, a toxic and reactive molecule, by alcohol dehydrogenase, and acetaldehyde is converted to acetate by aldehyde dehydrogenase. Each of the steps results in consumption of nicotinamide adenosine dinucleotide phosphate hydrogen (NADPH) and free radical formation.

Cigarette smoking similarly contains a lot of xenobiotics which can induce free-radical production and lipid peroxidation [4].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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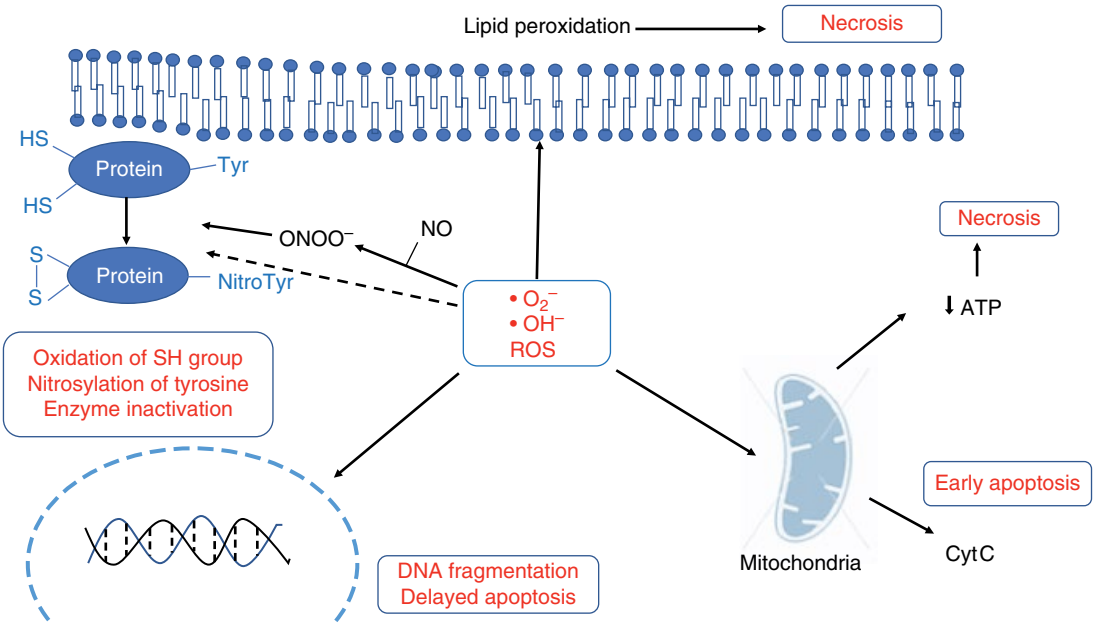


Figure 57.1 Intracellular free radicals can damage plasma membrane by lipid peroxidation. Mitochondria, which are the source of oxidative stress, get damaged which induces apoptosis by cytochrome c. Nitrosylation and oxidation of enzymes may result in their inactivation. Nuclear DNA may get fragmented inducing apoptotic pathways. ROS: reactive oxygen species.

Antioxidants

Antioxidants are substances that when present in low concentration compared to those of an oxidizable substrate significantly delay or inhibit oxidation of that substrate [5]. They can be classified into several groups: (i) cellular enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT); (ii) vitamins such as β-carotene, ascorbic acid, α-tocopherol; (iii) uric acid; and (iv) amino acids and proteins, which form complexes with transition metal ions. Cysteine is an important amino acid for the synthesis of glutathione. Methionine provides sulfur for the formation of cysteine and is thus an important dietary component for maintaining antioxidant defense. Selenium is a component of the GPx and Se-dependent enzyme thioredoxin reductase. These enzymes reduce hydrogen peroxide and lipid peroxides [6].

Primary defenses against oxidative stress include antioxidants vitamin E, vitamin C, β-carotene, glutathione, and uric acid. Second-line defense includes antioxidant scavenging enzymes that include SOD, CAT, and GPX. There exists a "redox homeostasis" within the cellular milieu and temporary exposure to ROS activate redox signaling (Fig. 57.2) [7].

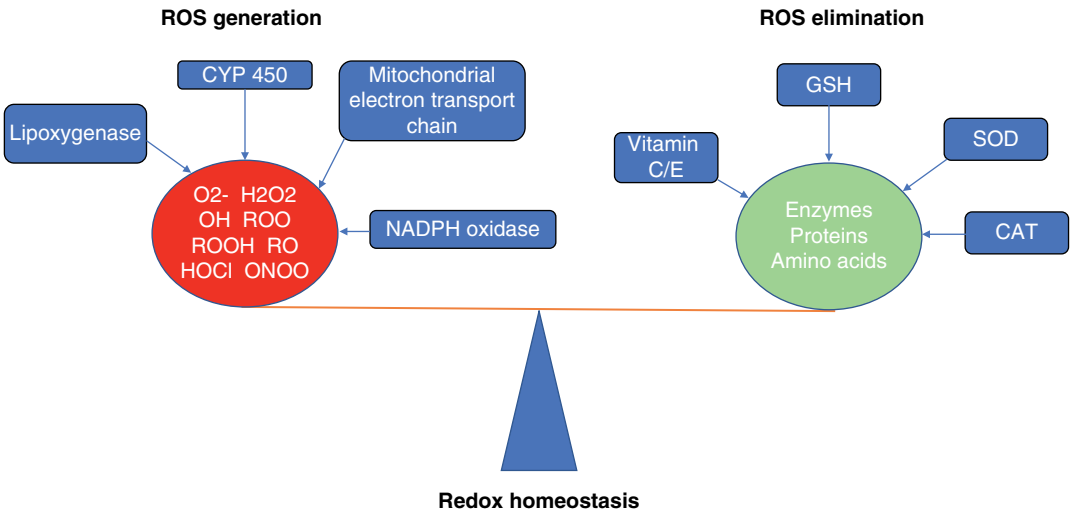


Figure 57.2 Redox homeostasis showing the balance between generation and elimination of reactive oxygen species (ROS).

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Assessment of Oxidative Stress and Antioxidant Status

Oxidative Stress Markers

Measurement of thiobarbituric acid reactive substances (TBARS) is the most commonly used assay and is a marker of lipid peroxidation. Lipid peroxidation causes damage to the cell membrane. Malonaldehyde (MDA) and 4-hydroxynonenal (4-HNE) are the most important products of lipid peroxidation and can be used as markers of lipid peroxidation. Lipid peroxidation is a key step in oxidative stress mediated injury [8,9]. Some sugars may react with thiobarbituric acid resulting in assay interference [10].

Antioxidant Status Markers

Antioxidants work in tandem and complement each other. Hence, measurement of individual antioxidants may not be a direct measure of total antioxidant capacity (TAC) of the body. The ferric acid reducing ability of plasma (FRAP) measures the reducing capacity of blood from ferric to ferrous ion. FRAP is an easy and reproducible assay to measure TAC of the body [11].

Oxidative Stress in CP and its Consequences

The concept of "oxidative stress" in the pathogenesis of chronic pancreatitis can be credited to Joan M. Braganza, who proposed the hypothesis that products of hepatic detoxification may cause pancreatic diseases due to reflux of bile containing these substances into the pancreas. It was proposed that aberrant function of hepatic mixed function oxidase (MFO) may be the root cause of pancreatic diseases [12].

Rose et al. [13] first suggested that antioxidant deficiency may play a role in the pathogenesis of CP. Antioxidant deficiency was observed in patients with CP and oxidative stress was subsequently hypothesized as an important pathophysiological mechanism for the development of CP. It was supported by the observation that a high concentration of lipid-based free-radical oxidation products were detected in the serum and duodenal bile during the relatively asymptomatic phase between the recurrent attacks of pancreatitis suggesting persistent oxidative stress [14]. Three possible mechanisms were suggested: (i) CYP induction by cigarette smoking [15]; (ii) exposure to volatile petrochemical products in occupational environment [16]; and (iii) reduced dietary intakes of methionine and vitamin C in alcoholics [17,18].

Xenobiotic-mediated injury may perpetuate repeated/chronic inflammation in CP. The phase I enzymes such as CYP1A2, CYP3A, and NADPH-CYP oxidoreductase rather than phase II enzymes were found to be induced in the surgical biopsies of pancreas in a study of drug-metabolizing enzymes. Phase II enzymes facilitate removal of xenobiotics after conjugation with GSH, but phase I enzymes may produce toxic intermediates. In addition, pancreatic acinar cells showed evidence of oxidative stress [19].

ROS can lead to acinar cell death in pancreatitis. ROS is a key mediator of CCK-induced apoptosis in experimental pancreatitis. This is mediated by increasing intracellular calcium leading to release of mitochondrial cytochrome c, which activates caspases causing apoptosis [20,21]. ROS can also activate pancreatic stellate cells (PSC). PSC may also generate ROS by NADPH oxidase, which mediates activation of PSC [22].

Evidence for Oxidative Stress and Total Antioxidant Status in CP

Lipid peroxide activity was studied by Basso et al. [23] in 49 patients with CP, 28 patients with pancreatic cancer, 40 controls, and 53 patients with extrapancreatic diseases. It was observed that lipid peroxide activity was increased in patients with CP during disease relapse and correlated with the degree of inflammation.

Szuster-Ciesielska et al. [24], studied the ability of blood neutrophils to produce superoxide anion and hydrogen peroxide spontaneously and after stimulation and showed that the resting production of these free radicals was significantly higher in patients with pancreatitis compared with controls. Superoxide dismutase and catalase activities were greater in patients with alcoholic pancreatitis than controls.

Patients with CP and pancreatic cancer had higher levels of Cu/Zn superoxide dismutase in the pancreatic juices collected endoscopically compared with controls. Immunohistochemical studies of Cu/ZN-SOD in pancreatic tissue showed localization to ductal cells, islet cells, and centro-acinar cells but to a much lesser extent to acinar cells [25].

Schoenberg et al. [26] studied lipid peroxidation products in the tissue and serum of patients suffering from acute ($n = 9$) and chronic pancreatitis ($n = 11$). In patients with CP, the products of lipid peroxidation such as conjugated dienes and malonaldehyde were higher in pancreatic tissue compared to controls (organ donor). Reduced glutathione was significantly decreased suggesting oxidative stress. Increased levels of tissue lipid peroxidation products and altered glutathione

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metabolism suggested ongoing peroxidation of lipids due to an enhanced generation of oxygen radicals.

Patients with alcoholic CP have low blood levels of many antioxidant factors despite adequate oral intake. In a study, serum levels of Vitamin A, Vitamin E, selenium, and glutathione peroxidase level were significantly lower compared to healthy controls despite no dietary differences in these micro-nutrients. The study hypothesized that such deficiency was probably due to pancreatic insufficiency and increased requirement due to oxidative stress [27].

In another study, Mathew et al. [28] evaluated antioxidants in patients with hereditary CP. Antioxidants levels in four groups were compared: hereditary CP, kindred but no pancreatitis, CP due to other etiology, and controls. Hereditary CP patients had lower antioxidant levels. Their kindred had higher vitamin E and selenium levels, which might have prevented them from having pancreatitis despite low glutathione peroxidase levels. Hence, the authors hypothesized that supplementation with vitamin E and selenium might be a good therapeutic option to decrease the frequency of pancreatitis in patients with CP.

Patients with CP in tropical areas had earlier onset of pancreatitis. In a study, Braganza et al. [29] showed that the bioavailability of beta-carotene and ascorbic acid was lower in tropical areas compared to temperate zones. The culinary practice that erodes bioavailability of these two antioxidants might have predisposed to pancreatic oxidative stress and earlier presentation of CP in tropical countries compared to temperate countries.

Whether presence of diabetes significantly modifies oxidative status in patients with CP was evaluated in another study. CP patients with or without diabetes were compared with type 1 diabetes and healthy controls for oxidant and antioxidant status as well as LDL oxidation status. Antioxidant status was altered in patients with CP particularly in those with diabetes. In these patients, vitamin E deficiency and elevated plasma glucose level were associated with significantly higher LDL oxidizability predisposing to atherosclerosis [9].

Uden et al. [17] found significantly low antioxidant levels of selenium, vitamin C, and vitamin E compared to controls in patients with idiopathic CP and suggested that selenium supplementation might be beneficial.

The question whether oxidative stress played any role in the progression of disease from recurrent acute to chronic pancreatitis was addressed in a recent study by Bopanna et al. [30]. The study included patients with idiopathic recurrent acute pancreatitis both in the acute phase and the quiescent phase to evaluate oxidative stress and found that patients had oxidative stress during the acute phase of illness and antioxidants levels were reduced. Taken together, the findings suggested that oxidative stress was associated with recurrent attacks of pancreatitis and might be contributing to the progression of recurrent acute pancreatitis to CP.

Hence, most studies have shown the presence of oxidative stress and decreased antioxidant levels in patients with CP. The low antioxidant levels may be due to dietary deficiency or impaired absorption resulting from pancreatic insufficiency or from increased consumption due to oxidative stress.

Role of Antioxidant Supplementation in CP

To mitigate oxidative stress and correct antioxidant deficiency, it was postulated that antioxidant supplementation might be beneficial. There are multiple randomized controlled trials (Table 57.1) and meta-analyses to address this issue.

The first RCT was conducted by Uden et al. [31]. It was a double-blind placebo-controlled crossover RCT. Twenty-three patients were recruited of whom only 20 were included in the final analysis (7 had alcoholic CP, 8 had idiopathic CP, and 5 had recurrent acute pancreatitis). One arm was given combination antioxidants (daily 600 µg selenium, 0.54 gm ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 gm methionine) and the other arm was given placebo. Total duration of treatment was 20 weeks with crossover at 10 weeks. Six patients on placebo had recurrent attacks compared to none in the antioxidant arm. The authors concluded that active treatment was associated with clinical improvement over and above placebo effect.

Banks et al. [32] subsequently studied the antioxidant allopurinol in patients with painful CP and compared it with placebo. There was no decrease in visual analog scale (VAS) score or McGill score with the intervention though the study was limited by a small sample size of only 16 patients. Bilton et al. [33] also failed to show any improvement in VAS score in a double-blind placebo-controlled RCT of combination antioxidants (daily 800 mg SAMe, 600 µg selenium, and 9000 IU β-carotene) compared to placebo.

Curcumin supplementation for 6 weeks did not show any improvement in VAS score compared to placebo in an RCT. Though the study showed improvement in GSH level in red blood cells and decrease in MDA levels, there was no improvement in pain [34].

In a double-blind placebo-controlled crossover RCT, 36 patients with CP were randomized to receive combination antioxidants (4 times daily 75 µg selenium, 3 mg β-carotene, 47 mg d-α-tocopherol, 150 mg ascorbic acid, and 400 mg methionine) or placebo for 20 weeks with crossover at 10 weeks. There was significant improvement in pain component of SF 36 score with the combination antioxidant therapy [35].

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Table 57.1 Summary of trials of antioxidant supplementation in chronic pancreatitis.

Author	Type of study	*N*	Intervention	Outcome measures	Results	Remarks
Uden 1990	Double-blind placebo-controlled crossover RCT	23	Combination antioxidants (daily 600 µg selenium, 0.54 gm ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 gm methionine) vs. placebo Duration: 20 weeks, no washout period	• VAS • McGill pain score • Descriptive pain score	• 1.01 (0.16–4.26) vs. 1.88 (0.22–5.76), NS • No significant difference • No clear difference • 6 patients in placebo had attack compared to none with intervention	Low risk of bias
Salim 1991	3 armed, parallel, double-blind, placebo-controlled RCT	78 (25 vs. 26 vs. 27)	4 times daily 50 mg allopurinol vs. 500 mg dimethyl sulfoxide vs. placebo Duration: up to 24 hours pain-free (mean = 45 hours)	• Number of pain-free patients • Discharge days	• 13 vs. 12 vs. 4 • 3 days vs. 3 days vs. 5 days	Unclear risk of bias
Bilton 1994a	Double-blind placebo-controlled crossover RCT	30	3 daily doses of 800 mg S-adenosyl methionine (SAMe) vs. placebo Duration: 20 weeks (no washout)	• VAS	No difference	Data not shown
Bilton 1994b	Double-blind placebo-controlled crossover RCT	14	Combination antioxidants (daily 800 mg SAMe, 600 µg selenium, and 9000 IU β-carotene) vs. placebo	VAS	No difference	Data not shown
Banks 1997	Double-blind placebo-controlled crossover RCT	16	Allopurinol 300 mg/d vs. identical placebo Duration: 10 weeks with 2 weeks washout after initial 4 weeks	• VAS score (0–100): difference in mean decrease from baseline • McGill's score (0–45): difference in mean decrease	• 2.8, $P = 0.24$ • -0.3, $P = 0.75$	Low risk of bias
Nandi 2002	Parallel placebo-controlled RCT	25	Combination of antioxidants (daily 600 µg selenium, 0.54 gm ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 gm methionine) vs. placebo Duration: 6 months	• Pain score (12 points) • Pain-free days/mo	• 1.25 vs. 3.62, NS • 3.75 vs. 4.12, NS	Unclear risk of bias
Durga Prasad 2005	Parallel single-blind placebo-controlled RCT	20	Combination antioxidants (3 times daily 500 mg curcumin and 5 mg piperine) vs. placebo Duration: 6 weeks	VAS score (after intervention)	5.81 (0.74) vs. 6.57 (0.74), NS	High risk of bias

(*Continued*)

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Table 57.1 (Continued)

Author	Type of study	*N*	Intervention	Outcome measures	Results	Remarks
Kirk 2006	Double-blind placebo-controlled crossover RCT	36	Combination antioxidants (4 times daily 75 µg selenium, 3 mg β-carotene, 47 mg d-α-tocopherol, 150 mg ascorbic acid, and 400 mg methionine) vs. identical placebo Duration: 20 weeks (no washout)	• Daily VAS • SF 36: pain component (change from baseline)	• Not analyzed • +17 points vs. -7 points, $P < 0.05$	High risk of bias
Bharadwaj 2009	Parallel double-blind placebo-controlled RCT	127 (71 vs. 56)	Combination of antioxidants (daily 600 µg selenium, 0.54 gm ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 gm methionine) vs. identical placebo Duration: 6 months	• Painful days/mo: decrease from baseline • Painful days/mo: after intervention • Pain-free participants	• 7.37 (6.75) vs. 3.21 (3.99), $P < 0.001$ • 1.68 (2.8) vs. 3.36(4.35), $P = 0.012$ • 23/71(32%) vs. 7/56 (13%), $P = 0.009$	Largest study to date with low risk of bias
Jarosz 2010	Open label parallel RCT	91 (46 vs. 45)	Combination antioxidants (vitamin C and vitamin E vs. standard treatment) Duration: 6 months	Pain-free participants	22/32 (68%) vs. 11/56 (31%), $P = 0.002$	High risk of bias
Siriwardena 2012	Parallel double-blind placebo-controlled RCT	70 (33 vs. 37)	Combination antioxidants (38.5 mg selenium, 113.4 mg d-tocopherol acetate, 126.3<tsmg ascorbic acid, and 480 mg l-methionine) vs. placebo Duration: 6 months	• Change in VAS • Average daily VAS • Pain-free participants	• -2.33 (2.09) vs. -1.97 (2.46), NS • 2.93 (1.96) vs. 3.05 (1.96), NS • 19 (58%) vs. 20 (54%), NS	Low risk of bias
Talukdar 2016	RCT	87	Antioxidant plus pregabalin vs. placebo for 2 months followed by open label antioxidants for 4 months in both groups	• Improvement in pain (VAS and Izbicki score)	• percent reduction of VAS (-50 [-80.0; -32.1] vs. -29.5 [-64.5; 0]; $P = 0.01$) • Izbicki score (14.5 [0; 21.3] vs. 30.0 [11.8; 41.3]; $P = 0.001$) • complete pain resolution (20 [47.6%] vs. 12 [26.7%]; $P = 0.04$)	Included patients had recurrence of pain after prior endoscopic or surgical therapy
Singh 2019	Parallel double-blind placebo-controlled RCT	107	Combination antioxidants (daily 600 µg selenium, 0.54 gm ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 gm methionine) vs. placebo	• VAS • Pain-free participants	• No difference • No difference	The primary outcome of the study was improvement in pancreatic functions and pain assessment was a secondary outcome

NS: not significant; VAS: visual analog scale.

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Table 57.2 Summary of meta-analyses on antioxidant supplementation in chronic pancreatitis.

Author	Study types included	Number of studies	Outcome measures	Conclusion
Ali et al. 2014 Cochrane systemic review	RCT	12 (585 participants)	Pain complaints pre- and post-intervention	Antioxidants can reduce pain slightly in CP. Adverse events in 1 in 6 patients may prevent use
Zhou et al. 2014	RCT	8 (573 participants)	Pain relief	Antioxidant administration effective in relieving pain
Rustagi et al. 2015	RCT	8 (446 participants)	Pain reduction	Benefit of antioxidant therapy for pain reduction (RR: 0.73; 95% CI: 0.58–0.91)
Mohta et al. 2020	RCT	4 (352 participants)	Pain relief Quality of life	No significant pain reduction or change in quality of life

The limitations of these studies were a small sample size, inclusion of predominantly alcoholic CP, nonstandardized quantification of pain, and short duration of antioxidant supplementation.

Bhardwaj et al. conducted a double-blind placebo-controlled RCT to study the role of antioxidant supplementation in patients with both alcohol-related and idiopathic CP. A total of 127 patients with CP (age 30.5 ± 10.5 years, 32 alcohol-related and 95 with idiopathic CP) were randomized to receive either antioxidants ($n = 56$; daily 0.54 gm ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, 600 µg selenium, and 2 gm methionine) or placebo ($n = 71$), for 6 months. There was a significant reduction in number of painful days per month in the antioxidant group (7.37 [6.75] vs. 3.21 [3.99], $P < 0.001$). Twenty-three out of 71 patients were pain-free in the antioxidant group compared to 7 out of 56 in placebo ($P = 0.009$). The reduction in levels of TBARS and increase in levels of FRAP were also significantly higher in the antioxidant group, which was commensurate with the clinical observation [36].

Another trial randomized 70 patients with CP to receive either combination antioxidant, ($n = 33$; 38.5 mg selenium, 113.4 mg d-tocopherol acetate, 126.3 mg ascorbic acid, and 480 mg l-methionine) or placebo ($n = 37$) for 6 months [37]. The study did not find improvement in VAS score or number of pain-free patients with the antioxidant therapy. However, there were several limitations of the study which prevented its generalizability: all the patients were receiving a mean of 85 mg/day opioids suggesting chronic neuropathic pain, more than half of patients had failed prior medical or surgical therapy suggesting that they have a severe unresponsive disease, and they continued to drink alcohol and smoke during the study period [38].

One study evaluated the combined role of antioxidants and pregabalin in patients with recurrence of pain following surgical/endoscopic therapy and showed that the combination therapy significantly reduced pain [39].

Four meta-analyses [40–43] have been done to date to study the role of antioxidant supplementation in pain relief in CP (Table 57.2). Three out of four meta-analyses have shown benefit with antioxidant therapy. In the Cochrane systemic review and meta-analysis [40], which evaluated 12 RCTs including 585 participants, there was a slight reduction in pain with the antioxidant therapy. It showed that adverse events might prevent use of antioxidants in one out of six patients. Effects on other outcomes such as use of analgesics, exacerbation of pancreatitis, and quality of life remained uncertain.

Conclusion

Pain is the predominant symptom in patients with chronic pancreatitis. There is compelling evidence that oxidative stress is involved in the pathogenesis of CP. Patients with CP are deficient in antioxidants due to impaired absorption and increased demand. Supplementation with antioxidants is beneficial in reducing pain in patients with CP.

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Pain Mechanisms in Chronic Pancreatitis

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Introduction

Pancreatitis is a complex, multifactorial pathology that involves the pancreatic gland. Two main types of pancreatitis are known: acute and chronic pancreatitis. Chronic pancreatitis (CP) is the step following an acute injury, which determines irreversible modifications to parenchymal structure, leading in turn to exocrine and endocrine insufficiency. To sum up this concept, a definition was coined: "chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" [1]. It is estimated that incidence of newly diagnosed CP ranges from 4 to 12 per 100,000 persons per year; male:female ratio is 1.5:1, and age at diagnosis is 35–55 years [2,3]. Alcohol abuse is a primary cause of pancreatitis (about 70% of cases). A miscellanea of other causes, among them cystic fibrosis tumor, pancreatic resection, congenital abnormalities, autoimmune, and genetic, are responsible for 10% of pancreatitis, while the etiology remains unclear for the remaining 20% [4,5]. Chronic inflammation of the pancreas is characterized by a series of histologic modifications, according to the "two-hit model": acute inflammation, due to the various etiologies mentioned above, determines injury to the pancreatic parenchyma. Sustained inflammation of the pancreas leads to activation of a profibrotic cascade, which replaces endocrine and exocrine cells and determines loss of function [6]. The clinical signs and symptoms of acute pancreatitis, in decreasing order of frequency, are: abdominal pain, weight loss, steatorrhea, malabsorption, history of alcohol abuse, history of recurrent pancreatitis. Pain is the first symptom, which is reported by patients in almost 75% of cases and it persists in 85–97% of cases [7]. Three typical pain profiles have been described: (i) acute intense pain associated with repeated episodes of acute pancreatitis (acinar necrosis) in the early stage; (ii) a spontaneous lasting pain relief in association with severe pancreatic dysfunction in the late stage of uncomplicated chronic pancreatitis; and (iii) a persistent severe pain (or frequent recurrent episodes of pain) usually in association with local complications such as pseudocysts, ductal hypertension, or extrapancreatic complications such as partial obstruction of the common bile duct, peptic ulcer, and opiate addiction [8]. Timing of evolution of pain and of the pathology is impossible to predict at the time of onset [9], but it is calculated that it takes about 18 years from onset of the pathology to complete destruction of pancreatic parenchyma (burnout), which leads to a paradoxical decrease of clinical pain [7].

The main difficulty in diagnosing chronic pancreatic pain is the assessment of its entity. With the aim of providing a standardized measure of this symptom, several instruments have been validated: one-dimensional scales that use numeric (usually 0 to 10), verbal, or visual descriptors to quantify pain or the degree of pain relief [8]; and multidimensional scales that measure aspects of pain (intensity, nature and location, impact of paint on mood or activity level) [10].

Figure 58.1 presents a graphical synthesis from suspect clinical findings to proposed treatment.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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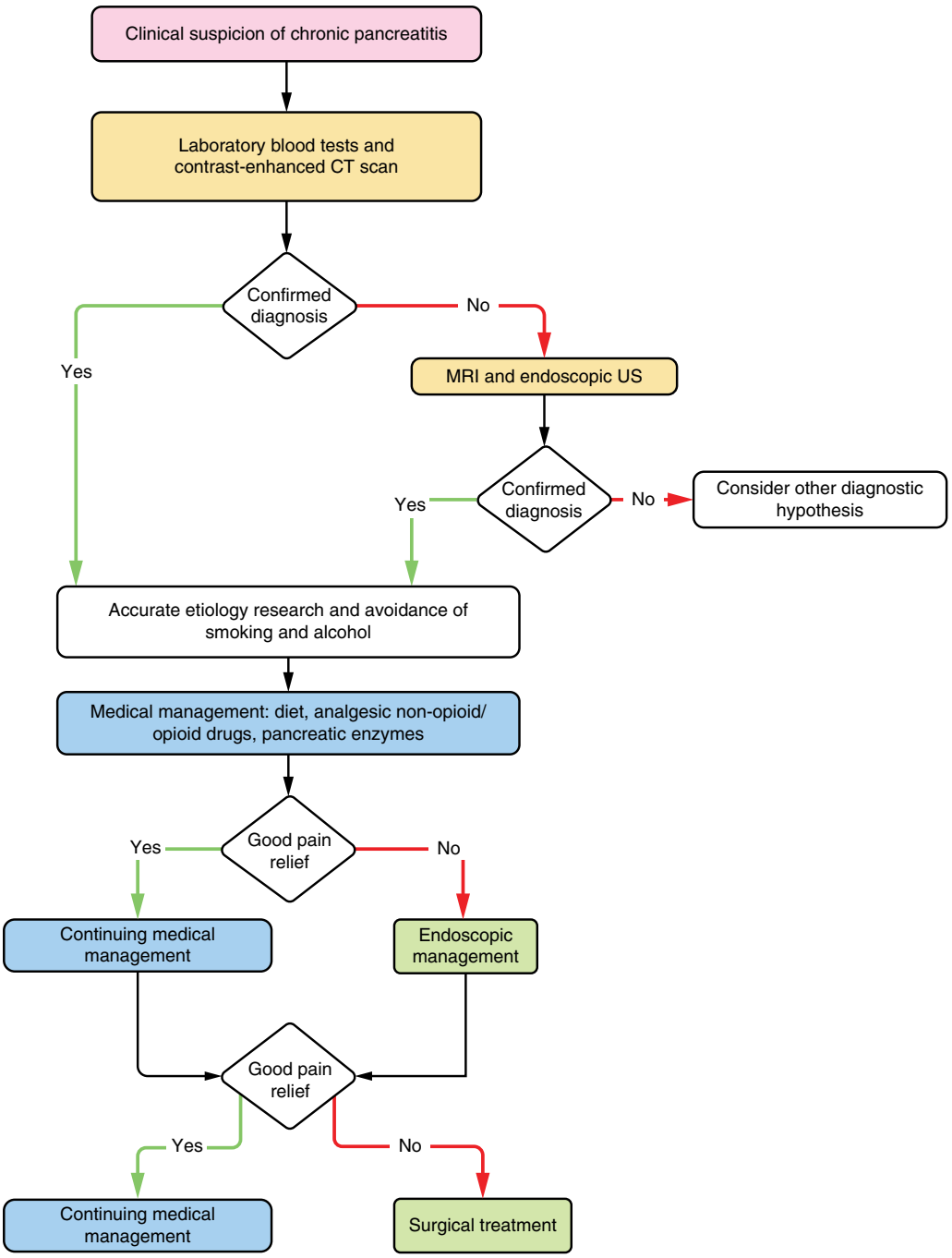


Figure 58.1 Algorithm for chronic pancreatitis.

Pathogenesis

Pathogenesis of pancreatic pain is still incompletely understood. First theories emerged at the beginning of the nineteenth century during comparative studies in relation to stones in salivary and biliary ducts [11]. Three levels of pain interest are proposed: extrapancreatic, intrapancreatic, and central.

Extrapancreatic Pain

Bile duct and duodenal stenosis due to extensive pancreatic fibrosis and inflammation have been considered extrapancreatic causes of pain [12]. Becker and Mischke described a pathologic condition named "groove pancreatitis" in 19.5% of 600 patients with CP [13]. This is characterized by the formation of a scar plate between the head of the pancreas and the duodenum. The scar

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complications are determined by the topography: disturbance in the motility of the duodenum, stenosis of the duodenum, and tubular stenosis of the common bile duct, occasionally leading to obstructive jaundice. These alterations have been suggested to be responsible for several symptoms present in CP and for postprandial pain due to compression of nerves and ganglia located between the pancreatic head and the duodenum [14].

Intrapancreatic Pain

Authors have identified several possible causes of intrapancreatic (or pancreatic) pain that can act together: ductal hypertension, parenchymal hypertension, parenchymal ischemia, pseudocysts, autoimmune disease, and neural remodeling.

Ductal Hypertension

Many investigators have related the origin of pain to increased pressure in pancreatic ducts due to strictures or stones [15]. It is calculated that normal pressure in the main pancreatic duct is between 7 and 15 mmHg, while in cases of CP, ductal pressure increases to 20–80 mmHg [16]. In ductal hypertension, alcohol plays an important etiopathogenetic role. Alcohol promotes lithiasis, which, in turn, promotes inflammation, which leads to strictures [17]. The "ductal hypertension hypothesis" as an explanation for pain in CP is supported by observations that decompression of a dilated pancreatic duct or pseudocyst frequently relieves pain [18]. Clinical trials have shown that relief from pain might be achieved by eliminating stones and strictures (surgery) or by reducing secretion (octreotide and somatostatine) [19]; however, it has been estimated that around 30% of the patients treated with decompressive surgery experience recurrent attacks of pain [20]. Conversely, some authors found no relationship between pain score and pancreatic pressure, although the intrapancreatic pressure was positively correlated with ductal changes, and they concluded that pancreatic parenchymal pressure is not closely related to pain in CP [21].

Interstitial Hypertension

According to this theory, pain is induced when increased pancreatic ductal and parenchymal pressure produce a compartment syndrome that causes ischemia [22]. This hypothesis is supported by experimental studies [23] which show increased interstitial pressure correlates with decreased blood flow in a feline model of CP. These abnormalities were reversed by surgical incision of the gland and draining the pancreatic duct, but were affected minimally by stenting the pancreatic duct. This would suggest that incision of the gland may be more important in relieving pain than ductal drainage. In addition, different studies [24,25] revealed that the degree of pancreatic fibrosis has no significant influence on pain generation since no correlation between the degree of fibrosis and intensity of pain could be demonstrated.

Ischemia

According to this theory, vascular resistance is augmented due to fibrosis, which may lead to hypoperfusion of the parenchyma. In a feline study, it was demonstrated that pancreatic perfusion in case of chronic inflammation is decreased by 40% [26].

Pseudocysts

Pseudocysts can cause intense pain in patients with CP. In the majority of cases (60%) treatment with octreotide results in a reduction in size and the eventual disappearance of the pseudocysts together with reduction of pain [27]. Enlargement of pseudocysts, causing compression of adjacent structures, might be a mechanism for pain generation.

Autoimmune Disease

Several authors have described patients with CP associated with autoimmune diseases. Sarles et al. [28] described a type of CP that might be caused by an autoimmune mechanism and termed it "primary inflammatory sclerosis of the pancreas." Yoshida and colleagues [29] reported a similar case and proposed that pancreatitis with these characteristics has to be considered as autoimmune pancreatitis. Current accepted terminology for this condition is lymphoplasmacytic sclerosing pancreatitis or autoimmune pancreatitis [30]. Pain is often associated with this type of inflammation although the genesis of this clinical symptom has not yet been investigated.

Neural Remodeling

Neurogenic inflammation as a result of pancreatic inflammation and neural remodeling has recently been linked to both acute and chronic pancreatitis. Neurogenic inflammation encompasses a series of vascular and nonvascular inflammatory responses, triggered by the activation of primary sensory neurons (C- or Aδ-type nerve fibers) and the subsequent release of inflammatory neuropeptides, including substance P (SP) and calcitonin gene-related peptide (CGRP), and has been validated in human as well as in animal models of acute and chronic pancreatic damage [31,32]. Pancreatic and central changes can be distinguished.

Pancreatic Changes

Keith et al. suggested initially that neural and perineural alterations might be important in pain pathogenesis in CP [33]. They concluded that pain severity correlated

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with the duration of alcohol consumption, pancreatic calcification, and the percentage of eosinophils in perineural inflammatory cell infiltrates, but not with duct dilatation. A subsequent study demonstrated an increase in both number and diameter of pancreatic nerve fibers in the course of CP [34]. In tissue specimens from patients with chronic pancreatitis, foci of chronic inflammatory cells were often found surrounding pancreatic nerves (called pancreatic neuritis), which by electron microscopic analysis exhibit a damaged perineurium and invasion by lymphocytes. The changed pattern of intrinsic and possibly extrinsic innervation of the pancreas in CP suggested that there could be an upregulation of neuropeptides that usually populate those enlarged nerves. In fact, a further study [35] showed that there were striking changes in peptidergic nerves in CP. The changes consisted of an intensification of immunostaining for CGRP and PS in numerous nerve fibers. Because both of these peptides are generally regarded as pain neurotransmitters, these findings provided evidence for direct involvement of pancreatic nerves in the long-lasting pain syndrome in CP. Later reports [30,36] revealed that the presence of growth-associated protein-43 (GAP-43), an established marker of neuronal plasticity, directly correlated with the pain scores in patients with CP. GAP-43 is a neuronal protein known to be involved in the development of axonal growth cones and presynaptic terminals, and mRNA and protein levels of GAP-43 are increased after neuronal lesions. In the chronically inflamed human pancreas, enzymatic and double fluorescence immunohistochemistry reveals a significant expression of GAP-43 in the majority of pancreatic nerve fibers. These immunohistochemical findings correlated with clinical and pathological findings in patients with CP, including the parenchyma–fibrosis ratio and the degree of perineural immune cell infiltration. Furthermore, a strong relationship with individual pain scores was present. The infiltration of pancreatic nerves by immune cells is significantly related to pain intensity, whereas pain scores do not correlate with the degree of pancreatic fibrosis or with the duration of the disease. The demonstration of a direct relationship between the degree of perineural inflammation and the clinical pain syndrome strongly supports the hypothesis of "neuroimmune interaction" as an important, if not predominant, factor in pain generation in patients with CP.

An interesting question concerns the mechanisms that contribute to the enlargement of pancreatic nerves. A recent study analyzed the expression of nerve growth factor (NGF) and one of its receptors (TrkA) in patients with CP [32]. NGF belongs to the neurotrophin family and plays a role in neuroblast proliferation and neuronal maturation, affecting neuronal phenotype and maintaining neuronal survival. NGF signaling is mediated via binding high- and low-affinity receptors. TrkA is present in dorsal root and peripheral ganglia cells of primary sensory nerves, and is involved in signal transduction of noxious stimuli and tissue injury. Inflammation results in an elevation of NGF levels in different diseases. Interestingly, NGF may itself have cytokine-like functions; it can modify mast cell, macrophage, and B-cell functions, but may also activate TrkA located on sensory and sympathetic nerve fibers innervating the site of inflammation, thus modulating neuroimmune interactions. In CP tissue samples NGF and TrkA mRNA expressions are markedly increased and enhanced in pancreatic nerves and ganglia. Comparison of the molecular findings with clinical parameters revealed a significant relationship between NGF mRNA levels and pancreatic fibrosis and acinar cell damage, and between TrkA mRNA levels and pain intensity. These findings indicate that the NGF/TrkA pathway is activated in CP and that this activation might influence nerve growth and the pain syndrome, most probably by modulating the sensitivity of NGF-independent primary sensory neurons through increasing channel and receptor expression [32]. Similar results showing positive correlation with pain intensity and frequency in patients with CP were reported for brain-derived neurotrophic factor gene expression, a member of the neurotrophin family [37]. In addition, upregulated NGF might influence the pain syndrome in CP patients by regulating transcription and synthesis of SP and CGRP, as well as through the release of histamine. The neuropeptide SP is the main tachykinin involved in neural transmission of sensory information, smooth muscle contraction, nociception, sexual behavior, and possibly wound healing and tissue regeneration [38,39]. SP has wide-ranging functional effects, including the crosstalk between nervous and immune systems by acting through its specific neurokinin-1 receptor (NK-1R). A recent report by Shrikande et al. [40] demonstrated a significant correlation between NK-1R and clinical–pathologic findings in patients with CP. In CP samples, NK-1R mRNA expression and protein were localized mainly in nerves, ganglia, blood vessels, inflammatory cells, and occasionally in fibroblasts. A significant relationship between NK-1R mRNA levels and intensity, frequency, and duration of pain in CP patients was reported. The expression of NK-1R in inflammatory cells and blood vessels also points to crosstalk between immunoreactive PS nerves and inflammatory cells and blood vessels, and further supports the existence of a neuroimmune interaction that probably influences the pain syndrome and chronic inflammatory changes in CP. In addition, a recent study demonstrated that PS mRNA expression levels were higher in CP tissues compared with controls, whereas

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neprilysin (NEP) mRNA levels showed no significant differences between CP patients and healthy subjects. In CP patients, PS serum levels correlated with those in tissues, and after surgical resection SP serum levels were reduced compared to preoperative values. Failure of NEP to overexpress in CP tissues was associated with significant miR-128a overexpression, suggesting that in an PS/NEP-mediated pathway NEP fails to provide adequate surveillance of SP levels and this failure of NEP might be microRNA associated [41]. The exact mechanisms involved in the interaction between inflammatory cells and nerves and ganglia—neuroimmune crosstalk—are not yet fully clarified. Different cytokines have been shown to interact with SP in various paradigms for pain and inflammation. SP directly stimulates the release of interleukin 8 (IL-8) from macrophages. IL-8 release generates hyperalgesia by stimulation of postganglionic sympathetic neurons. A significant increase of IL-8 mRNA was reported in CP tissue samples [42]. IL-8 was present mainly in macrophages surrounding the enlarged pancreatic nerves, in remaining acinar cells, and often in ductal cells. IL-8 mRNA expression was positively correlated with the inflammatory score and the presence of ductal metaplasia in CP tissue samples. The reported findings in the literature on the interaction of SP and IL-8, in combination with what has been reported in CP, suggests that the increased mRNA expression of IL-8 in CP could in part be mediated by SP released from sensory pancreatic nerves. In addition, the release of IL-8 from the remaining exocrine pancreatic parenchyma suggests the fascinating hypothesis of an intrinsic maintenance of the inflammatory response after the initial damage to the pancreatic gland, thus sustaining progression and evolution of the disease. In addition, in a rat model it was found that repeated caerulein stimulation causes experimental pancreatitis that is mediated in part by stimulation of vanilloid receptor type 1 (VR1) on primary sensory neurons, resulting in endogenous SP release [43]. These results were confirmed in human pancreas [44]. In fact, an activation of the VR1 in pancreatic tissues from patients with pancreatic cancer and CP is known. This increase was correlated with pain score in those patients. The release of PS and Na+/K+-ATPase (NKA) from primary afferent (sensory) nerve endings to various stimuli is now considered to be induced by activation of the capsaicin (vanilloid) receptor (VR1).

Central Involvement

Patients with CP have lower thresholds to pain in response to deep abdominal palpation than healthy individuals (reflecting secondary referred hyperalgesia in the musculature) [45]. Furthermore, the area of referred pain is expanded in patients with CP who are subject to experimental electrical stimulation of viscera with changes in evoked potentials in the brain [46–48]; these data have also been confirmed by magnetic resonance imaging. These patients report hyposensitivity to cutaneous stimulation, probably as a result of altered descending inhibitory influences on spinal nociceptive neurons [49] and hyperalgesia to rectosigmoid stimulation, accompanied by impairment in diffuse noxious inhibitory control, a phenomenon that reflects descending central inhibition of pain, thought to be a countermeasure to noxious stimulation [50]. Central sensitization is associated with reduced efficacy of invasive endoscopic and surgical treatments directed at the pancreas [51]. In contrast to the previous sentences, many patients with continuous pain do not have structural complications or evidence of inflammation: this could be the case of a neuropathic pain [52].

Conclusion

Pain is the most frequent clinical feature in patients with chronic pancreatitis. Many components are responsible for pain at intrapancreatic, extrapancreatic, or central nervous system level, with different expression in relation to the individual patient, nociceptive level, and comorbidities. There is a complex network among neuropeptides, immune cells, cytokines, and NGF. Neuropeptides released from the enteric nervous system and their spatial relationship with inflammatory cells play a key role in pancreatic pain. A fuller knowledge of the physiopathology of pain may lead to a complete and effective medical and surgical treatment of chronic pancreatitis and its manifestations.

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Pain Management in Chronic Pancreatitis

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Introduction

Abdominal pain is the most common symptom in chronic pancreatitis (CP), and it remains a clinical challenge. Pain affects about 90% of patients along the course of the disease and can present in various forms [1,2]. The classical description of pancreatic pain is a constant, dull, epigastric pain that radiates to the back and is worsened by intake of high-fat foods [3]. Intensity can present in forms ranging from a barely noticeable sensation to immense, continuous pain. Some patients experience episodes of severe abdominal pain, whereas others experience a daily aching pain that may be exacerbated by acute flares [3]. Pain pattern has traditionally been looked at as either type A pain (intermittent pain with pain-free intervals in-between) or type B pain (constant pain with or without exacerbations) as described by Ammann et al. [4], but recent research concluded that several shifts between pain patterns can occur during the course of the disease [5]. Regardless of the type of presentation, pancreatic pain highly affects quality of life and is a risk factor for hospitalizations [6,7]. In an examination of 540 American CP patients in the NAPS2 (North American Pancreatitis Study 2) cohort, most patients reported at least one hospitalization in the last year, 25% were on disability benefits, and there was no association between the duration of the disease and pain severity [1].

Pathophysiology

Pain in CP is poorly understood, and the underlying mechanisms are still debated. However, generally, it is agreed that pancreatic pain has elements of nociceptive pain, obstructive factors, and neuropathic/neuroplastic pain [3,8].

Nociception is the process whereby the sensory nervous system encodes noxious stimulations. It involves the activation of specific neural processes leading to an action potential that forwards the signal through the dorsal horn of the spinal cord and through ascending pathways to the limbic, thalamic, and cortical regions of the brain. Nociception can lead to the perception of pain, but as outlined below, pain is a subjective experience including affective and cognitive components, together with suffering and changes in behavior.

It is hypothesized that ductal and mechanical alterations can cause pain, especially ductal obstructions and local inflammatory masses. However, radiological findings are not correlated with pain severity [3,9], and postoperative long-term pain relief is dependent on many other factors [10].

The perception of pain is generally induced by tissue injury, but the neural structures can become sensitized over time. Sensitization will induce a greater neural response to noxious stimulations and increase the sensation of pain, leading to hyperalgesia. Sensitization can occur both peripherally in the primary nociceptors and centrally at the spinal level or higher levels, including the brain [11].

In CP, continuous inflammation can cause the pancreatic nerve fibers to convey signals to the brain, which is perceived as pain. The inflammation will cause the pancreatic tissue to break down, and the nerves can then be exposed to toxins and chemicals, leading to nerve hypertrophy, an increase in density, and an increased number of nerve endings [12]. These findings correlate with pain intensity and support the theory of neuropathic pain [13]. In such cases, spontaneous firing from the damaged

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nerves and central sensitization, and lack of normal inhibition can amplify the pain.

Pancreatic nociception seems to be affected significantly in CP, where increased excitability is linked to an upregulation of several molecules, including the vanilloid receptor TRPV1, calcitonin gene-related peptide (CGRP), nerve growth factor (NGF), and the protease-activated receptor 2 (PAR-2) [8]. This upregulation is believed to drive neural sensitization, starting peripherally and progressing centrally.

Pain in CP can also be secondary, related to complications of CP and treatment [14]. For example, CP patients are at increased risk of developing peptic ulcers and bacterial overgrowth in the small intestines. Furthermore, the analgesic treatment, especially opioid treatment, may result in severe side effects that can increase pain, including constipation and opioid-induced hyperalgesia. All of these complications need to be addressed appropriately to reduce pain.

Pancreatic pain does, however, comprise more than just nociception and pain intensity. Cognitive dimensions of pain include how the patient perceives him/herself in pain and predispositions for coping with pain, including temper and personality traits. Affective dimensions include depression and anxiety, which affect pain processing and the perception of pain. Finally, behavioral dimensions, such as grimacing, crying, and limping, can induce empathy in relatives and secondarily increase pain behavior. However, this negative spiral can ultimately also increase pain perception [15].

This multifactorial nature needs to be taken into account when managing pain in CP. However, patients differ with respect to pathophysiology, genetic and social factors, etc., and treatment should be tailored to the individual rather than a one-size-fits-all approach [16].

Pain Assessment

The clinician should always start with a thorough pain assessment to guide treatment. Pain intensity, pain pattern, factors that provoke or worsen pain can be important when determining which mechanisms are involved in the development of pain. In addition, this information can be used when evaluating whether the pain is nociceptive or neuropathic. Evaluation should include questions on pain intensity and characteristic features, pain interference on physical and emotional functioning, and quality of life assessment [17]. For details, the reader is referred to a recent guideline paper in pain assessment of CP [14]. Unfortunately, pain assessment tools developed specifically for CP have proven to be either dominated by unidimensionality, lack of validity and reliability testing, or poor coverage [18]. For example, the Izbicki pain score developed for CP has been used in several studies, although it has never been formally validated [19,20]. Other pain questionnaires such as the Brief Pain Inventory have also been used extensively in CP and it is validated for nonmalignant pain; however, it lacks focus on features characteristic of pancreatic pain [21]. As a result, the COMprehensive Pain Assessment Tool (COMPAT) has been developed to include all core dimensions of pain and aspects specific to CP [22]. In addition, a short-form was recently developed to increase the clinical usability, comprising five pain dimensions to characterize pancreatic pain, including pain severity, pain pattern, factors provoking pain, qualitative pain assessment, and spreading pain. It has been validated and tested to be reliable in three centers in Denmark, New Zealand, and the United States [23].

As many pain assessment questionnaires do not include quality of life assessment, they can be accompanied by questionnaires such as, for example, the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire for quality of life assessment [24].

Besides pain assessment tools, quantitative sensory testing (QST) has been examined as a diagnostic test for assessing somatosensory function in CP. QST is a method for determining how patients respond to painful stimulations. For example, a QST technique called the Pancreatic QST (P-QST) protocol uses bedside pressure testing, repetitive stimulations, and conditioned pain modulation testing to evaluate the nociceptive responses indirectly [25]. Studies using P-QST have phenotyped patients based on pain patterns and correlate increasing widespread hypersensitivity with pain intensity, pain interference, and quality of life [26]. In addition, neurophysiological examinations, including P-QST, can be used to guide treatment according to the presence of segmental hyperalgesia and deficient descending pain inhibition [27]. However, these methods are only available in the most advanced laboratories and are still considered research tools.

Noninterventional Pain Treatment

Pain management should start with optimizing lifestyle factors. Alcohol consumption is a significant risk factor for the development of acute-in-chronic pancreatitis. It has also been linked to the occurrence of severe pain [9]. Likewise, smoking is related to pancreatic pain as there is an increased risk of pain with an increasing number of daily cigarettes [9]. Therefore, abstinence from alcohol and smoking is an important part of hindering the progression of chronic pain and acute flares into chronic pain. It can be supported

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with medications for alcohol dependence, such as naltrexone, nicotine substitution, cognitive therapy, or mindfulness-based therapy [27]. However, even in abstinence from alcohol and smoking, the pain often persists.

Pain treatment should be managed in an interdisciplinary fashion, starting with an open discussion on treatment goals. An alignment of expectations is important, as some patients might expect complete resolution of pain, which is seldom achievable. A psychological evaluation is also essential, as comorbid depression and anxiety can worsen the sensation of pain as pain, anxiety, and depression are neuroanatomically and neurochemically linked [28]. Cognitive therapy can also be used to improve both affective mood disorders and improve pain-coping [29].

Neuromodulation has also been used successfully in treating pancreatic pain by modulating brain plasticity where mechanisms such as hyperpolarization, activation of endogenous opioids, and descending inhibition may also play a role [27,30]. It can suppress activity or promote the facilitation of the targeted area, but high-quality randomized controlled studies (RCT) are lacking. A small RCT showed that acupuncture was beneficial in CP, but the effect is short-lasting [31]. Pilot studies have shown an effect of transcranial magnetic stimulations and spinal cord stimulation, but studies have lacked a valid placebo arm and as such are subject to major bias [32].

Endoscopic and Surgical Pain Treatment

Endoscopic and surgical pain treatment is based on the rationale that pain originates from the pancreas's structural changes, such as main duct obstruction due to strictures or stones or inflammatory masses in the pancreas. Endoscopic treatment is used in the case of obstruction of the main pancreatic duct, where endoscopic retrograde cholangiopancreatography (ERCP) procedures can maintain drainage from the main pancreatic duct by pancreatic papillotomy, by extraction of pancreatic stones, or temporary stent placement [33]. However, the "plumbing theory" where ductal obstruction is the main cause of pancreatic pain is still debated. Although studies on endoscopic treatments have shown significant improvement in pain intensity in most patients, the studies are biased by several factors, including patient selection, short follow-up period, poor pain assessment methodology, and especially lack of sham control [32]. To circumvent these biases, an ongoing RCT (SCHOKE trial) randomizes patients to either active or sham extracorporeal shock-wave lithotripsy and endoscopic treatment, and currently, 50 patients are enrolled [34].

In randomized studies, surgery has proven to be superior to endoscopic treatment [20]. Surgical procedures include resection, either partial or total pancreatectomy, surgical drainage, and combinations. The argument for surgical treatment is that eliminating the source of the nociceptive pain could result in decreased firing from primary afferents and lead to decreased pain [32]. Total pancreatectomy with islet cell transplantation has gained increasing popularity but carries the risk of neuropathic pain development. Furthermore, metabolic consequences can be severe, and technical challenges remain an obstacle [11]. As studies with sham interventions are not possible with pancreatic surgery, controlled studies where patients are followed strictly for several years after surgery are needed, which may identify the role of surgery in CP [32]. However, most series have shown that a significant proportion of the patients still suffer from pain, and therefore pharmacological management is still needed.

The rationale for surgery is also applied when using neuroablative procedures to treat pain. This argument is supported by the fact that local treatments such as neural blocks can alleviate pain in peripheral nerve injury [35]. However, although neural blocks can initially affect pain intensity, studies show that they do not reduce the risk of developing allodynia or hyperalgesia [36], and nerve destruction may, in the long run, worsen neuropathy, and hence pain [30].

Pharmacological Pain Management

Simple analgesics are recommended as the first line of treatment in painful CP, especially paracetamol/acetaminophen. Nonsteroidal anti-inflammatory drugs (NSAID) can be used in selected cases but are of limited value due to gastrointestinal toxicity and CP patients' predisposition for peptic ulcers [27].

Second to simple analgesics is adjuvant therapy consisting mainly of anticonvulsants, antidepressants, and anxiolytics. In the anticonvulsive drug group, only pregabalin has been evaluated in RCT in CP and proven to provide moderate pain relief [37,38]. It has also been shown that pregabalin has inhibitory effects on central sensitization by reducing spreading hyperalgesia [39]. In addition, randomized controlled studies have shown that segmental hyperalgesia is predictive of the analgesic effect of pregabalin in CP [40]. Pregabalin is licensed for neuropathic pain and fibromyalgia but has also been used in other painful conditions with good results [41].

Antidepressants have never been examined as analgesic treatment in CP patients. However, as the noradrenergic system plays an important role in endogenous pain

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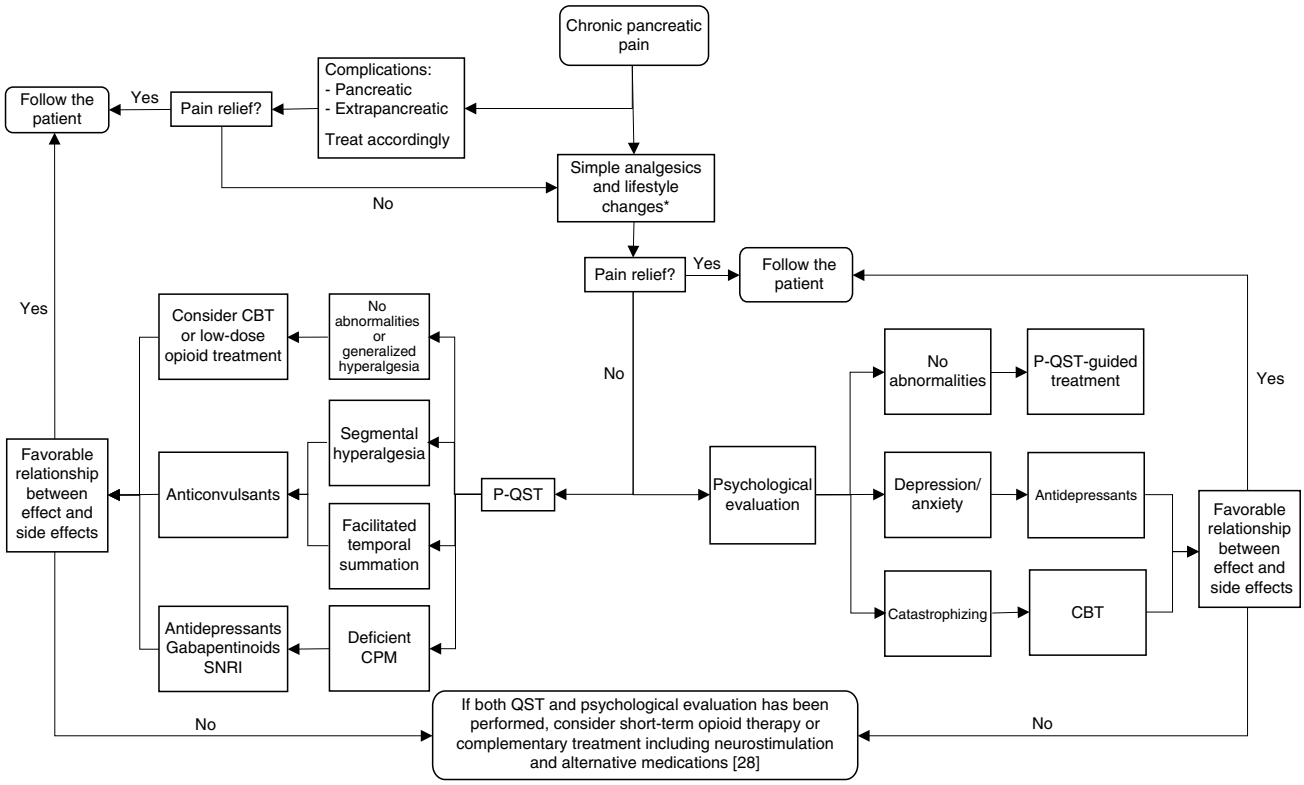


Figure 59.1 An example of a mechanism-based treatment algorithm. Simple analgesics include NSAID and paracetamol/acetaminophen; complementary treatments include acupuncture, vagal nerve stimulations, etc. P-QST*: quantitative sensory testing; CBT: cognitive behavioral therapy; CPM: conditioned pain modulation; SNRI: serotonin and norepinephrine reuptake inhibitors. *Optimize nutrition and add antioxidants in selected cases, cessation of alcohol and tobacco use.

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modulation and antidepressants have proven effective in neuropathic pain [42], the effects may be transferable. It can also be questioned whether RCT in CP patients are needed for all analgesics. Although these patients have many specific features, there is evidence that treatment is likely to be based on the level of the individual rather than at the level of the disease [43]. Hence, data from studies in other pain patients can likely be extrapolated to CP. For example, Arendt-Nielsen and colleagues have shown that the function of the endogenous pain modulatory system predicts the analgesic effect of duloxetine in diabetic neuropathy, and other types of tricyclic antidepressants have been shown to improve the ability to modulate pain [44]. In addition, antidepressants can also be used to treat comorbid depression and anxiety, as the involvement of norepinephrine and serotonin in these diseases can affect pain processing and increase pain sensation.

Although pain management with simple analgesics and adjuvants is preferable, many patients need opioids to dampen their pain. It is necessary to closely monitor patients on opioid treatment, as adverse effects are common and include symptoms such as constipation, nausea, and opioid-induced hyperalgesia, which significantly affect the quality of life; for details, see [45,46]. Furthermore, it is estimated that only about 25% of CP patients benefit from opioid treatment, and it is necessary to evaluate treatment effects often [27]. Tramadol possesses a weak opioid agonist activity and affects the serotonin- and norepinephrine uptake [47], thereby having a dual-action effect. It is shown to be superior in South African CP patients and has fewer gastrointestinal side effects [48]. However, the results have not been validated in other ethnicities.

In general, the problem with analgesics is not the efficacy but the side effects. It is outside the scope of this chapter to describe the balance between effects and side effects and how to balance between them to the benefit of the patients, but the reader is referred to [49].

In Figure 59.1, a proposal for noninvasive treatment of pain in CP is shown.

Conclusion

Pain management remains a challenging and frustrating part of caring for patients with CP, as many issues remain unsolved.

Treatment has to be tailored to the individual, and successful pain management begins with good communication, where it is important to agree upon treatment goals early in the process. The analgesic strategy is multimodal and may include invasive treatments, medical treatments, and adjuvant treatments, bearing in mind that pain in CP is a combination of nociceptive and neuropathic/neuroplastic pain.

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Adjunctive Therapy in Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas for which there is no cure. Therapies in CP are directed at managing symptoms of the disease, mainly the dominant symptom of abdominal pain. Patients with evidence of pancreatic ductal obstruction are often managed with endoscopic or surgical therapy to relieve obstruction in addition to analgesia, whereas patients without clear signs of ductal obstruction are managed medically. The foundation of medical management consists of analgesic therapy, including both opioids and non-opioid analgesics. Adjunctive therapies are used to address pain by targeting mechanisms of pain that differ from traditional analgesia, as well as treating concomitant affective disorders, digestive disorders, and malnutrition. Pain treatment studies in CP are difficult to compare as endpoints vary widely between studies; however, the clinical need for pain treatment in this population persists and requires creativity and open-mindedness on the part of healthcare providers [1]. This chapter will review adjunctive therapies in CP, which are meant to serve as complementary therapies addressing pain or CP sequelae that are inadequately treated by traditional analgesia or interventions.

Therapies for Affective Disorders

Pain-related factors in CP including anxiety and depression can overlap and have a cumulatively detrimental effect on patients with CP [2]. Affective psychiatric disorders including anxiety and depression are highly prevalent in patients with CP, and frequently coexist [3]. In a cross-sectional analysis of an international cohort of CP patients, the prevalence of anxiety or depression symptoms was seen to be 46.8% and 38.6%, respectively, and their presence was associated with increased severity of pain and interference of pain with daily living [3]. The presence of depression in this study was independently associated with decreased quality of life, further highlighting the impact that psychiatric comorbidity can have in this patient population [3]. Assessment for and treatment of affective disorders concomitant with CP should be a high priority in clinical practice and symptoms can be detected effectively with questionnaire screening instruments.

Antidepressant Medications

Medical therapy for affective disorders including tricyclic antidepressants (TCA), selective serotonin uptake inhibitors (SSRI), and serotonin noradrenergic reuptake inhibitors (SNRI) have been recommended by clinical guidelines for treatment of painful CP as part of a multifaceted approach to therapy due to their analgesic effects (SNRI and TCA) and effect on concomitant depression (all three) [1]. Although they may be used in clinical practice, there is little data on the prevalence of their use or their effects in this population. The North American Pancreatitis Study 2 (NAPS2) group assessed the association between constant severe pain and genetic loci for depression and noted that 56% of that population self-reported taking an SSRI when asked for current medications [4]. There is much evidence for neuropathy in CP [5]. Multiple studies have been conducted to assess the efficacy of duloxetine, an SNRI, at treating neuropathic pain in diabetic neuropathy, fibromyalgia, and pain associated with depression, prompting a Cochrane review in 2009 and subsequent update in 2014 [6,7]. Together, the studies showed that duloxetine is effective

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in reducing pain in diabetic neuropathy, as well as for pain symptoms of depression. The direct analgesic effect of duloxetine is considered to be independent of the drug's effect on depression symptoms [8], making it particularly relevant in patients with painful CP and concomitant depression. Studies in other chronic pain conditions have shown antidepressant medications broadly to have varying degrees of direct analgesia, with SSRI medications being the least analgesic but having a more acceptable tolerance profile than others [9]. While these results may be extrapolated to subgroups within the CP population, it is noted that no clinical trials have evaluated the effect of SSRI or other antidepressant medications in CP patients specifically.

Psychosocial Therapies

When regarded through the lens of the biopsychosocial model of illness, painful CP is understood as a complex phenomenon where pain, quality of life, stigma, self-blame, and addictive behaviors (for a subset of patients) impact and often exacerbate one another [10]. Psychologic therapies including mindfulness therapy and cognitive behavioral therapy are important tools to impact these forces individually. Combining any such therapies with interventions intended to address addictive behaviors including alcohol-, tobacco-, or opioid-use disorders is a priority in this population as the first two are independent risk factors for progression of CP and all can exacerbate or amplify the pain experience.

Mindfulness therapy, a talk therapy often linked to Buddhism, encourages patients to focus nonjudgmentally on the present lived experience and teaches coping mechanisms for dealing with challenges including stress and pain. In a pilot study of 10 CP patients with pain compared with 5 healthy controls, a 28-day telephone-based mindfulness therapy intervention was completed, showing improvement in social aspects of quality of life as measured by the SF-36 [11]. While there was no significant improvement in physical quality of life, and the study was limited by small sample size and a broad definition of CP, the effort did establish feasibility of such an intervention and illustrates the potential impact this could have for CP patients suffering from poor quality of life.

Cognitive behavioral therapy (CBT), a psychosocial intervention aiming to challenge cognitive distortions and improve emotional regulation and coping, has also previously been tested in an internet-based randomized, controlled pilot trial of 30 subjects with painful CP [12]. Not only was the intervention deemed feasible and acceptable, but the proportion of those who responded with reduced pain intensity and pain interference at 3 months was significantly greater in the internet-based CBT group than the control group. Psychological therapies show significant promise in CP patients with pain who are suffering from concomitant psychiatric illness and should be strongly considered in this patient subpopulation.

Although published literature on these types of interventions remains rare, patients who are suffering from painful CP and additional psychiatric illness may strongly benefit from referral to expert providers of psychosocial therapies, and there is at least some evidence that they are effective.

Treatments for Neuropathy

Neuropathy is an additional contributor to the experience of many patients with CP, and pain related to this can be particularly challenging to treat [5]. Alterations in pain processing due to changes in the nerves themselves or in patterns of transmission of pain signals can result in pain that is resistant to traditional analgesia.

Medications

Pregabalin, a lipophilic analog to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), has been approved by the US Food and Drug Administration for treatment of neuropathic pain and may have a role in treatment of painful CP. Pregabalin has previously been shown to reduce the pain intensity of patients with CP in a randomized, double-blind, placebo-controlled trial of 64 patients after 3 weeks compared to placebo [13]. In a separate placebo-controlled randomized trial of 90 patients, those who received a combination of antioxidant therapy and pregabalin were shown to have significant reduction in pain intensity, non-opioid analgesic requirement, and hospital admissions for pain during the 12-week study period compared to those who received placebo [14]. A randomized, double-blind, placebo-controlled study of 88 patients with recurrent pain following pancreatic ductal clearance additionally showed significant reduction of pain intensity after 8 weeks of therapy in those who received antioxidants and pregabalin compared with placebo [15]. It is noted that in the study from Sureshkumar et al. [13], patients with concomitant major depression, and those with intractable pain who had previously failed medical management were excluded, and in the study from Talukdar et al. [14], patients who had received high-potency narcotics were excluded. Given the prevalence of major depression and narcotic use among CP patients, these results are potentially difficult to extrapolate to the broader CP population. Additional neuromodulators including olanzapine, quetiapine, ketamine, and others may have effect in CP

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pain though they have not been specifically studied in this population. The role of neuropathic agents is additionally discussed in the chapter on pain management, and the role of antioxidant therapy is further discussed in a dedicated chapter in this text.

Nerve Blocks

Blockade of specific nerves or nerve groups has been attempted for painful CP with varying degrees of success. Celiac plexus blockade is a technique performed via radiographic, CT-guided, or endoscopic-guided approaches in which steroids and local anesthetic are injected at the celiac plexus [16]. Response rates following therapy vary across studies but in general are lower than 60% [17,18]. The duration of response is only approximately 3–6 months, making this more of a temporizing measure than a treatment from which durable pain response is expected. Importantly, the risk of nerve damage associated with the procedure may actually worsen neuropathy, leading some to consider this treatment obsolete in painful pancreatic disease that is nonmalignant [19].

A small study of subcostal transversus abdominis plane blockade has shown reduction in pain from myofascial pain syndrome associated with CP [20]. This study was limited by the fact that the technique is ineffective for visceral pain as well as for pain from ongoing pancreatic inflammation: there was additionally no control arm making the results less robust. A single-blinded randomized crossover trial of acupuncture did show pain relief from treatment as compared to sham, but the effect was short-lived and disappeared after one week [21]. Several other small studies have shown some degree of benefit in research settings from experimental interventions including cervical transcutaneous neuromodulation, and transcranial magnetic stimulation [22,23]. The potential for clinical use of these techniques are limited by the fact that they are often administered only in research settings, require specific expertise, have short-lived effects, and are not widely available.

Central Sensitization

Central sensitization, a phenomenon of altered processing of nociception, has been described in patients with painful CP and is thought to be a critical aspect of the pain experience in this disease [24]. The presence of central sensitization has the potential to render traditional therapies such as decompression of an obstructed pancreatic duct or surgical drainage procedures ineffective in providing pain relief [25]. Techniques to reliably identify patterns of central sensitization including manifestations of widespread hyperalgesia or altered central pain modulation have previously been only available in research settings; however, a bedside technique intended for clinical adaptation has been recently developed [26]. Pancreatic quantitative sensory testing (P-QST) differentiates CP patients into distinct phenotypes by characterizing their nociceptive patterns and identifies patients with characteristics of central sensitization [27]. There is no treatment for central sensitization; however, both pregabalin and S-ketamine have shown promise in initial trials in modulating measures of hyperalgesia [28–30]. A randomized trial of S-ketamine treatment has been proposed but not yet completed [31].

Therapy for Nutritional Disorders

Malnutrition is a frequent complication of CP due to exocrine pancreatic insufficiency (EPI) and maldigestion [32]. This can be further exacerbated by concomitant disorders of delayed gastric transit, small intestinal bacterial overgrowth (SIBO), and sarcopenia [33–36]. While nutritional evaluation of CP is covered elsewhere in this text in detail, diagnosis of concomitant gastrointestinal disorders, vitamin and mineral deficiencies, and their treatment or supplementation may be effective adjuncts in the treatment of CP. Delayed intestinal transit, bloating from fat malabsorption, and neuropathy due to underlying vitamin deficiency are all possible sources of pain in CP complicated by malnutrition [37]. Diagnostic testing to include anthropometric, biochemical, and clinical markers of malnutrition for those patients at high risk on an annual basis have been recommended as a means of identifying those patients with possible vitamin and mineral deficiencies complicating their underlying CP [37].

Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy (PERT) is designed to assist with the absorption of fat, protein, and micronutrients in EPI. Pain reduction from PERT is mostly secondary to decreased symptoms of maldigestion including hypermotility of the colon in the setting of steatorrhea, though some contribution from suppression of pancreatic enzyme release may be possible [38,39]. In a large systematic review and meta-analysis of clinical trials PERT has been shown to improve fat absorption in patients with CP both compared to patient baseline levels and compared to therapy with placebo [40]. In the same study, PERT was also shown to improve abdominal pain without significant adverse events. The perceived efficacy of PERT (by patients) for treatment of pain in CP in the absence of EPI was found to be low (36.3%); perceived efficacy of PERT rose only to 50% in patients with

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both EPI and pain [41]. High-quality large rigorous studies on the efficacy of PERT for malnutrition in CP are needed, as is more consistent education for practitioners regarding indications for PERT therapy and potential benefit. Evaluation of an insured US population showed that both testing for EPI and adequate dosing of prescribed PERT were infrequent and inconsistent, suggesting that this therapy is underutilized and used in a suboptimal fashion in CP patients overall [42].

Vitamins, Antioxidants, and Octreotide

Fat-soluble vitamin levels are a frequent concern in patients with CP, especially in patients with symptoms of fat malabsorption. Vitamin D deficiency is the most common fat-soluble vitamin deficiency in CP patients (>50%), though it also common in patients without CP [32]. Vitamin A and E deficiencies have been seen in approximately 15% and 25% of CP patients, respectively [32]. Supplementation of fat-soluble vitamins is recommended to avoid the potentially serious complications of prolonged or severe deficiency including night blindness (vitamin A), neuropathy (vitamin E), and mineral bone disease such as osteopenia or osteoporosis (vitamin D). In particular, the prevalence of osteopathy in CP patients has been found to be significantly higher than that of the general population, and assessment and treatment has been recommended as part of routine care [43–45]. Diagnosis and supplementation of water-soluble vitamin and micronutrient deficiencies in patients with poor diet or other markers of malnutrition are also recommended.

Indications for, efficacy of, and evidence regarding antioxidant use is reviewed in a separate chapter, but they are mentioned here as part of the adjunctive armamentarium for painful CP, through reduction of acinar cell injury by protecting against oxidative stress [41]. It is noted that their use is infrequent and dosing is quite varied across practitioners, and reported data has been highly variable on their efficacy [41,46,47]. Similarly, octroeotide—a synthetic somatostatin analog that has an inhibitory effect on pancreatic secretion—has been utilized to decrease pancreatic stimulation and release of enzymes. Its use in CP has been infrequent, and the reported efficacy for symptoms of CP has been highly variable [41].

Cannabinoids

Reported cannabinoid use has increased in recent years as an analgesic agent for patients with painful CP concomitant with the spread of medically directed marijuana therapies, though high-quality randomized study data is scarce and cannabinoids represent a heterogenous group of chemical substances [48]. Delta-9 tetrahydrocannabinol (THC), the most abundant cannabinoid in the plant, was tested in a phase-2 placebo-controlled clinical trial of patients with chronic abdominal pain, but unfortunately did not show any significant improvement compared to placebo [49]. This study was notably limited by heterogeneity of the etiology of abdominal pain in the studied patients, with CP and post-surgical patients combined into a single group. A separate small study was not designed to evaluate pain response to cannabis, but detected a reduction in opioid use, hospitalizations, and emergency room visits for CP patients after their enrollment in a state-directed therapeutic cannabis program compared to before their enrollment in the program [50]. A recent observational study shows that medical marijuana is used more frequently in patients maintained on chronic opioid therapy than those who are not on chronic opioids, suggesting that its utility is mainly seen as an adjunctive agent in this patient population [51].

Conclusions

Adjunctive therapies in CP are initiated because existing analgesic and interventional therapies result in suboptimal relief of symptoms for this disease. A thorough evaluation for concomitant and complicating disorders should be conducted, and directed adjunctive agents can be initiated based on the individual patient situation after traditional therapies for CP have been optimized. The evidence for the efficacy of adjunctive therapies in CP remains quite limited even though there are hints that they can form part of an overall treatment regime for painful CP.

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Pancreatic Cancer Risks in Chronic Pancreatitis

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Introduction

In the late nineteenth century, the German pathologist Rudolf Virchow proposed that there was a close link between inflammation and cancer, based on cellular studies made possible by microscopy. Since then it has been observed that inflammatory diseases such as esophagitis, gastritis, and colitis sometimes precede the development of cancer in these organs. Throughout the twentieth century, anecdotal reports of pancreatitis preceding pancreatic cancer have emerged. These isolated reports suggested a possible link between chronic pancreatitis and pancreatic cancer and eventually led to a large retrospective cohort analysis conducted near the end of the twentieth century. In this chapter, we review and summarize the evidence linking chronic pancreatitis and pancreatic cancer.

Descriptive Findings

Acute pancreatitis, chronic pancreatitis, and pancreatic cancer are the three most common pancreatic diseases. How does their incidence compare? Acute pancreatitis is one of the commonest gastrointestinal disorders and has an estimated incidence of about 13–45/100,000 per year [1]. The incidences of chronic pancreatitis and pancreatic cancer are similar to each other, with age-standardized incidence rates of around 10/100,000 per year.

Figure 61.1 illustrates the relationship between these three diseases and the potential pathways for progression from acute to chronic pancreatitis and, in some patients, to pancreatic cancer. In patients with gallstone-related pancreatitis, cholecystectomy performed on a timely basis eliminates the major source for gallstones and precludes additional attacks. However, acute pancreatitis also develops from many other causes, and if the cause is heavy drinking, smoking, autoimmunity, or a

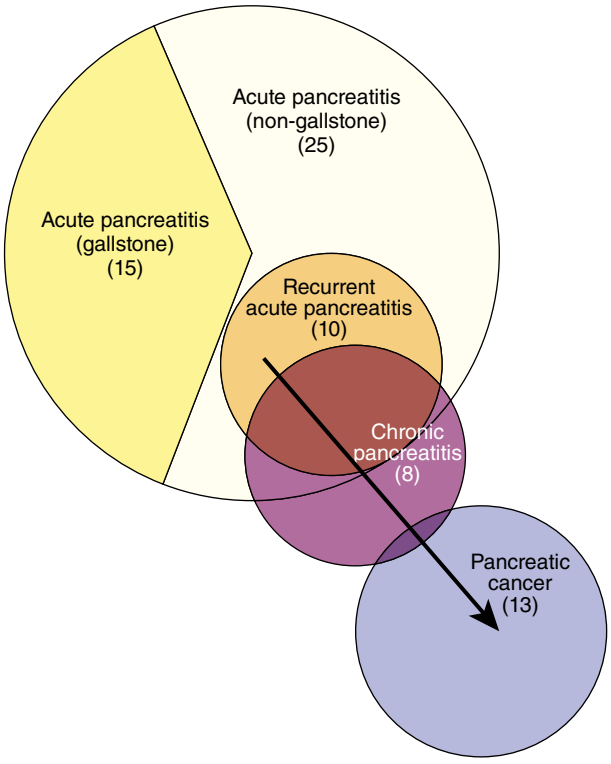


Figure 61.1 Incidence rates for pancreatic diseases in the United States. Numbers inside circles indicate incidence rates per 100,000 population. The arrow indicates the progression from benign to malignant disease. Note the small overlap between the circles representing chronic pancreatitis and pancreatic cancer. *Source:* Yadav and Lowenfels 2013 [1]. With permission of Elsevier.

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genetic disorder, recurrent attacks of acute pancreatitis (recurrent pancreatitis) may occur and disease progression may then lead to chronic pancreatitis. Of patients who develop chronic pancreatitis, a small proportion will develop pancreatic cancer. The average age at diagnosis of chronic pancreatitis in patients with alcohol-related disease is about 45–55 years, approximately a decade earlier than the average age of onset of pancreatic cancer. This time sequence indicates that the direction of causality is compatible with a progression from benign to malignant disease.

Other than age, what are some of the other similarities and differences between chronic pancreatitis and pancreatic cancer? For both diseases, smoking and obesity are recognized risk factors, whereas heavy drinking, which is strongly linked to chronic pancreatitis, is associated only with a modest increased risk for pancreatic cancer [2]. Both diseases are also more frequent in black than in white populations, and diabetes frequently accompanies both diseases.

Measuring the Strength of the Pancreatitis–Pancreatic Cancer Association

After initial reports from single centers by Ammann and coworkers in 1984 [3] and Rocca and coworkers in 1987 [4] who described the gradual increase of pancreatic calcifications and pancreatic dysfunction with increasing duration of the disease and suggested an increased risk of pancreatic, as well as extrapancreatic cancer, in patients with chronic pancreatitis, Lowenfels and coworkers conducted the first multicenter cohort study. Among 2015 patients with well-documented chronic pancreatitis from six countries followed up for a minimum of 5 years after the diagnosis of chronic pancreatitis, the risk of pancreatic cancer was 14.4 (95% Cl: 8.5–22.8) times higher than that in the background population. The risk was similar in all study countries and in patients with either alcoholic or nonalcohol pancreatitis [5]. Over a follow-up period of up to 20 years, the cumulative incidence of pancreatic cancer was 4%. This implies that chronic pancreatitis, although a strong risk factor, explains only a small proportion of the total burden of pancreatic cancer. Also in contrast to the 29 patients who died from pancreatic cancer, 137 patients in the group died from other types of cancers. Because of lifestyle factors such as smoking and heavy alcohol drinking, most cancer deaths in patients with chronic pancreatitis will be from nonpancreatic cancer.

Since publication of this report, several additional studies have looked at the relationship between chronic pancreatitis and pancreatic cancer [6–29]. Raimondi and coworkers published an initial meta-analysis in 2010 based on 18 additional studies [30] with a pooled relative risk (RR) of 13.3 (95% CI: 6.1–29) for well-defined chronic pancreatitis. In 2014, Tong and coworkers published a systematic review of epidemiologic studies linking pancreatitis and pancreatic cancer [31]. This report contained 14 case-control studies and 3 cohort studies and found a pooled odds ratio of 7.1 (95% CI: 6.4–7.8). As in the previous meta-analysis, the results were stronger in cohort studies than in case-control studies. In a large pooled analysis of 10 case-control studies, Duell and coworkers reported a nearly threefold increased risk of pancreatic cancer in patients where there was a minimum of 2 years separating the diagnosis of pancreatitis from pancreatic cancer [10] More recent reviews and meta-analyses were performed by Kirkegard and coworkers [32] and Ghandi and coworkers [33]. Based on these reports and more recent studies, we prepared an updated meta-analysis of 26 studies, stratified by broad type of chronic pancreatitis (Fig. 61.2). The pooled risk estimates are as follows: RR = 12.0 (95% CI: 7.7–18.7) for 19 studies in patients with definite chronic pancreatitis [3,5–22], RR = 69 (95% CI: 56–85) for three studies in patients with hereditary pancreatitis [23–25], RR = 109 (95% CI: 56–211) for two studies in patients with tropical pancreatitis or similar forms of idiopathic pancreatitis from India [26–27]. For two studies comparing the risk of pancreatic cancer in *SPINK1*-related pancreatitis compared to idiopathic pancreatitis, the pooled RR = 20.3 (95% CI: 9.1–45.3) [28–29].

Among recent major representative studies, a nationwide report from Denmark provides further evidence for a strong link between pancreatitis and pancreatic cancer [16]. In this follow-up study of nearly 12,000 patients with chronic pancreatitis and nearly 120,000 matched controls the authors found a 6.9-fold increased risk of death from pancreatic cancer in pancreatitis patients compared with the control population. Again, the risk of pancreatic cancer was similar in patients with either alcoholic or nonalcoholic pancreatitis. Based on an electronic medical record system, Hao and coworkers [18] examined data from 1656 patients with chronic pancreatitis from Shanghai Hospital, China and confirmed a markedly increased risk of pancreatic cancer (SIR = 20.2; 95% CI: 12.5–30.9) especially in heavy smokers. More recently, Munigala and coworkers [21] performed a retrospective study of US Veterans Administration identifying as many as 21,785 patients with chronic pancreatitis, of whom 226 developed pancreatic cancer 2 years after chronic pancreatitis (HR = 4.28; 95% CI: 3.74–4.89). The risk was consistent and sustained beyond 5 years and 10 years of follow-up. Finally, Vujasinovic and coworkers assessed the cumulative incidence of pancreatic cancer in 581 patients with definite chronic pancreatitis from Karolinska University Hospital, Stockholm, Sweden [34]. Excluding patients diagnosed with pancreatic cancer

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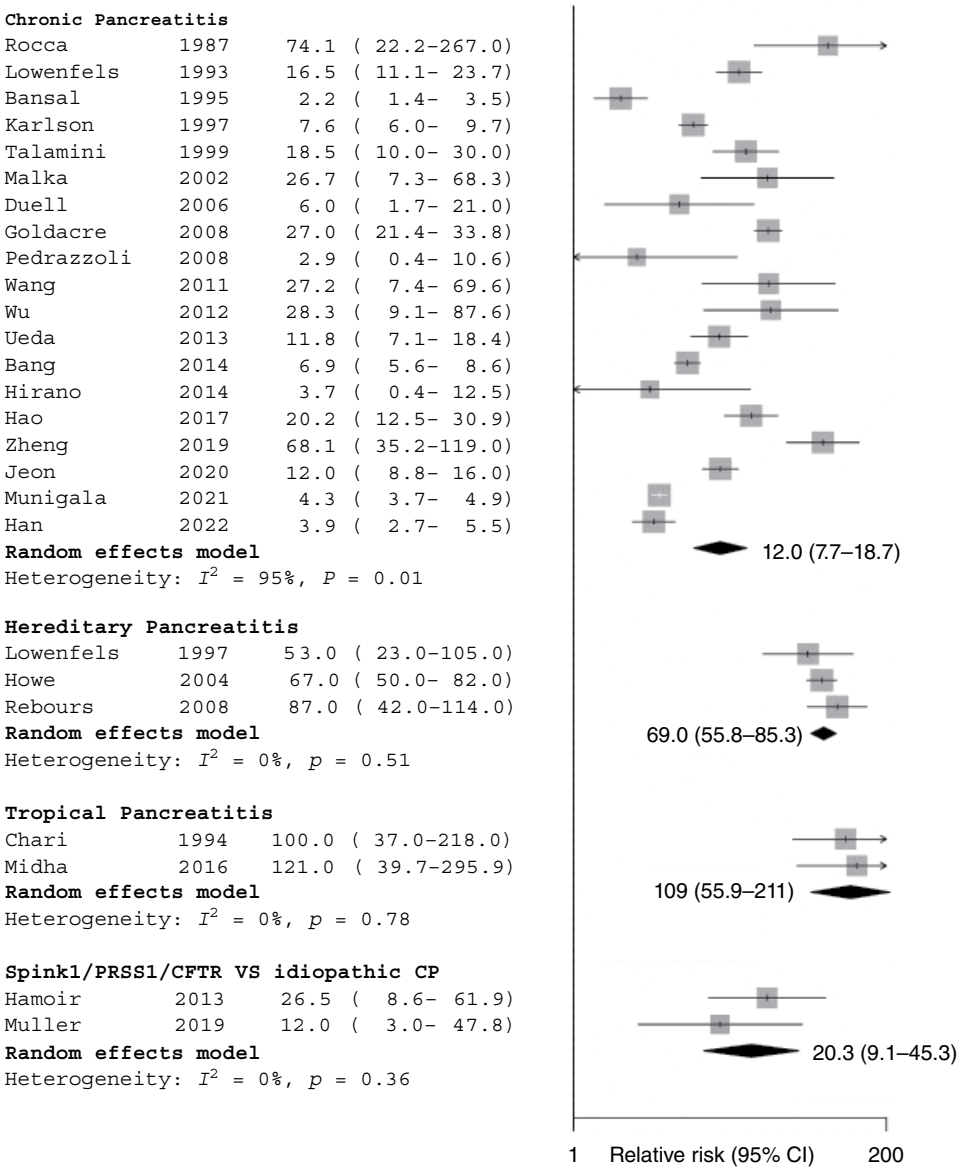


Figure 61.2 Meta-analysis showing study-specific and summary risk estimates with 95% confidence intervals for the association between different types of pancreatitis and pancreatic cancer.

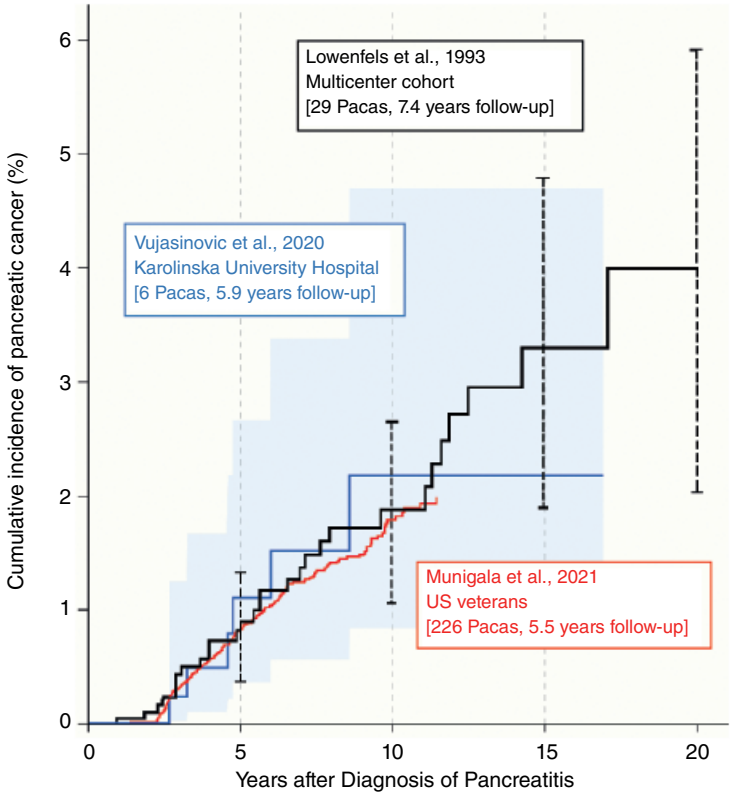
within 2 years from the diagnosis of chronic pancreatitis, the incidence rate of pancreatic cancer was 0.2% annually, a rate similar to that observed in the initial multicenter study by Lowenfels and coworkers [5] and the latest Veterans Administration study [21] (Fig. 61.3).

Discussion

Reviewing the evidence accumulated over several decades reveals a strong link between chronic pancreatitis and pancreatic cancer. Clinicians must still be aware of reverse causality because one symptom of pancreatic cancer can be sudden onset of pancreatitis in the absence of known risk factors. However, the evidence from several long-term follow-up studies with exclusion of early-onset pancreatic cancer confirms the pancreatitis–pancreatic cancer link. The findings of this relationship in the pancreas agrees with information from other organs, and confirms Virchow's nineteenth-century hypothesis. As yet we do not have a full understanding of the mechanisms underlying the transformation from a nonmalignant disease to cancer.

All the reports indicate that the cumulative risk of pancreatic cancer in patients with long-standing confirmed chronic pancreatitis is low—probably less than 5%. This implies that until we develop noninvasive screening procedures with greater sensitivity and specificity than are currently available, screening patients with chronic pancreatitis is not likely to be rewarding.

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Patients at risk

Lowenfels	1,552	1,160	599	244	64
Vujasinovic	581	303	103	18	–
Munigala	21,765	12,074	2,949	2	–

Figure 61.3 Cumulative incidence of pancreatic cancer in patients with chronic pancreatitis from three selected cohort studies [5,21,34].

Hereditary pancreatitis due to inherited *PRSS1* mutations is a rare inherited autosomal dominant genetic disorder that causes early-onset pancreatitis characterized by recurrent attacks eventually leading to chronic pancreatitis. As with other risk factors, such as smoking, long duration of exposure increases the risk of cancer. Because patients with this type of pancreatitis have about a 70% lifetime risk of developing pancreatic cancer, already in 2001, minimally invasive imaging screening with endoscopic ultrasound (EUS), multiphasic helical computed tomography (CT) or magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) have been proposed for patients with the hereditary pancreatitis phenotype, beginning at the age of 40 years [35]. Recent international consensus guidelines recommend surveillance in affected individuals with hereditary pancreatitis due to inherited *PRSS1* mutations, but estimate that the risk of pancreatic cancer in patients with chronic pancreatitis associated with *SPINK1* or other germline mutations including those of *CFTR*, *CTRC*, *CPA1*, and *CEL* is not high enough to justify surveillance [36].

What are fruitful areas for additional research that might benefit patients with underlying pancreatitis? Pancreatic cysts are now being detected with increasing frequency and we need to be able to identify or confirm subgroups of these patients who have an increased risk of pancreatic cancer [37].

Pancreatic cancer can mimic nonmalignant disease such as autoimmune pancreatitis, leading in some patients to unnecessary pancreatic surgery [38,39]. We need to develop biological tests and/or biomarkers that can reliably distinguish between chronic pancreatitis and pancreatic cancer. Finally, collecting and storing biologic samples from patients with well-documented chronic pancreatitis will help us improve our understanding of the gradual transition of pancreatitis to pancreatic cancer.

The irreversible pathologic changes characteristic of chronic pancreatitis make this disease difficult to treat and the progressive cellular disruption of glandular and ductal tissues leads eventually, in some patients, to pancreatic cancer. Efforts to reduce lifestyle factors such as smoking and alcohol drinking in patients with recurrent

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bouts of acute pancreatitis offer an opportunity to reduce the burden of this disabling disease and prevent the occurrence of pancreatic cancer [2]. Advising all patients with CP to lead a healthy lifestyle aimed at avoiding risk factors for progression of CP and pancreatic cancer was specifically emphasized in the recent international consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis [36].

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Evidence of Endoscopic and Interventional Treatment of Chronic Pancreatitis and Pseudocysts

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Indications for Interventional Endoscopic or Surgical Therapy

Belt-like upper abdominal pain is regarded as a cardinal symptom of chronic pancreatitis (CP), together with weight loss, steatorrhea, and diabetes mellitus. In the absence of causal therapeutic options, treatment is restricted to symptom control by means of enzyme replacement, pain therapy, and optimal control of endocrine insufficiency. The complexity of disease management is justified as morphology on imaging and pain level do not correlate in most patients and an impressive ductal obstruction or intraductal calcification may be associated with little pain and subtle findings on imaging may be associated with a significant loss of quality of life due to constant pain [1]. Comparative trials with sham interventions to evaluate the placebo effect or the natural course of the disease have rarely been conducted, one example being the trial by Seza et al. Between 30% and 60% of patients develop complications of their disease such as strictures of the common bile duct, inflammatory masses, pancreatic pseudocysts, or pancreatic duct strictures or ductal stones, which require interventional or surgical treatment. Chronic pancreatitis with severe pain requiring constant analgesics should be treated by interventional or surgical procedures dependent on the symptom-causing pathogenic features [2]. The presence of an inflammatory mass clearly favors a surgical resection. In the case of a dilated pancreatic duct due to strictures and/or ductal stone both endoscopic as well as surgical drainage procedures are effective. The indication of an endoscopic drainage has not been fully clarified in randomized controlled trials (RCT). Endoscopic treatment of a dominant stricture of the main pancreatic duct is often followed by pain relief in the short term [3,4]. Retrospective studies have reported long-term pain relief in 32–68% of patients [4]. Two randomized controlled studies directly compared endoscopic procedures with resection or a surgical drainage procedure [1,5,6]. Those studies proved surgery to be superior to endoscopy with respect to long-term outcome; however, due to limitations in the study design, a reliable evidence-based assessment remains difficult under the current lack of consideration of the placebo effect, the natural course, and a possible selection bias. Nevertheless, endoscopic drainage can achieve a long-lasting complete or partial pain relief in at least one-third of patients; it is associated with lower mortality and does not impede surgery as a second-line therapy [6]. In the presence of a resectable pancreatic mass suspected to be caused by pancreatic carcinoma surgical resection should be performed. Without surgery, life expectancy for patients with pancreatic carcinoma is less than 1 year; after successful resection 20–25% of patients may survive more than 5 years [7–9]. Gastric outlet obstruction secondary to CP requires surgical or endoscopic treatment for persistent clinical symptoms. A noninterventional management supplemented by endoscopic dilatation may be sufficient for an adequate quality of life in at least 30% of cases. According to the natural course of CP further intervention will be necessary in about 30–60% of patients [10]. As there are no studies directly comparing the efficacy of pancreatic head resection, bypass surgery, and endoscopic insertion of self-expanding metal stents (fcSEMS) [11], the decision may be taken in view of the patient's comorbidities. Symptomatic stenosis of the common bile duct (CBD) will develop in 10–40% of cases requiring endoscopy with dilation and stent insertion. The outcome of endoscopic therapy in patients without acute inflammation of the pancreas has improved with

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new techniques but is still not entirely satisfactory. Stent therapy rarely resolves a stricture beyond 1 year of therapy [12], in particular in the presence of calcifications within the pancreatic head [13]. Lasting patency rates have significantly improved with the use of fcSEMS. Surgical resection should be performed if symptoms or cholestasis persist after temporary endoscopic therapy not longer than a year. For obstructive chronic painful pancreatitis with ductal dilatation of more than 5 mm, a recent trial (ESCAPE) recommended earlier surgery after a maximum of 6 months of opiate pain medication without clinical improvement or preceded by 3 months of endoscopic therapy without symptom improvement [14]. Fragmentation and removal of stones within the pancreatic duct by extracorporeal shock wave lithotripsy (ESWL) have somewhat replaced surgery since its introduction in 1989. Several retrospective studies have shown ESWL as an effective and safe management option for pain relief in chronic calcifying pancreatitis with pancreatic main duct stones greater than 5 mm [15], for which ESWL followed by ERCP may be the standard of care. Intraductal lithotripsy under direct endoscopic vision is a promising technique in evolution. Interventional endoscopic options in CP will be discussed in more detail below.

Treatment of Pancreatic Cysts

According to the revised Atlanta classification a pancreatic pseudocyst is an encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrotic tissue content. This entity usually arises in connection with CP [16]. A walled-off necrosis (WON) is defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs >4 weeks after the onset of necrotizing pancreatitis [16]. The prevalence of pancreatic pseudocysts in CP ranges between 20% and 40% [17]. They occur with the highest frequency in patients with alcoholic CP (70–78%), followed by idiopathic CP patients (6–16%), and biliary pancreatitis patients (6–8%) [17,18]. Approximately 40% of the fluid collections resolve spontaneously within the first 6 weeks after an acute attack of pancreatitis. In contrast, spontaneous remission of pseudocysts after 12 weeks is a rare event. Complications are observed in up to two-thirds of cases encompassing pain, infection, hemorrhage, cystic rupture, or obstruction of adjacent organs such as cholestasis, gastric outlet obstruction, or vascular stenosis. A multivariate analysis showed a pseudocyst/WON size <4 cm as the only favorable factor for spontaneous resolution [19]. The increase in size of a pseudocyst/WON to over 5 cm in diameter is associated with an increased risk of complications [20]. Asymptomatic pseudocysts >5 cm in diameter which do not resolve within 6 weeks can be an indication for treatment. The aim of this intervention is to avoid possible complications that may occur later in the course of the disease, such as a cyst rupture, infection or hemorrhage, the likelihood of such complications being approximately 50%. However, symptomatic pseudocysts should undergo treatment regardless of their size.

Only limited information is available with regard to interventional therapy of pancreatic pseudocysts for pain management. Most of the data at hand are based on retrospective case series [21–24], but three systematic reviews are available [25–27]. Pain relief will be achieved in a large number of patients (about 80%). Although medical management of CP can result in pain relief, in a certain percentage of patients, interventional or surgical drainage is still the more effective form of pain management regardless of the drainage procedure.

A diagnostic needle aspiration of the cyst may be performed for suspected infection or for suspected cancer. If needle aspiration of the cyst confirms an infection, then drainage is indicated. Surgical treatment should be carried out if malignancy is suspected. In 28% of all MRI scans of the abdomen, a cystic lesion of the pancreas is discovered as an incidental finding [28] when population-based cohorts are investigated, albeit most of these cysts are smaller than 1 cm in diameter. More than two-thirds of these lesions are dysontogenetic cysts or pancreatic pseudocysts. Of the cystic lesions that are not pancreatic pseudocysts but genuine cystic neoplasms, 30% are benign serous cystadenomas. Forty-five percent of the resected lesions are mucinous-cystic neoplasms and 25% intraductal papillary mucinous neoplasms (IPMN). Solid pseudopapillary tumors or cystic acinar cell carcinoma are rather rare entities. For the differential diagnosis of cystic tumors in asymptomatic patients, the question of a connection to the pancreatic duct (IPMN and pancreatic pseudocysts) and of the size of the cystic lesion (indication for resection in the case of IPMN or therapeutic indication for pseudocyst) is essential. Diagnostic needle aspiration of a cyst with the aid of EUS helps in differentiating between premalignant cystic neoplasms, cystic malignancies, and pseudocysts. In case the fluid analysis reveals a CEA >400 ng/mL, a variably increased or low amylase (lipase), high viscosity, mucin or epithelial cells in the cyst content, then a mucinous neoplasm must be assumed [28–30]. In addition to CEA and amylase/lipase, low pancreatic cyst fluid glucose has been established as a marker for the differentiation of mucinous versus non-mucinous pancreatic lesions. In 609 cystic lesions examined, a systematic review showed significantly increased pooled sensitivity (91% vs. 56%; $P < 0.001$)

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and diagnostic accuracy (94 % vs. 85 %; $P < 0.001$) compared to CEA alone [31].

If a connection to the pancreatic duct is excluded the final diagnosis of a mucinous cystic neoplasm (MCN) can be made. A serous cystadenoma is diagnosed in 30% of cystic lesions and virtually never turns into a malignant lesion. In this case aspiration of the cyst is negative for mucin, CEA, and amylase. Cytology reveals a glycogen-rich epithelium. Surgical, percutaneous, or endoscopic drainage of pancreatic pseudocysts demonstrate comparable results regarding technical success, efficacy, and recurrence rates [26,32]. Percutaneous drainage is associated with the risk of external fistula and may affect the patient's quality of life. Endoscopic drainage is less prone to complications when compared to surgical procedures. A systematic review of retrospective series of endoscopic and surgical drainage showed similar morbidity (13.3% vs. 16%) and long-term pseudocyst recurrence (10.7% vs. 9.8%) but lower mortality (0.2% vs. 2.5%) achieved by an endoscopic drainage [33]. Therefore, the endoscopic approach should have first preference as it is less invasive and more convenient for the patient. In a recent RCT that compared endoscopic versus surgical cystogastrostomy for pancreatic pseudocyst drainage endoscopic treatment was associated with shorter hospital stays, improved physical and mental health status of the patients, and lower costs [32]. However, the decision between endoscopic and surgical drainage should take into account the cyst location and additional pathophysiological features. Surgical drainage may be the preferable therapy in hemorrhagic pseudocysts as endoscopic drainage is associated with a higher risk of bleeding. Approximately 10% of pseudocysts recur in the long term after endoscopic drainage (Table 62.1). Although initial therapy of nonhemorrhagic pseudocysts should be endoscopic drainage, surgery may follow in case of recurrence. Drainage of pseudocysts can be carried out by transgastric, transduodenal, or transpapillary routes. Transmural drainage should be done under endoscopic ultrasound (EUS) guidance to assess the pseudocyst location, size, wall, content, and adjacent blood vessels. Two RCT compared transmural drainage with and without EUS guidance [34,35]. No difference was observed in terms of morbidity and clinical outcome but technical success was higher with EUS. The success rate in 1018 published patients with transmural drainage of a pseudocyst was 87% (Table 62.1), with more recent studies reporting success rates of more than 90%. The mortality rate in larger case series involving more than 30 patients was 0.2%, the recurrence and complications rates are reported to be around 9% and 13%, respectively. Without antibiotic prophylaxis the procedure-related incidence of an infection of a pseudocyst and the risk of development of a pancreatic abscess increases [36,37]. Antibiotic prophylaxis for transmural or transpapillary drainage of pancreatic pseudocysts is recommended in recent guidelines based on expert opinion [4,38]. Double-pigtail stents should be used for transmural drainage of pancreatic pseudocysts because straight stents are associated with more frequent and severe complications in a retrospective study [39]. Early stent retrieval within 2 weeks after cyst resolution was associated with a higher rate of recurrence in a prospective randomized trial suggesting that long-term stent placement for more than 2 months may prevent recurrence without an increase of severe adverse events [40]. In its clinical guideline ESGE recommends transmural drainage of pancreatic pseudocysts by inserting at least two double-pigtail plastic stents, which should not be retrieved before at least 2 months of stenting [4]. Recently, short, lumen-apposing, fully covered, self-expandable metal stents (LAMS) have been developed for EUS-guided drainage of peripancreatic fluid collections.

In CP with advanced pancreatic ductal changes, especially with pancreaticolithiasis, a pseudocyst should be considered and treated as part of an overall therapeutic concept. For small pancreatic cysts, the tendency to regress due to persistent inflammatory stimuli is a maximum of 26%, so that even in the case of small symptomatic cysts, an interventional or surgical procedure may be considered in the individual patient context.

Due to its ease of use and the large diameter, the LAMS may make drainage of peripancreatic fluid collections more effective, particularly the endoscopic debridement of WON [41,42]. Despite initial reports on bleeding, recent meta-analyses demonstrated superior efficacy and safety compared to plastic stents in the management of peripancreatic fluid collections [43,44]. The basic question of an ideal timing for WON drainage in case of infected pancreatic necrosis has been studied in the POINTER trial. With regard to mortality and the comprehensive complication index (which includes all major complications), there was no significant difference between immediate catheter drainage (catheter drainage within 24 hours after randomization) and postponed catheter drainage (stage of walled-off necrosis, when necrotic collections were largely or fully encapsulated). However, the cohort of the later WON drainage installation (partly percutaneous, partly EUS-assisted) required fewer interventions overall, especially in terms of the number of necrosectomies required, and patients stayed in hospital for a correspondingly shorter time [45]. Of note, the median time to "immediate catheter drainage" was after a mean of 24 days (median, 24 days; interquartile range, 20 to 30) after onset of symptoms and postponed catheter drainage after a mean of 34 days (median, 29 days; interquartile range, 24 to 40) after onset of symptoms (mean difference, –10 days; 95% confidence interval [CI],

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Table 62.1 Summary of transmural endoscopic pseudocyst/walled-off pancreatic necrosis drainage, including studies of: traumatic pancreatic pseudocysts [74], pancreatic abscess [79,85]; acute pseudocysts [81]; infected pseudocysts [83]; symptomatic peripancreatic fluid collections [43,87]. (Two studies compared in a prospective randomized trial ultrasound-guided vs. conventional transmural drainage of pseudocysts [32,31].)

	Number of patients	Success rate	Recurrence rate	Complications
Kozarek et al., 1985 [75]	4	50%	0%	25% (1 dead)
Cremer et al., 1989 [76]	33	85%	12%	9%
Sahel et al., 1991 [77]	37	86%	5%	14%
Bejanin et al., 1993 [78]	26	73%	15%	15%
Funnell et al., 1994 [79]	5	100%	0%	0%
Binmoeller et al., 1995 [48]	20	80%	23%	30%
Smits et al., 1995 [80]	25	88%	13%	20%
Vitale et al., 1999 [81]	27	82%	18%	4%
Libera et al., 2000 [82]	17	88%	6%	24%
White et al., 2000 [83]	20	100%	0%	10%
Giovannini et al., 2001 [84]	15	100%	0%	7%
Norton et al., 2001 [85]	17	82%	7%	18%
Baron et al., 2002 [86]	64	81%	12%	17%
Sharma et al., 2002 [87]	33	97%	15%	15%
Cahen et al., 2005 [39]	64	70%	5%	39%
Antillon et al., 2006 [88]	33	94%	3%	6%
Hookey et al., 2006 [47]	101	95%	16%	11% 1% (1 dead)
Kahaleh et al., 2006 [89]	99	94%	n.a.	19%
Kruger et al., 2006 [90]	35	94%	12%	0%
Weckman et al., 2006 [91]	68	90%	5%	10%
Varadarajulu et al., 2008 [34]	29	100%	n.a.	3% 3% (1 dead)
Park et al., 2009 [35]	60	83%	15%	8%
Varadarajulu et al., 2011 [92]	154	100%	1.5%	5%
Will et al., 2012	32	97%	15%	10%
Total	**1018**	**87%**	**9%**	**13%**

–19 to –5) and thus even "the immediate drainage group" followed current guideline recommendations.

Whether an ERCP with the attempt of draining the pseudocyst via the papilla should be performed instead of a primarily transgastric or transduodenal drainage is still a matter of controversy. According to retrospective studies, transpapillary drainage seems to be associated with lower morbidity (mainly pancreatitis) and similar long-term success but was used for smaller pancreatic cysts than transmural drainage [4,46–48]. It is reported that 22–57% of pancreatic pseudocysts may have a connection with the pancreatic ductal system [49]. Thus, an ERP can precede endoscopic transmural drainage in order to detect a connection with the duct or to exclude a rupture of pancreatic ducts (8% after acute necrotizing pancreatitis). Transmural drainage in the presence of an undetected rupture of the pancreatic duct or an association of the pancreatic pseudocyst with an obstructed pancreatic duct is less promising with regard to long-term outcome of therapy [50,51]. Treatment of pancreatic duct obstruction and—if possible—bridging of a pancreatic duct rupture is recommended in these cases.

Therapy of Pancreatic Duct Stenoses and Ductal Stones

Ductal and interstitial hypertension and possible pancreatic ischemia accompanying outflow obstruction due to pancreatic duct stenoses or ductal stones may play an

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important role in the pathogenesis of pain. The aim of endoscopic and surgical decompression therapy in patients with CP and pain and/or clinical episodes of acute pancreatitis is to remove the obstruction and to allow outflow of exocrine pancreatic juices into the duodenum. Biliary techniques such as sphincterotomy, dilatation, ESWL, and stent insertion have been modified for the pancreatic duct. Endoscopic decompression represents an alternative to surgery and is associated with low morbidity and low mortality. Endoscopic interventions do not interfere with surgery that might still be necessary later in the course of the disease. Clinical success after endoscopic reduction of the intraductal pressure does provide some indication of the later result of surgical drainage or a resection procedure.

Pancreatic ductal stones are a consequence rather than the cause of CP. They can, however, lead to consecutive outflow obstruction and thus cause pseudocysts or fistulae development, recurrent exacerbations or contribution to the pathogenesis of pain. Under these conditions, treatment of pancreatic ductal stones seems appropriate. Endoscopic treatment appears particularly suitable for treating solitary stones and obstructions close to the papilla or in the body of the pancreas. After pancreatic sphincterotomy, pancreatic duct stones <5 mm may be extracted without prior fragmentation. Radiopaque obstructing stones ≥5 mm should be fragmented by ESWL followed by extraction of the fragments by ERCP [4]. There is evidence from a prospective randomized trial that the subsequent endoscopic removal of the fragments is not a prerequisite for the effectiveness of the procedure [52]. One large-scale single-center retrospective study with follow-up of 272 patients after ESWL and ERCP for >60 months reported no pain in 60% of patients, mild to moderate pain in 36%, and episodic severe pain in 4% of patients [53]. Recurrence of intraductal calculi was seen in 23% of patients. A recent meta-analysis of 27 studies (total of 3189 patients) showed that ESWL is useful for clearing pancreatic duct stones greater than 5 mm and for decreasing pain [15]. The pooled proportion of patients with absence of pain at follow-up (median 2 years) was 53% (95% CI: 50.8–54.6) and mild to moderate pain was 33% (95% CI: 31.4–35.5). Quality of life improved in 88% and complete ductal clearance was achieved in 71%. However, no studies have compared the treatment of ductal stones with the natural course or a sham intervention. In principle, individual pancreatic duct stones that cause pain due to obstruction of the outflow of pancreatic secretion are treated with ESWL, pancreaticoscopic electrohydraulic lithotripsy or laser lithotripsy. A current prospective study investigating the effectiveness of direct EHL-guided lithotripsy showed promising results regarding feasibility and safety of EHL [54].In two older studies, in which endoscopic treatment was compared with surgery, i.e., drainage operation, the results after surgery were significantly better with respect to long-term pain reduction [1,5]. Recent data from the multicenter, prospective ESCAPE trial point in the same direction. Patients with symptomatic pancreatic duct stenosis, a blockage of the pancreatic duct and a duct width of >5 mm experienced an advantage of early surgery compared to a "step-up approach" with optimized medical therapy, endoscopic intervention, and “delayed” surgery: complete or partial pain reduction at 18-months follow-up in 58% vs. 39%; $P = 0.1$) [14]. However, neither the complication rate of surgery nor surgical mortality were taken into account as endpoints, which are nevertheless of considerable importance in guiding patients. The treatment of pain in patients with diffuse calcifications by means of ESWL has not been substantiated in any studies.

Patients with dominant pancreatic duct strictures with a prestenotic dilatation ≥6 mm in diameter, which may be responsible for pain, recurrent exacerbations, maintenance of a pseudocyst, fistula, or other complications, can be treated by endoscopic dilatation and plastic stent placement [4]. Removal of the obstruction of the pancreatic duct is effective for the treatment of pain on short to intermediate terms. Success rates between 65% and 95% have been reported [4]. In the largest hitherto examined cohort of 1021 patients, a long-term reduction (mean 4.5 years) of pancreas-related pain was achieved in 85% of cases [55]. However, 24% underwent surgery during further follow-up, which—on an intention to treat basis—reduced the rate of successful treatment to 65%. In 79% of the patients stent therapy for control of pain had to be repeated within 1 year and in 97% within 2 years. The only randomized study recruited 41 consecutive patients with CP with a dominant pancreatic duct stricture to either receive pancreatic duct stenting or to serve as control. During a mean follow-up of 62.5 ± 20.9 months pain recurred in 15% of patients with pancreatic duct stenting (3/20) and in 50% of control patients (11/22) ($P < 0.05$). Progression of exocrine insufficiency in the stent group was significantly slower than in the control group ($P < 0.05$), while endocrine function showed no difference between groups [56]. Preliminary studies suggest temporary placement of fcSEMS into the pancreatic duct for pain relief may be a safe and effective short-term treatment [57–59]. Their potential advantage versus plastic stents is the longer period of stent patency. A recent meta-analysis found fcSEMS comparable to multiple plastic stents in the treatment of symptomatic refractory pancreatic duct strictures, but the risk of adverse events was increased [60]. However, long-term results are so far not available. Uncoated self-expandable metallic stents are not recommended due to the rapid proliferation of duct epithelium as a reaction to the metal

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mesh graft. Plastic stents inserted into the pancreatic duct can induce secondary changes with subsequent fibrosis and strictures [61,62]. There are currently no reliable data available regarding the necessary duration of stent therapy. Some authors recommend treatment over 1 year with an exchange of the stent at least every 3 months [4]. Other centers suggest exchanging the stent in case of reoccurring symptoms. A question which should be solved in a randomized trial. Improved pain management, however, was achieved by a pancreatojejunostomy in two RCT [1,5,6]. Endoscopic therapy led to pain reduction or complete pain relief in 32% [5] and 61% [1], respectively, whereas this was achieved in 75% [5] and 86% [1], respectively, by pancreatojejunostomy. However, endoscopic drainage can achieve a long-lasting complete or partial pain relief in a substantial proportion of patients, and does not impede surgery as a second-line therapy.

Endoscopic Treatment of Bile Duct Obstruction

Obstruction of the common bile duct (CBD) will develop in 3–46% of patients with CP [63]. Indications for endoscopic intervention include significant cholestasis, cholangitis, prevention of secondary biliary cirrhosis, and differentiation of the cause of pain (obstruction of the CBD vs. CP). Long-term success rates can be achieved in one- to two-thirds of the patients dependent on the endoscopic drainage modality [4]. Thus endoscopic therapy is indicated as an interim procedure until definitive surgery, for example as an acute intervention in septic patients, or in patients unfit for surgery, or in those unwilling to undergo surgery. Complications include stent occlusion and cholangitis. Prophylactic antibiotic therapy together with ursodeoxycholic acid has not been proven to be effective [64–66]. Endoscopic drainage should, therefore, be of limited duration.

Immediate endoscopic drainage should be performed in the case of obstructive cholangitis. Although no published studies have compared endoscopic therapy to observation without drainage as treatment of mechanical cholestasis as part of the therapy for cholangitis is important and well substantiated by clinical experience. If CP causes distal obstruction of the bile duct with cholestasis or obstructive jaundice, then either surgical treatment or endoscopic stent therapy can be performed. A retrospective analysis of all patients treated with an average observation period of 45 months demonstrated that stent therapy for the obstruction of the CBD in patients with CP has no additional effect beyond 1 year [12]. Surgical treatment should therefore be pursued for recurrence of CBD obstruction after 1 year of stent therapy. A prospective study showed an even worse long-term effect of stent management of distal bile duct obstruction in patients with calcifying pancreatitis (long-term effect 9%) [13]. In these cases surgical treatment is clearly preferred.

The placement of multiple plastic stents into the biliary stricture of patients with CP is superior to insertion of single plastic stents. In prospective, nonrandomized and retrospective studies the success rate after insertion of up to five plastic stents into the CBD was higher than after a single stent with long-term success rates of up to 92% of patients during a period of 12–48 months after stent removal [67–69]. A prospective nonrandomized study at 13 centers in 11 countries treated 187 patients with benign biliary strictures by fcSEMS [70]. Removal was scheduled at 10–12 months. On an intention-to-treat basis the stricture resolution rate was 76%, and the rate of stricture recurrence was 14.8% (95% CI: 8.2–20.9%) during follow-up of 20 months. Thus, effective long-term success was achieved in 62.7% of patients. A randomized controlled study compared insertion of multiple plastic stents with a single fcSEMS in 112 patients for treatment of benign biliary strictures during 1 year [71]. The resolution rate of biliary strictures was 85.4% with plastic stents and 92.6% with fcSEMS ($P < 0.001$). The mean number of ERCP to achieve resolution was significantly lower for fcSEMS than for plastic stents. The recurrence rate within 1 year of follow-up did not differ significantly between groups (14% with fcSEMS vs. 5% with plastic stents).

In a large meta-analysis of 1298 patients with benign biliary stenosis who were treated with fcSEMS, a lasting therapeutic success with complete regression of the biliary stenosis was achieved in 83% [72]. For the subgroup of patients with biliary stricture due to a chronic inflammatory process of the pancreas, there was a somewhat greater heterogeneity compared to postoperative benign bile duct strictures, but also comparable results. fcSEMS were as effective as multiple plastic stents but required fewer ERCPs. Thus, fcSEMS placement appears to provide an advantageous alternative to plastic stents in the management of benign biliary strictures. Exchange of single plastic stents should be undertaken at least every 3 months because otherwise occlusion of the stent may cause cholangitis. The exchange interval is less critical with the insertion of multiple stents and is much longer if fully coated metal stents are used. Those are patent for up to 9 months [73]; however, partial obstruction by sludge or stones often occurs.

The management of chronic bile duct obstruction after unsuccessful attempts of endoscopic treatment should be surgical. If there is an indication to treat cholestasis by surgery, a preoperative endoscopic insertion of a stent into the bile duct should only be undertaken if (i) surgery cannot be done promptly, or (ii) cholangitis is present.

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A multicenter prospective randomized study examined the effect of preoperative endoscopic stent insertion into the CBD for mechanical cholestasis secondary to carcinoma of the head of the pancreas before pancreas resection. Preoperative drainage significantly increased the rate of complications (39% severe complications without drainage vs. 74% with drainage). Therefore, in the absence of cholangitis, bile drainage is not indicated if surgery can be performed promptly [74]. A short individual life expectancy of a patient, a high comorbidity, and a difficult, foreseeable technical feasibility of an operation (e.g., marked collateral circulation secondary to portal hypertension), are all in favor of an endoscopic treatment of bile duct obstruction.

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Major Pancreatic Resection for Chronic Pancreatitis: Indication, Goals, and Limitations

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Definition of Chronic Pancreatitis

A multidisciplinary expert consensus proposed a new mechanistic definition of chronic pancreatitis (CP) in 2016 [1]. CP is defined as "a pathologic- fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathological responses to parenchymal injury or stress." Major international societies have adopted the mechanistic approach. It is based on a conceptual model with five stages ranging from A (at risk) to E (end-stage CP) (Fig. 63.1).

Timing and Goals of Major Pancreatic Resections

Based on the mechanistic approach, surgical therapeutic interventions need to take place in stage C (early CP) or stage D (established CP) rather than in stage E (end-stage of CP) with irreversible features and complications of CP.

Therefore, a potential surgical intervention needs to occur months after the initial acute pancreatitis event (early CP, stage C). To facilitate preventive and therapeutic interventions in time, it requires a multidisciplinary team (gastroenterologists, advanced endoscopists, radiologists, pancreatic surgeons, pain, and nutritional specialists), which initiates diagnostics and therapeutic interventions at the sentinel event, since up to 35% of patients with an initial episode of acute pancreatitis will develop CP within 3–8 years [2,3].

The basis of any intervention in time is an accurate diagnosis of early CP. The mechanistic definition includes a second part: "Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, and dysplasia." Therefore, the mechanistic definition does not require prominent imaging features to diagnose early CP. Unfortunately, a consensus for a definition of early CP or diagnostic criteria could not be established within the international working group in 2017 [4].

Until consensus is reached, potential surgical interventions remain based on imaging combined with patients' pain burden.

While computed tomography is the most appropriate baseline imaging modality for CP, it cannot exclude a CP or be used exclusively to diagnose early CP (stage C). Magnetic resonance cholangiopancreatography (MRCP) and secretin-stimulated MRCP are more accurate for detecting subtle changes in the early stages. The role of endoscopic ultrasound is limited to inconclusive MRCP results or (planned) therapeutic interventions [5]. ERCP should not be used for diagnostic purposes [6].

The conceptional model predetermines successful interventions as early as possible to prevent end-stage CP with fibrosis/sclerosis, exocrine and endocrine insufficiency, and chronic pain syndrome. The goal of surgical intervention in time can only be reached if the old paradigm "surgery is the last option" is abandoned. Surgery in an early stage of CP has the potential to achieve the main goals, namely, to mitigate disease progression, pain control without chronic opioid dependency, and restore quality of life [7,8], preserve exocrine function [9], prevent rather than manage local complications (bile duct or bowel obstruction, portal vein compression, splenic vein thrombosis, fistula, or pseudocyst and pseudoaneurysms/erosion of large vessels).

While the change of lifestyle and conservative treatment will often remain the first step, the period of medical pain management should be limited by the multidisciplinary team from the beginning due to the risk of opioid

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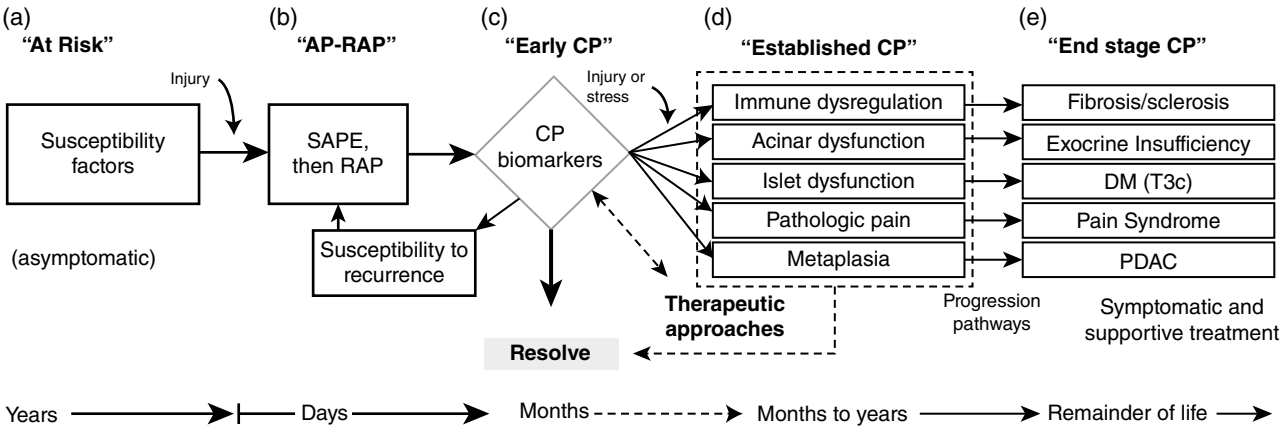


Figure 63.1 The basis of the mechanistic approach is a conceptual model of CP. AP-RAP: acute pancreatitis and recurrent acute pancreatitis; CP: chronic pancreatitis; DM (T3c): diabetes mellitus type IIIc or pancreatogenic diabetes mellitus; PDAC: pancreatic ductal adenocarcinoma; SAPE: sentinel acute pancreatitis event. *Source:* Whitcomb et al. 2016 [1]. With permission of Elsevier.

dependency and the development of neuropathic pain [10]. Failure of conservative pain management should lead to discussing endoscopic and surgical options as equivalent options for first-line interventional treatment within the multidisciplinary team and the patient. The treatment advice should consider the following data: early surgery leads to more pain relief and less postoperative opioid use [9,11–14], multiple endoscopic interventions are associated with reduced success in terms of long-term pain relief after surgery [8], and 40–75% of CP patients will require surgery in the course of the disease [15]. Most recently, the randomized ESCAPE trial results support these findings [16]. The early surgery approach was superior, with lower pain scores over 18 months than the endoscopy first approach. Complete pain relief was achieved in almost 60% of the early surgery group vs. 40% in the endoscopy first group. One-third of patients in the endoscopy group were referred to undergo surgery because of failed endoscopic treatment.

Limitations of Major Pancreatic Resections

Although surgical intervention is a significant key to success in patients suffering from CP, some circumstances limit surgical options. In advanced stages of CP cachexia, severe malnutrition, and sarcopenia are often evident and associated with higher perioperative morbidity and mortality [17]. Accordant nutritional therapeutic options must be considered before surgery to obtain optimal surgical results. A complete portal thrombosis with portal hypertension is a relative contraindication for surgery. The risk of bleeding and perioperative complications is significantly increased in this subgroup of patients. Preoperative recanalization of the mesentericoportal axis with subsequent surgery should be limited to high-volume centers with accordant expertise [18–20].

Surgical Strategies Based on Morphological Characteristics

Surgical interventions need to be based on the following goals:

- Effective in terms of long-term pain management and local complications (restore quality of life);
- Preservation of maximum endocrine and exocrine function;
- Safety (low morbidity and mortality;
- Long-term sufficient drainage of the pancreatic duct.

Based on these goals, the primary surgical strategies and indications will be summarized and expanded upon in subsequent chapters. The recommendations are based on the international consensus guidelines published in 2019 [21]. Differing treatment strategies at the authors' institution are emphasized if indicated.

Chronic Pancreatitis with Enlarged Pancreatic Head without Strictures or Stones in Pancreatic Corpus and Tail

In patients with a morphology characterized by a solely enlarged pancreatic head (inflammatory mass) without pathologies in the pancreatic corpus or tail, a duodenum-preserving pancreatic head resection (DPPHR) may be the treatment of choice. All DPPHR procedures have the advantage of maintaining the physiological gastroduodenal passage and common bile duct continuity.

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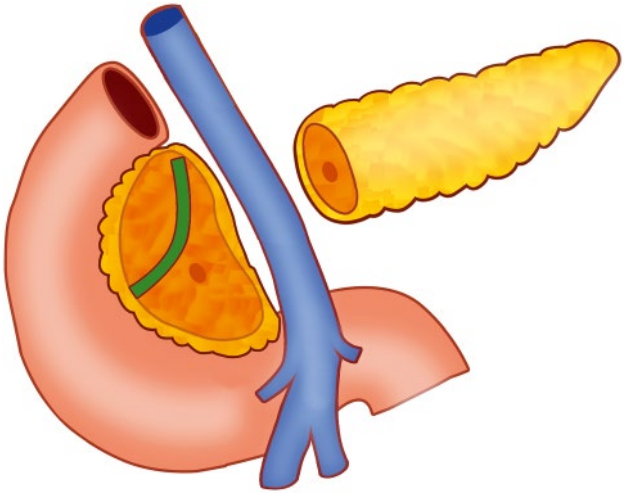


Figure 63.2 Beger procedure: subtotal resection of the pancreatic head with transection of the pancreas above the portal vein. *Source:* Faik G. Uzunoglu.

DPPHR variations in these patients consist of the Beger- or Berne procedure. The Beger procedure is characterized by a subtotal resection of the pancreatic head with transection of the pancreas above the portal vein (Fig. 63.2). The Berne procedure avoids a complete transection of the pancreas above the portal vein (Fig. 63.3). The inflammatory periportal fibrosis with or without portal vein thrombosis carries a high risk of bleeding complications that might be difficult to control.

An alternative to DPPHR variations is the (pylorus-preserving) pancreaticoduodenectomy. This procedure is often not the treatment of choice because of surrounding vessels' involvement by the pancreatic head's inflammatory mass. In terms of long-term pain relief, no differences are evident, as well as regarding morbidity, pancreatic fistula rate, or operative time. The DPPHR group was superior in quality of life, postoperative weight gain, and more exocrine function impairment within a systematic review and meta-analysis [22].

At the authors' institution, the (pylorus-preserving) pancreaticoduodenectomy is only the treatment of choice in uncertain cases with high suspicion of malignancy and if malignancy cannot be ruled out securely by frozen section analysis or in case of bowel obstructions that cannot be resolved sufficiently by DPPHR.

Chronic Pancreatitis with Dilated Main Duct with or without Enlarged Pancreatic Head

In patients with a morphology characterized by duct dilatation ≥5 mm with or without an enlarged pancreatic head, a modified DPPHR such as the Frey or Hamburg procedure may be the treatment of choice.

Like the Berne procedure, the Frey procedure does not include the division over the superior mesenteric portal vein. Still, it combines the DPPHR with a longitudinal opening of the pancreatic duct up to 1–2 cm from the splenic hilum (Fig. 63.4). While the Frey procedure is the treatment of choice for patients with main duct dilatation with an enlarged pancreatic head, sufficient data is lacking on whether the Frey procedure or solely the longitudinal opening of the pancreatic duct should be preferred in patients with standard size pancreatic head. If the surgeon's choice of treatment favors the longitudinal opening solely, it should be done in an extended manner within 1 cm of the duodenum to decompress the

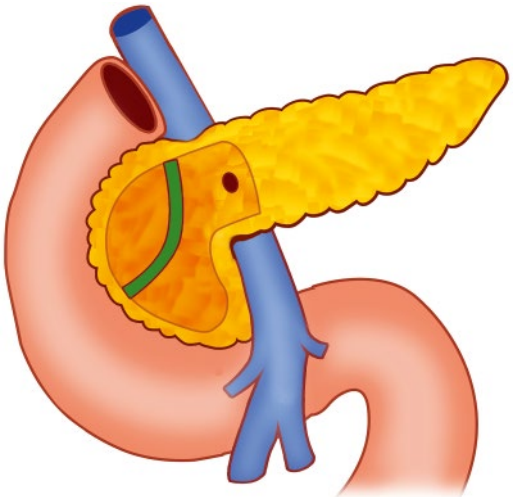


Figure 63.3 Berne procedure: avoidance of complete transection of the pancreas above the portal vein. *Source:* Faik G. Uzunoglu.

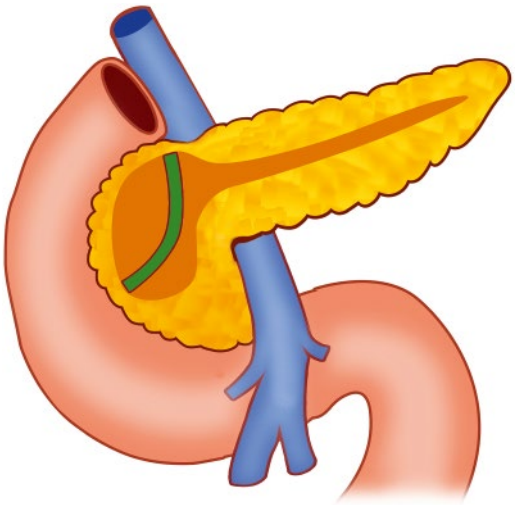


Figure 63.4 Frey procedure: limited pancreatic head resection, avoidance of complete transection of the pancreas above the portal vein, longitudinal opening of the pancreatic duct. *Source:* Faik G. Uzunoglu.

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complete pancreatic duct, including Wirsung and Santorini's ducts [23,24].

At the authors' institution the standard of care in patients with or without enlargement of the pancreatic head is the "Hamburg procedure" (Fig. 63.5). Like the Frey and Berne procedures, the division of the pancreas above the mesentericoportal axis is avoided. Still, comparable to the Berne procedure, the extent of the coring of the pancreatic head is customized to the individual morphology of the pancreas and extended, including the uncinate process if necessary. The extended coring of the pancreatic head, including the uncinate process compared to Frey, secures the bile duct decompression to the full extent and prevents a potential recurrence of common bile duct compressions. At the same time, decompression of the complete pancreatic duct system, including Wirsung and Santorini's ducts, is assured.

If, during the decompression of the intrapancreatic common bile duct, an injury to the intrapancreatic bile duct occurs, reinsertion of the distal common bile duct into the pancreatic resection cavity is frequently performed. Considering the high incidence of anastomotic strictures after reinsertion [25], this procedure has been abandoned at the authors' institution, and the DPPHR procedure is combined with a bilioenteric anastomosis.

Regarding the longitudinal opening of the pancreatic duct in the body and tail of the pancreas, the Hamburg procedure is characterized by a V-shaped opening of the main pancreatic duct instead of the solely longitudinal opening during the Frey procedure. The rationale here is the drainage of pancreatic duct side branches of second- and third order for securing long-term drainage of the pancreatic body and tail, especially in sclerosing (small duct) CP or extended calcifications of the pancreatic parenchyma in the pancreatic body and tail [26].

Chronic Pancreatitis with Isolated Left-Sided Strictures or Stones without Enlarged Pancreatic Head

In patients with left-sided symptomatic stones that are not reachable for endoscopic interventions, including extracorporeal lithotripsy, as well as in patients with left-sided strictures or complete duct disruption (e.g., after acute necrotizing pancreatitis) with patent pancreatic head and body, the longitudinal opening of the left-sided pancreatic duct (Partington and Rochelle) may be the treatment of choice (Fig. 63.6). Distal pancreatectomies should be avoided to prevent impaired exocrine function whenever possible.

At the authors' institution, the longitudinal opening is performed V-shaped. In selected cases and depending on the morphology of the pancreas, the senior author performs a stapled complete transection of the pancreas (if necessary, including a segmental resection) before the dilatated duct area followed by a V-shaped resection of the remnant left-sided pancreas with accordant drainage by a Roux limb. From the authors' point of view, the complete transection often allows a safer anastomosis to the left-sided pancreatic remnant. Indications for concurrent splenectomy in this setting include a perisplenic pseudocyst, splenic vein thrombosis, or fibrotic encasement of the splenic vessels.

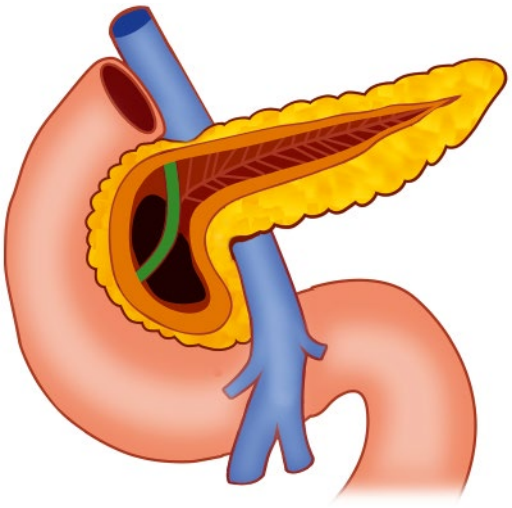


Figure 63.5 Hamburg procedure: avoidance of complete transection of the pancreas above the portal vein, extended coring of the pancreatic head, including the uncinate process. V-shaped opening of the main pancreatic duct for drainage of side branches of second- and third order for securing long-term drainage of the pancreatic body and tail. *Source:* Faik G. Uzunoglu.

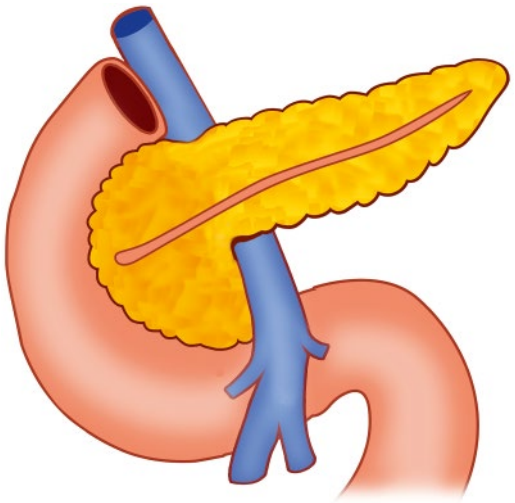


Figure 63.6 Extended Partington and Rochelle: longitudinal opening of the left-sided pancreatic duct within 1 cm of the duodenum to decompress the complete pancreatic duct, including Wirsung and Santorini's duct. *Source:* Faik G. Uzunoglu.

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Pancreatic Drainage Procedures: Techniques and Results

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Introduction

Compared to the general population, chronic pancreatitis (CP) is associated with a fourfold increase in mortality [1] and an increased risk for pancreatic malignancy. About 5% of patients with CP will develop pancreatic cancer over 20 years [2]. Its progressive inflammatory destruction of the pancreatic parenchyma is usually accompanied by intractable pain, a loss of exocrine and endocrine pancreatic function, clinically evident as malabsorption and pancreatogenic diabetes.

The pathogenesis of pain in CP is likely multifactorial. One potential mechanism may be increased intraductal pressure and obstruction of the pancreatic ductal system. Inflammation itself together with alterations in pancreatic nerve fibers, including an increase in nerve fibers and neurogenic inflammation may also contribute to the typical pain commonly associated with CP. Changes in the central nervous system and alterations in central pain processing may also contribute to pain associated with CP. The characteristic abdominal pain often leads to impaired social and work life due to recurrent hospitalizations [3].

Currently, endoscopic or interventional treatment is considered the first step in the treatment of patients with CP. Endoscopic treatment that relieves the pancreatic ductal system (endoprothesis, stone extraction, extracorporeal shock wave lithotripsy, or ductal dilatation) improves pain for up to 1 year [4]. Multiple interventions improve pain in about 65% of the cases and reduce the rate of patients requiring surgical intervention [5].

However, stent replacement often has to be performed 3-monthly and may require multiple hospital admissions [6,7]. After unsuccessful endoscopic treatment, about 49% of the patients still require surgery within 1 year [8]. While endoscopic duct drainage may provide long-term success in the presence of isolated proximal duct stenosis and in the absence of an inflammatory mass of the pancreatic head and calcifications, surgery is superior to endoscopic therapy in the latter case [9] and may also be more cost-effective [10].

Moreover, early surgical intervention may also prevent disease progression, preserve pancreatic function, and improve long-term pain control [9,11–13]. The initial findings of the Cahen study have recently been validated in another randomized trial conducted in the Netherlands (ESCAPE trial): patients with large duct disease and opioid-dependent pain of less than 6 months' duration were randomized to receive upfront surgery versus endoscopic treatment. At 18 months follow-up, there was significantly better pain control in the upfront surgery group (58% vs. 39% pain relief), with lower number of interventions, comparable pancreatic function as well as 0% mortality [14].

Indication for Surgery

The most common indication for surgery for CP is intractable pain despite pharmacological and/or endoscopic intervention. Other indications for surgery are local complications, such as duodenal or biliary stenosis, symptomatic pseudocysts, pancreaticopleural fistula, a disconnected pancreatic duct, pancreatogenic ascites, or suspicion of neoplasm. All procedures attempt to reduce pain and resolve organ complications while preserving exocrine and endocrine function. Their long-term efficacy is commonly evaluated by the restoration of quality of life and successful rehabilitation. Three distinct groups of procedures can be employed to treat CP: drainage procedures, procedures combining drainage and resection, and resecting proce-

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dures. The choice of procedure depends on the morphologic features of the pancreatitis. Drainage combined with resection of the pancreatic head (Beger procedure [15]), Frey procedure [16]) is commonly chosen if an inflammatory mass of the pancreatic head is present, resecting procedures (pylorus-preserving pancreaticoduodenectomy, Whipple procedure) are used if malignancy is suspected. The majority of patients with CP (85%) have an inflammatory mass of the pancreatic head and thus require drainage combined with resection or resection of the pancreatic head [17] (Fig. 64.1). However, drainage procedures are the procedure of choice in patients with a dilated pancreatic duct (≥5 mm) without an inflammatory mass [18]. Another indication for surgical drainage may be cavernous transformation of the portal vein with collaterals in the case of long segment portal vein stenosis. However, short segmental portal vein or mesenterico-portal vein stenosis with portal hypertension may also be alleviated during pancreatic head resection by decompressing the stenosis [19]. Resection of the pancreatic head is even possible after interventional recanalization of the portal vein for nonfixated portal vein thrombosis. Drainage procedures are thus not mandatory in this situation [20].

Drainage Procedures

The first drainage procedure of the pancreas in humans was performed in 1911 through transcutaneous catheter placed in the pancreatic duct [21]. The procedure provided pain relief and the patient survived for 30 years. More than 50 years later, the procedure was modified and a distal pancreatectomy, splenectomy, and pancreaticojejunostomy were performed [22]. The procedure was further refined as a distal pancreatectomy and side-to-side pancreaticojejunostomy[23]. The latero-lateral panceaticojejunostomy still in use today was first described in 1960 [24].

A Partington–Rochelle procedure (Fig. 64.2) is comprised of an incision of the pancreatic duct at the anterior surface of the pancreas from the tail to the head of the pancreas. Calculi in the pancreatic ducts can then be removed and segmental stenosis can be relieved. The procedure is completed by a Roux-en-Y jejunal limb sutured side-to-side to the pancreatic duct [24].

Drainage procedures are associated with low morbidity and mortality rates (about 1%). However, drainage is inferior to resection regarding pain management and complication management [18,25–36] (Fig. 64.3).

As a hybrid procedure with partial resection of the pancreatic head, the Frey procedure is often also considered a drainage procedure. It is comprised of an excoriation of the pancreatic head combined with an incision of the pancreatic duct at the anterior surface of the pancreas to the tail of the pancreas (Fig. 64.4). The procedure is completed by a Roux-en-Y jejunal limb sutured side-to-side to the excoriated pancreatic head and pancreatic duct [16]. Compared to the Partington–Rochelle procedure, the Frey procedure improves the long-term outcome. Compared to other resection procedures, the outcome achieved by the Frey procedure is equivalent regarding pain control, quality of life, and exocrine and endocrine organ function [34,37–40].

A rare form of CP, termed "small duct disease" affects the whole organ. It is not associated with a dilated

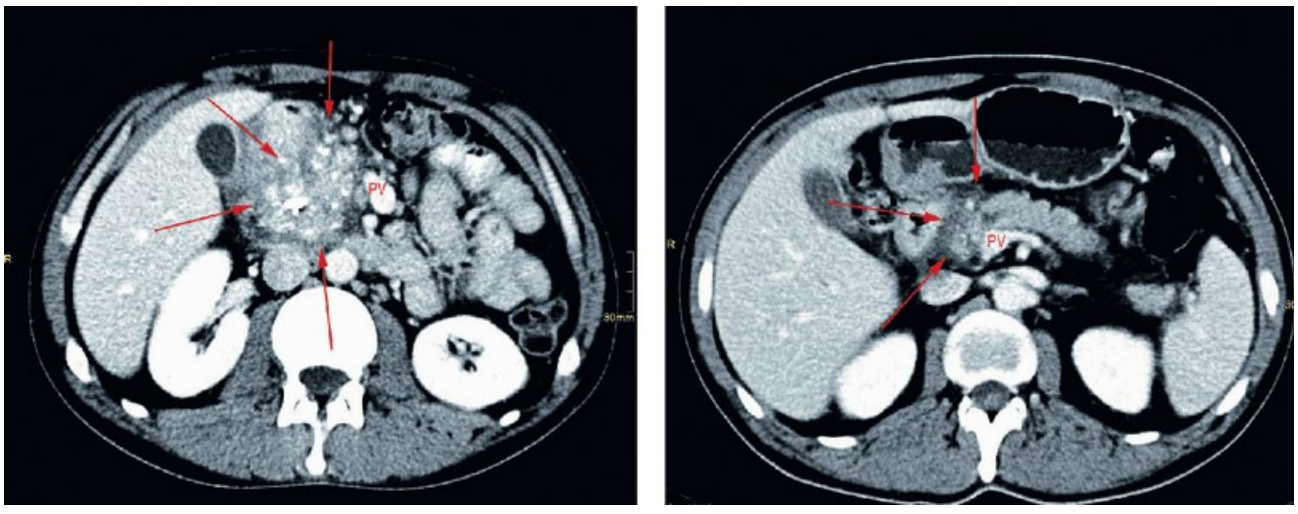


Figure 64.1 CT scan of chronic pancreatitis. (a) The majority of patients with chronic pancreatitis have an inflammatory mass of the pancreatic head and thus require drainage combined with resection or resection of the pancreatic head. (b) Drainage procedures are the procedure of choice in patients with a dilated pancreatic duct (≥5 mm) without an inflammatory mass. PV: portal vein.

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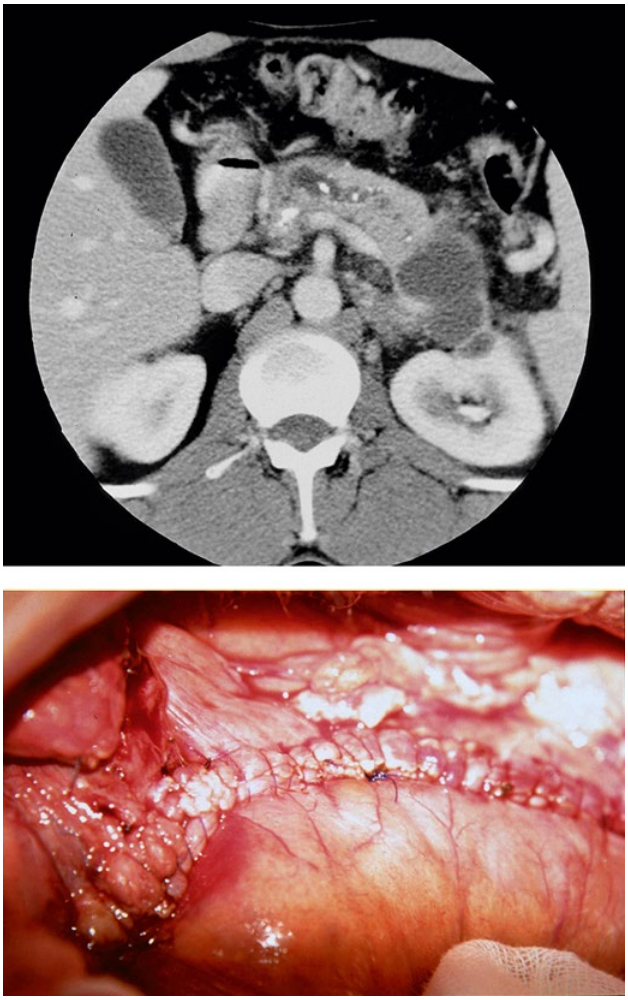


Figure 64.2 Partington–Rochelle procedure. Upper panel: CT scan showing a dilated main pancreatic duct and pancreatolithiasis in chronic pancreatitis. Note the retention cyst in the pancreatic tail caused by chronic ductal hypertension. Lower panel: situs after completion of latero-lateral pancreatojejunostomy.

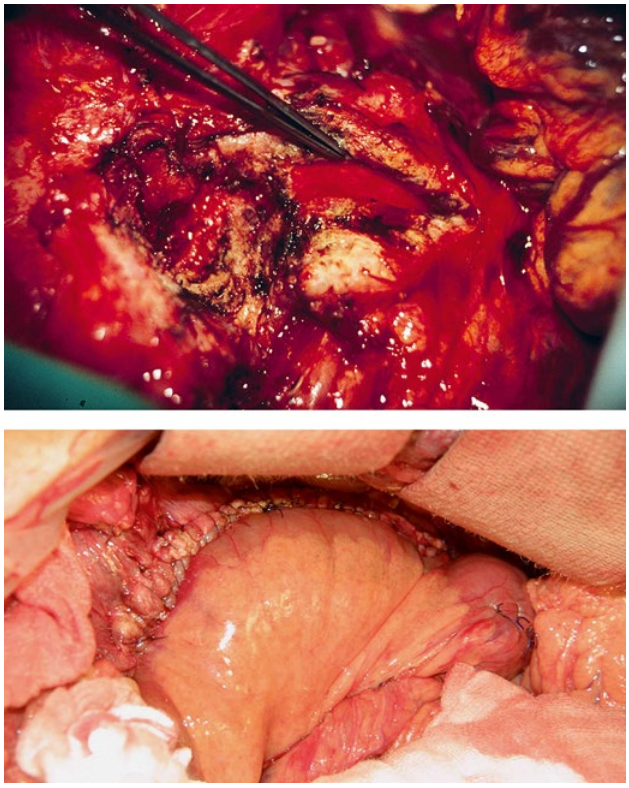


Figure 64.4 Frey procedure. Upper panel: situs after excoration of the pancreatic head and longitudinal excision of the anterior wall of the main pancreatic duct. Lower panel: situs after completion of latero-lateral pancreatojejunostomy.

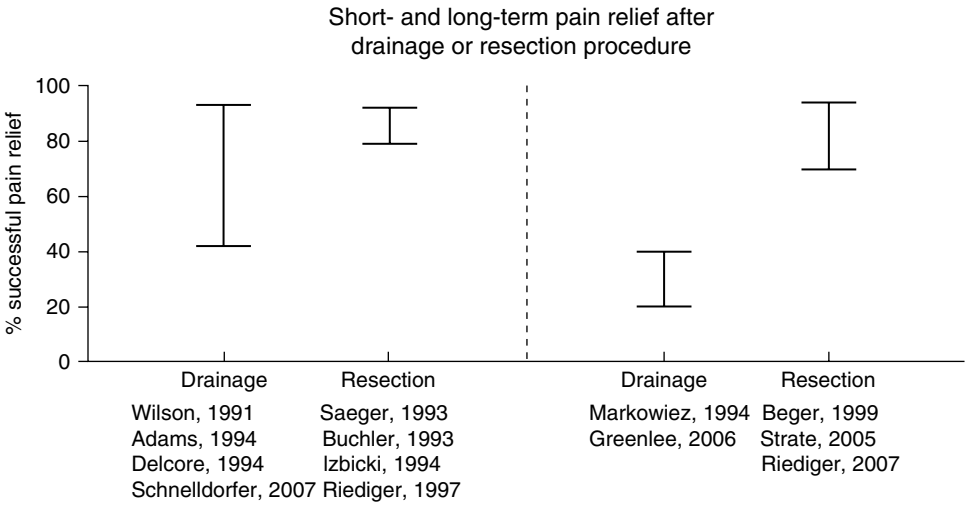


Figure 64.3 Drainage procedures are inferior to resection regarding pain management.

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pancreatic ductal system and may easily be misdiagnosed as autoimmune pancreatitis. Treatment of choice for this small duct disease is the longitudinal V-shaped excision of the ventral pancreas. The procedure combines extensive drainage with a limited resection [41]. This drainage procedure may provide long-term pain relief and an improved quality of life in the majority of patients. Compared to V-shaped excision, resection may not be as effective in the treatment of small duct disease [42].

Conclusion

Taken together, pure drainage procedures such as the Partington–Rochelle procedure are often not sufficient to provide acceptable pain and complication control due to a frequently observed inflammatory mass of the pancreatic head. In the absence of an inflammatory mass, they provide good results with low morbidity and mortality. In the presence of an inflammatory mass, hybrid procedures such as the Frey procedure or V-shaped excision are as effective as resection.

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65

Duodenum-Preserving Pancreatic Head Resections for Chronic Pancreatitis: Techniques and Results

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Introduction

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors, who develop persistent pathologic responses to parenchymal injury and stress [1]. Common features of CP include pancreatic atrophy, tissue fibrosis, upper abdominal pain, duct distortion and strictures, and in the late course of the disease, inflammatory head mass, calcifications and pancreatic duct stones, duodenal dystrophy, functional exocrine insufficiency, diabetes mellitus, and cellular dysplasia.

The mechanistic definition of CP, recently published as the result of an international proposal, reflects the complex nature of CP. Alcohol abuse and cigarette smoking are the most frequent causes of CP. After a preclinical period of up to 12 years, the majority of patients develop abdominal complaints and upper abdominal pain as first signs of the disease. In the late stage, local complications are caused by the progressive inflammatory process, enhanced by alcohol consumption and cigarette smoking. Patients referred for surgical treatment suffer severe abdominal pain; 30–50% show alcoholic CP exhibiting an inflammatory mass in the head of the pancreas, frequently causing common bile duct (CBD) obstruction [2,3]. Infrequently, severe obstruction of the duodenum, portal vein compression or thrombosis and splenic vein occlusion are clinically relevant. Pathomorphologically, main duct stenosis with prestenotic duct dilation and side branch duct stenoses are observed (Table 65.1). In terms of the natural history of CP, see Chapter 40; for early stage CP, see Chapter 50; for the epidemiology and pathophysiology of alcoholic CP, see Chapter 48; and for strategies for surgical treatment, see Chapter 63.

Are Duct Stenting and Endoscopic Interventions an Alternative to Surgery?

Duct stenting, endoscopic dilatation of pancreatic main duct stenosis and endoscopic stone extraction for obstructive CP, have been reported by a number of recent studies with good results. However, sphincterotomy and stenting of the pancreatic main duct is considered a temporary treatment. The risk of stent occlusion and migration and the need for long-term control of upper abdominal pain are the limitations of the interventional endoscopic treatment modalities. Data from prospective, randomized mono-institutional trials comparing endoscopic therapy with surgical treatment have been published [9,10]. Short-term pain relief was similar in both groups. The long-term outcome after a 1- to 3-year follow-up revealed major advantages for the surgical treatment in regard to pain control and frequency of rehospitalization compared to interventional stenting.

Who Benefits from Surgical Treatment?

Surgery for CP is essentially a palliative treatment. The primary goals of surgical treatment for CP are [1] long-term pain control, and [2] control of CP-associated complications of adherent tissues. Upper abdominal pain refractory to medical treatment in combination with local complications is the most frequent setting for surgical treatment (Table 65.2) [3]. Preservation of exocrine and endocrine pancreatic functions are secondary but equally important goals of surgical treatment. Most patients with CP are under

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Table 65.1 Frequency of local complications of chronic pancreatitis.

	Literature		Ulm*
CBD stenosis	23%	Gregg 1982 [4]	43%
Inflammatory head tumor		Beger 1980 [2,49]	74%
Pseudocysts	30%	Ahmad 2006 [5]	32%
Necroses	49%	Amman 1996 [6]	9%
Obstruction of duodenum	0.8%	Aranha 1984 [7]	23%
PV + SMV, SV obstruction thrombosis	10–20%	Warshaw 1997 [8]	16%

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PV: portal vein; SMV: superior mesenteric vein; SV: splenic vein.

Table 65.2 Indication to apply duodenum-preserving pancreatic head resection for chronic pancreatitis.

- Upper abdominal pain refractory to medication
- Inflammatory mass of pancreatic head
- Biliary stenosis
- Single/multiple narrowing of pancreatic main duct
- Compression of portal vein/SMV
- Severe stenosis of peripapillary duodenum
- Clinical symptomatic pseudocyst/persisting
- Pseudocyst after failure of endoscopic treatment
- Pancreas divisum after failure of endoscopic treatment

55 years and professionally active [4]. Social and occupational rehabilitation and improvement of the quality of life are additional primary goals for the long-term outcome.

Kausch-Whipple Resection or Hemipancreatectomy Still Standard Treatment for Chronic Pancreatitis?

Currently, pancreaticoduodenectomy (PD), left or distal hemipancreatectomy and total pancreatectomy are still applied for CP. The disadvantages of these major pancreatic resections are (i) unnecessary sacrifice of pancreatic and peripancreatic biliary and gastroduodenal tissues, and (ii) the surgery-inherent loss of duodenal and pancreatic tissue is associated with increased impairments of the endocrine and exocrine pancreatic functions in the long-term outcome. New onset of diabetes mellitus and exocrine insufficiency have been overwhelmingly documented after PD and hemipancreatectomy [11–23]. Long-term observation showed that patient survival was shorter after duodenopancreatectomy for CP compared to an organ-preserving surgical procedure [24].

Indication and Rationale for Duodenum-Preserving Pancreatic Head Resection

Surgical treatment of CP is presently dominated by organ-preserving surgical procedures. Introduced by Partington–Rochelle [25], the intestinal drainage procedure of the pancreatic main duct and the duodenum-preserving subtotal pancreatic head resection and their modifications have the advantages of tissue sparing and maintenance of pancreatic functions [26]. Based on contrast-enhanced CT, MRI and MRCP, the majority of pathomorphologic changes of CP are observed predominantly in the pancreatic head, frequently associated with an inflammatory mass and obstruction of the CBD. Infrequently, the inflammatory tumor in the pancreatic head causes portal vein and superior mesenteric vein compression and obstruction of the duodenum. To resolve these complications, resection of the pancreatic head is recommended. Duct drainage procedures in CP are only indicated in the subgroup of patients with pancreatic main duct stenosis and dilatation extended into the duct of the body and tail. With regard to long-term pain control, duct drainage procedures without resection of the pancreatic head are associated with a reappearance of an abdominal pain syndrome in about one-third of patients observed after a >5-year follow-up [27]. A duct drainage procedure in CP is considered unnecessary in patients with a dilated body-tail duct without duct obstructions when the pancreatic head is resected. Long-term follow-up observations after PD and DPPHR have shown a long-lasting pain control after head resection without an additional duct drainage procedure [28,29]. The effectiveness of duodenum-preserving pancreatic head resection has been proved, whereby randomized controlled trials (RCT) and long-term observations of 5–10 years showed completely pain-free patients in 80–90% of cases. For patients with an inflammatory head mass who were treated with a duct drainage procedure without subtotal pancreatic head resection, a risk persists for the development of a biliary stenosis in the long-term follow-up with the need for biliary stenting, respectively re-surgery.

Surgical Technique of Duodenum-Preserving Total Pancreatic Head Resection for Chronic Pancreatitis

DPPHR comprises three different surgical steps:

1) Exposition of the pancreatic head with identification of the portal vein, respective inferior mesenteric vein, and the supraduodenal CBD; tunneling of the pancreatic neck in front of the portal vein.

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2) Subtotal resection of the pancreatic head to conserve the intrapancreatic CBD.
3) Reconstruction with an excluded jejunal loop, executing two pancreatic anastomoses.

Steps (1) and (3) are almost identical to the surgical steps performed in the Kausch-Whipple procedure.

An extensive Kocher maneuver should be avoided to preserve the vessels on the dorsal side of the pancreatic head. The anterior gastro-duodenal artery is identified and ligated near the common hepatic arteries. The posterior-superior branch of the pancreaticoduodenal artery and the inferior-anterior pancreaticoduodenal artery should be carefully preserved. Subtotal resection of the pancreatic head is performed from the ligamentum hepatoduodenale along the intrapancreatic segment of the CBD, including the uncinate process (Figs. 65.1 to 65.3). Bleeding vessels arising in the transected tissue are immediately sutured (Fig. 65.4). Preservation of the dorsal capsule of the pancreatic head and the dorsal branch of the gastroduodenal and pancreaticoduodenal vessels are recommended to maintain sufficient perfusion of the wall of the duodenum and papilla. Reconstruction of the gastrointestinal tract is performed with an excluded jejunal loop (Fig. 65.5). Two modifications of the duodenum-preserving pancreatic head resection are presently in use. In patients displaying a prepapillary CBD stenosis, which persists due to an inflammatory process in the wall of the CBD, after subtotal head resection, an additional biliary anastomosis by an incision of the CBD is executed [30] (Fig. 65.5).In patients who show multiple stenosis and dilations of the main duct in the body and tail, the pancreatic main duct is opened longitudinally on its ventral surface extending toward the tail of the pancreas. A side-to-side anastomosis is executed in addition to the head resection [31].

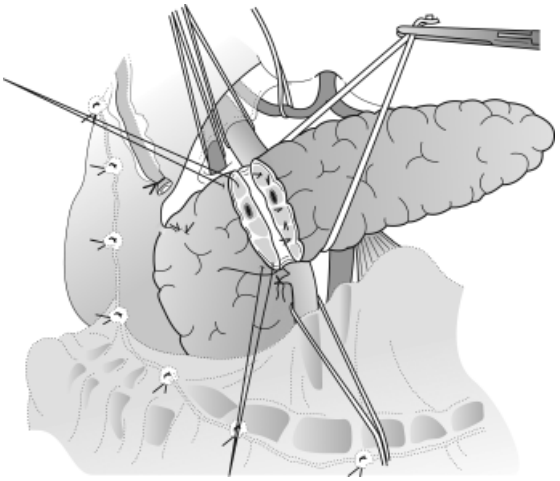


Figure 65.1 Duodenum-preserving pancreatic head resection after tunneling of the portal vein behind the pancreas. Resection line is the duodenal side of the portal vein.

Berne Modification of the Beger Procedure

In 2001, Gloor et al. published results of a small institutional series of subtotal pancreatic head resections renouncing tunneling of the portal vein and sparing transection of the pancreatic neck [32]. Using pancreatic

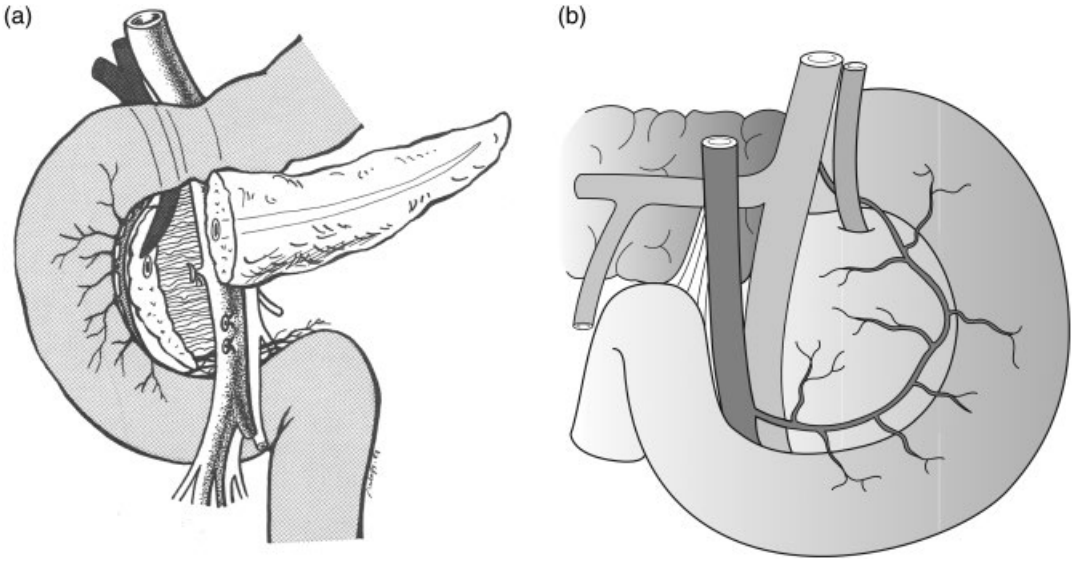


Figure 65.2 (a) After finishing the subtotal pancreatic head resection, a shell-like rest of the pancreatic head along the duodenal wall. Bleeding vessels, which are frequently closed by single suturing using five O-sutures. (b) The dorsal capsule of the pancreatic head is preserved to maintain blood flow to and from the duodenal wall. The dorsal pancreaticoduodenal arcades and inferior pancreaticoduodenal artery are preserved.

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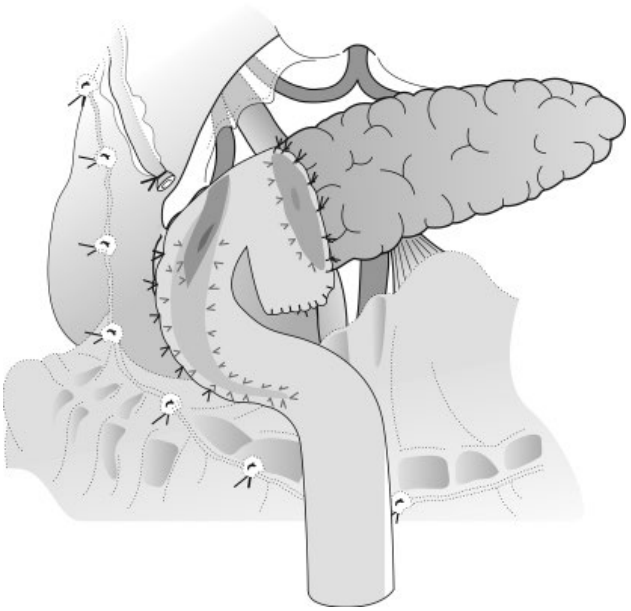


Figure 65.3 Reconstruction of the upper jejunal loop after subtotal resection of the pancreatic head requires exclusion of the first jejunal loop and creation of an end-to-side duct-to-mucosa anastomosis between the pancreatic neck and the jejunum (two-layer anastomosis). Anastomosis between the shell-like remnant of the pancreatic head and the excluded jejunal loop (end-to-side anastomosis) is also performed. A Roux-en-Y anastomosis between the excluded jejunal loop and the first jejunal as side-to-end anastomosis is included.

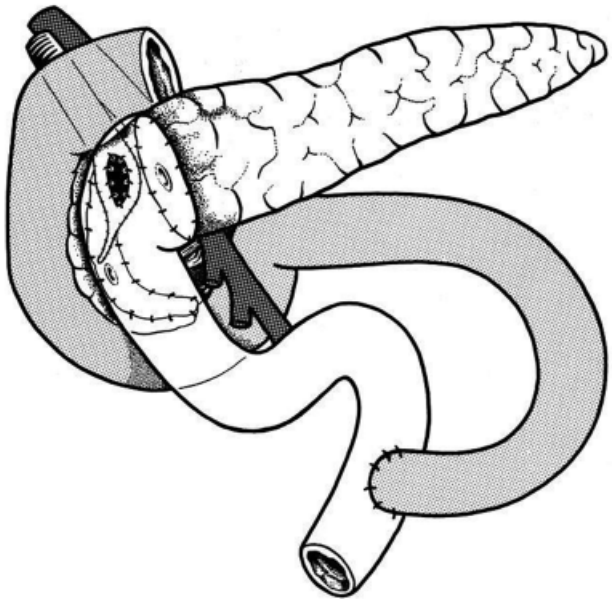


Figure 65.4 In case of extended narrowing of the intrapancreatic segment of the common bile duct caused by an inflammatory process in the wall of the common bile duct, an internal biliary anastomosis is additionally executed by incision of the prepapillary common bile duct of 10–12 mm.

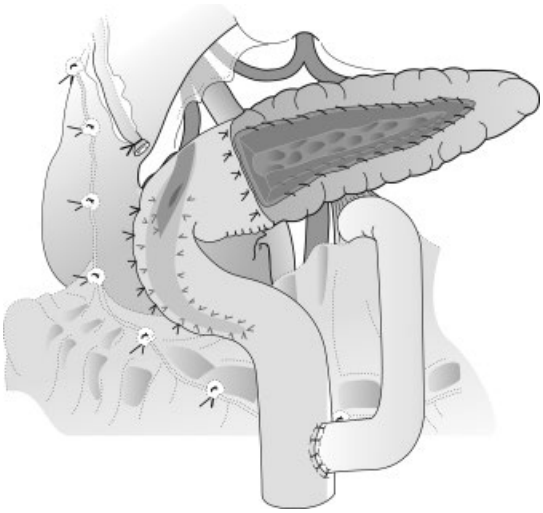


Figure 65.5 Where the pancreatic main duct shows multiple duct stenoses and dilatations, duct drainage of the pancreatic main duct from the head to the tail is additionally applied by a side-to-side anastomosis with the excluded jejunal loop.

tissue dissection devices, a subtotal resection of the pancreatic head between the pancreatic neck at the level of the intrapancreatic course of the CBD is achieved. The subtotal coring-out resection of the pancreatic head and decompression of the intrapancreatic CBD are the main surgical goals of the DPPHR Berne modification. The restoration of the pancreatic secretion flow into the upper GI tract is achieved by an anastomosis with an excluded jejunal loop and the pancreatic tissue along the tissue resection line. This technique avoids a second anastomosis between jejunal loop and the shell-like pancreatic head remnant as is recommended for the subtotal DPPHR. The Berne modification is associated with the risk of postpancreatectomy bleeding due to the extended pancreatic resection surface. Additionally, the incomplete, partial pancreatic head resection does not effect a decompression of the intrapancreatic CBD, leading to biliary bile flow obstruction into the duodenum.

Early Postoperative Course

Early severe postoperative complications are infrequent (Table 65.3). Severe, surgery-related complications are <10% according to Clavien-Dindo III. Local bleeding, which appears as intestinal blood loss, caused by arterial leakage from the shell-like rest of the pancreatic head and anastomotic leakage, which appears as evacuation of intestinal content into the drainage bag, is observed in <2% of cases. Severe intestinal bleeding, leakage of the pancreaticojejunostomy and surgical-side infection around the pancreatic head are reasons for reintervention [26]. Between the second and fifth postoperative days, patients

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Table 65.3 Early postoperative results after duodenum-preserving subtotal pancreatic head resection in 603 patients.*

	Patients *N*	Frequency
Pancreatic fistula	20	3.3%
Pancreatic anastomosis leakage	9	1.5%
Biliary leakage	3	0.5%
Intra-abdominal abscess	17	2.8%
Intra-abdominal hemorrhage	17	2.8%
GI anastomosis insufficiency	2	0.3%
Delay of gastric emptying	9	1.5%
Frequency of reoperation	34	5.6%
Hospital mortality	5	0.81%

* Beger et al. 2008 [33]/John Wiley & Sons.

are on regular oral nutrition (Table 65.4). The glucose metabolism is maintained at the preoperative level up to the fifth postoperative year (Table 65.4). When measuring the C-peptide and insulin response 3–36 months postoperatively after intravenous and oral glucose load, they remained at the reoperative level. However, the concentration of glucagon and pancreatic polypeptide (PP) displayed a highly significant decrease after stimulation [34–36].The loss of glucagon and PP delivery into the blood explains the observation that up to 10–12% of patients experienced a postoperative improvement of the disrupted glucose metabolism, because both hormones are produced predominantly in the endocrine tissue of the pancreatic head.

Long-Term Outcome after Duodenum-Preserving Pancreatic Head Resection

After a median observation period of 5.7 years and a follow-up rate of 94%, control of pancreatic pain is complete and long-lasting in approximately 90% of cases (Table 65.5). In terms of pain and attacks of pancreatitis, DPPHR changes the natural course to a silent disease. Preoperatively, each patient had 2.7 hospitalization periods, whereas after a median follow-up of 5.7 years, only 9% of the patients experienced a rehospitalization. Due to the persistent destruction of the functional parenchyma of the pancreas inherent in CP, the frequency of diabetes mellitus is increasing as well as the level of exocrine insufficiency [37–39]. Major advantages of duodenum-preserving subtotal pancreatic head resection for CP are conservation of the duodenum and the CBD and temporary maintenance of the endocrine pancreatic functions. More than five RCT have been published comparing DPPHR with Kausch-Whipple duodenopancreatectomy, with DPPHR superior in terms of postoperative morbidity, maintenance of glucose metabolism, an absence of delayed gastric emptying, and a low frequency of rehospitalization [40–45] (Table 65.6).

The Frey Procedure—an Alternative Surgical Approach for all Patients with Chronic Pancreatitis?

In 1987, Frey et al. published a technique for CP in six patients; the authors recommended a coring-out technique of ventral pancreatic head tissue combined with longitudinal pancreaticojejunostomy for CP [46]. In 1994, Frey propagated a variation of the LR-LPJ procedure, extending the coring out to the dorsal part of the pancreatic head, which results in a partial head resection, but left the intrapancreatic segment of the CBD predominantly embedded by pancreatic tissue. The Frey procedure, taking out some tissue ventrally from the pancreatic head, is rather a modification of the Partington–Rochelle duct drainage procedure. When

Table 65.4 Endocrine and exocrine pancreatic functions in chronic pancreatitis after duodenum-preserving subtotal pancreatic head resection.

		Bittner 1992* 15 pts, 3 mo*	Ikenaga 1995** 42 pts, 36 mo*	Eddes 1997*** 19 pts, 3–6 mo*
Endocrine I/OGTT		preop = postop	new DM 29 %	preop = postop
	k-value	postop $P < 0.01$	preop = postop	
	Insulin	preop = postop	preop = postop	
	C-peptide	preop/postop NS		postop reduced $P < 0.05$
	Glucagon	preop/postop $P < 0.001$		postop reduced $P < 0.05$
	PP (AUC)			postop reduced $P < 0.05$
Exocrine	BT-PABA		postop reduced $P < 0.01$	postop reduced $P < 0.05$

* Bittner et al. 1994 [34].
** Ikenaga et al. 1995 [35].
*** Eddes et al. 1997 [36].

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Table 65.5 Results of long-term follow-up: endocrine functions and pain pattern after DPPHR for chronic pancreatitis.

	Preoperative	Late postoperative		
	1972–1998 504 pts	1984* 2.0 yr[a] 56 pts	1988** 3.6 yr[a] 109 pts	1997*** 5.7 yr[a] 303 pts
OGTT normal/reduced	246 (49%)134 (26%)	66%	48%26%	39%17%
IDDM	124 (25%)	–	26%	44%
Pain-free[b]		92.8%	89%	91.3%
Continuing abdominal pain		7.2%	11%	8.7%
Abdominal complaints		–	12%	12%
Rehospitalization, preop. attacks of acute pancreatitis(100%; 2.7 hospitalizations/pt.)		14% (8/56)	11% (11/109)	

[a] Median years follow-up.
[b] No or rare pain.
* Beger 1985 [37].
** Beger1989 [38].
*** Beger 1999 [39].
pts: number of patients; OGGT: oral glucose tolerance test; IDDM: insulin-dependent diabetes mellitus.

Table 65.6 DPPHR versus PD for chronic pancreatitis—results of a meta-analysis *Source:* Adapted from [45].

	DPPHR (93 pts)	PD (91 pts)
Complete pain relief	Equal	
Blood transfusion	$P < 0.01$	
Pancreatic fistula	Equal	
DGE	$P < 0.01$	
Overall postoperative morbidity	Equal	
Hospital stay	$P < 0.01$	
Exocrine insufficiency	$P < 0.01$	
Endocrine insufficiency	$P < 0.08$	
Postoperative weight gain	$P < 0.01$	
Occupational rehabilitation	$P < 0.01$	
Quality of life	$P < 0.01$	

DGE: delay of gastric emptying; DPPHR: duodenum-preserving pancreatic head resection; pts: number of patients; PD: pancreaticoduodenectomy.

performing the Frey procedure as a subtotal pancreatic head resection in CP, the long-term outcome is similar to the DPPHR [47]. However, in many institutions that perform a duodenum-preserving resection in CP by coring-out of the pancreatic head tissue, it is executed as a partial ventral pancreatic head resection. The long-term outcome regarding pain control after ventral coring-out of pancreatic head tissue is reestablishment of upper abdominal pain in approximately one-third of the patients [29]. An additional risk of the Frey procedure lies in the incomplete decompression of the CBD due to partial ventral coring-out of pancreatic head tissue, whereby the patient will postoperatively suffer from cholestasis and attacks of cholangitis due to persistence or reappearance of the duct compression by pancreatic tissue mass. Re-surgery after the Frey procedure is a well-documented indication for redo-surgery because of persistence of biliary stenosis [48,49].

Results of RCT Comparing PD and DPPHR for Chronic Pancreatitis – The ChroPac Trial

The results of the prospective, randomized, multi-institutional ChroPac trial published in 2017, reported clinical evidence that favors PD for CP [51]. However, the evidence of the ChroPac trial results is limited owing to the striking heterogeneity of the compared procedures (PD group included Whipple or PPPD and DPPHR group included three different procedures: Beger, Berne, and Frey) [51]. Furthermore, 8 of 18 participating surgical institutions contributed only 1 patient per year in the 4-year allocation period of the trial. The randomization protocol resulted in an unusually frequent accumulation of very advanced CP in the DPPHR group. Metabolic data of pancreatic functions in the ChroPac study were not determined, but taken from the patients' records at the participating institutions. The results of the four mono-institutional prospective RCT comparing PD and DPPHR for CP were based on 170 patients following DPPHR and 160 patients following PD [40–42,44]. These trials provided high-quality evidence of the advantages of DPPHR

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for CP regarding a significantly lower frequency of early postoperative, severe complications, an absence of surgery-associated, early postoperative endocrine and exocrine metabolic morbidity, and postoperative reestablishment of an adequate quality of life. These results, albeit derived from mono-institutional RCTs underline the advantages regarding early surgery-related morbidity and late postoperative maintenance of endocrine and exocrine pancreatic functions following DPPHR compared to PD.

Long-term follow-up in median 15 years after DPPHR and PPPD for CP revealed a significantly reduced survival when PPPD was used for CP compared to DPPHR Hamburg modification. Patients initially included in a prospective, randomized controlled clinical trial had a median survival after PPPD of 11.3 years, whereas following DPPHR the median survival was 14.5 years. The highly significant survival benefit after application of a modified duodenum-preserving pancreatic head resection for CP was clearly associated to the maintenance of the endocrine and exocrine pancreatic functions due to duodenum preservation [24].

Summary

Duodenum-preserving resection of the head of the pancreas is a low-risk procedure for patients with CP, particularly for those who have developed an inflammatory mass in the pancreatic head. Subtotal resection of the pancreatic head does not result in a significant reduction of the exocrine and endocrine functions of the pancreas. Owing to the limited nature of the intervention, hospital and late mortality rates are low. More than 80% of the patients with CP have experienced long-lasting relief of pain after duodenum-preserving head resection. For patients with a stenosis of the intrapancreatic common bile duct, an internal biliary anastomosis establishes long-lasting normal bile flow. For patients with multiple duct stenosis in the left pancreas, duct stones, calcifications and duct dilations, an additional pancreaticojejunostomy, additional to subtotal pancreatic head resection, relieves recurrent attacks of pancreatitis and restores pain-free survival and quality of life.

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66

Total Pancreatectomy with Islet Autotransplant

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> *The surgeon is a doctor who can operate and knows when he should not do it.*
>
> Emil Theodor Kocher (1841–1917)

Introduction

Chronic pancreatitis (CP) is a difficult disease with a common progression to pancreatic exocrine insufficiency, diabetes mellitus, and narcotic dependence due to chronic pain over years to decades. Typical medical therapies include pancreatic enzyme supplementation and other medical therapy, interruption of pancreatic toxins (especially alcohol), and endoscopic interventions. While this is successful in many patients, there remains a subset of patients without adequate responses to medical and endoscopic interventions.

Typical surgical interventions have relied on the ability to either extirpate the segment of pancreas most affected by the CP, or by a variation of pancreatic duct drainage. These interventions have been proven to be effective in appropriately selected patient populations [1,2]. However, there are several subgroups of patients that are not as amenable to classical surgical interventions, including those with so-called minimal change or small duct pancreatitis, and those with familial disease, including *SPINK1*, *PRSS1*, *CTRC*, *CFTR*, and other mutations predisposing to CP.

In 1977, the first total pancreatectomy with islet autotransplantation procedure was performed by D. Sutherland and colleagues at the University of Minnesota, in part to better understand isolated pancreatic islet function after transplantation into the portal venous system. Interestingly, this operation was successful both in resolving the chronic pain from CP, and in long-term preservation of islet cell function [3,4]. Since that time, an experimental procedure performed at one institution has become a frequently performed operation at more than two dozen centers across the world with more than 1000 cases reported [5].

This procedure is unique in several ways. In addition to having a surgeon skilled in performance of one of the more challenging cases in surgery today, the key component of a successful procedure requires the presence of an experienced islet cell isolation facility, and a team of caregivers experienced in selecting and caring for the patient's issues such as diabetes mellitus, malnutrition, pain management, and exocrine dysfunction through surgery and recovery. Unlike typical transplantation, patients receiving islet autotransplantation do not require immunosuppression as they are receiving their own tissue. Given these components, mortality from this operation is <1% in reported series, but with morbidity expected after a pancreatectomy (up to 60%) [6].

Evaluation of the Patient with Chronic Pancreatitis for Surgical Intervention

The primary goal of performing a total pancreatectomy and islet autotransplantion is to provide relief of pain. An appropriate evaluation of the patient provides information about how best to develop an individualized treatment plan for each patient. Components of a typical evaluation for patients with CP considering surgery involve historical review (looking for pancreatic interventions and histopathology), imaging, and focused laboratory testing to evaluate markers for and etiology of CP, pancreatic exocrine and endocrine function (Table 66.1). Tumor markers should be considered, especially in older patients, to evaluate the possibility of

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Table 66.1 Evaluation of patients for TPIAT: common components.

History:
Drugs and alcohol
Genetic testing
Imaging
Pancreatic interventions
Episodes of pancreatitis
Imaging:
Computed tomography
Magnetic cholangiopancreatography
Endoscopic ultrasound
Laboratory:
Fecal elastase
Ca19-9, CEA
Hemoglobin A_{1C}
Functional testing:
Pancreatic function tests
Mixed meal testing

TPIAT: total pancreatectomy with islet autotransplant; CEA: carcinoembryonic antigen.

cancer as an etiology of pancreatitis. Other causes of chronic abdominal pain should be considered in each patient and investigated as appropriate. Many younger patients without obvious etiology should receive genetic counselling and testing. Evaluation by a medical psychologist is frequently helpful as interventions are considered.

Decision-Making Process

Candidates for TPIAT at our institution are evaluated and discussed after evaluation by a multidisciplinary group including gastroenterology, surgery, endocrinology, nurse coordinators, health psychology, genetics, dietetics, social services, and pain management. Our approach to interventions follows Fig. 66.1, with therapy tailored to the individual patient. Many patients will benefit from a medical or endoscopic intervention. In those patients with calcifications and dilated duct, a drainage procedure such as a Frey or Beger procedure are often offered, as recovery is shorter and long-term outcomes in properly selected patients are good [2].

Many patients who have failed medical or endoscopic interventions have small-duct or minimal-change chronic pancreatitis (MCCP). This disease is characterized by chronic inflammatory destruction of the gland with subsequent exocrine/endocrine dysfunction and persistent abdominal pain without main duct dilation [7]. In the setting of small duct/minimal change disease total pancreatectomy represents the only valid surgical option for the treatment of pain [8,9]. Additionally, patients with genetic/familial disease are more likely to develop recurrent or progressive disease [10].

Patients who are being considered for a TPIAT meet the criteria in Table 66.2 [11], with proven pancreatitis, a significant effect on lifestyle, no reversible cause of pancreatitis, failure to respond to appropriate medical and endoscopic management, and adequate islet cell function.

There are a number of contraindications to this procedure, which include active drug abuse or alcoholism (we require 6 months of sobriety), active cardiac and respiratory disease with high perioperative risk, poorly controlled psychiatric disease, and inability to comply with postoperative care [16]. Additionally, pancreatic cancer or diffuse neoplasm and preexisting liver disease, including cirrhosis, portal hypertension or portal vein thrombosis are contraindications for major pancreatic resection or intraportal islet transplant [12,13]. Finally, patients with diabetes mellitus without C-peptide response will receive poor islet cell yields and poor postoperative graft function so TP alone is offered without the IAT [14].

A total pancreatectomy with islet autotransplantation is performed for management of a patient's pain. Previous learning has suggested that the pain from CP may "burn out" or resolve over 1–2 decades, although recent evidence suggests that this may not be the case [15]. A thorny issue is the question of when to intervene with surgery for patients suffering from chronic pain due to pancreatitis. A number of groups have investigated this

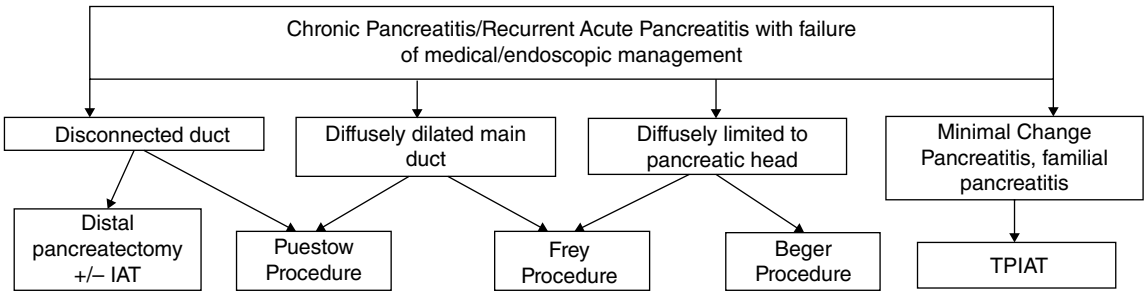


Figure 66.1 Decision tree for patients who have failed nonsurgical treatment for acute recurrent or chronic pancreatitis. TPIAT: total pancreatectomy with islet autotransplant.

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Table 66.2 University of Minnesota criteria for total pancreatectomy and islet autotransplantation (must fulfill 1–5).

1) Diagnosis of chronic pancreatitis, based on chronic abdominal pain of ≥6 months duration and at least one of the following:
   - Pancreatic calcifications on computerized tomography scan.
   - At least two of the following: ≥4/9 criteria on EUS, compatible ductal or parenchymal abnormalities on secretin MCRP; abnormal endoscopic pancreatic function tests (peak HCO_2 ≤ 80 mmol/L).
   - Histopathology confirmed diagnosis of chronic pancreatitis.
   - Compatible clinical history and documented hereditary pancreatitis (e.g., *PRSS1* gene mutation).
   - History of recurrent acute pancreatitis (more than one episode of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase greater than three times upper limit of normal).
2) At least one of the following:
   - Daily narcotic dependence
   - Pain resulting in impaired quality of life, which may include: inability to attend school, recurrent hospitalizations, or inability to participate in usual, age-appropriate activities
3) Complete evaluation with no reversible cause of pancreatitis present or untreated
4) Failure to respond to maximal medical and endoscopic therapy
5) Adequate islet cell function (nondiabetic or C-peptide positive)

MRCP: magnetic resonance cholangiopancreatography.
Source: Adapted from [11].

question, and repeated data suggests that outcomes after surgery for pancreatitis (including TPIAT and other operations) are improved with duration of chronic pain of 3 years or less [16,17].

Islet Cell Laboratory

The critical nature of an effective islet cell laboratory cannot be overstated. The presence of at least partial graft function is critical to maintain goal glycemic control and reduce glycemic variability, and insulin independence is associated with better quality of life after TPIAT [18]. Islet laboratories with significant annual experience have better islet yields on long-term graft function than those who do fewer isolations [19].

An important distinction in the setting of islet autotransplantation is that the US Food and Drug Administration does not consider these islets a manufactured biologic product. This requires processing of the islets under current Good Tissue Practice but not the more stringent current Good Manufacturing Practice regulations. In this setting, the goal of processing islets is to maximize islet yield, and not purity.

For the islet isolation step, after removal the whole pancreas is taken immediately to the islet facility, where it undergoes enzymatic and mechanical digestion to separate the pancreatic islets from acinar and pancreatic ductal tissue. Digestion is aided by use of the Ricordi Chamber, which enhances exposure of the pancreatic tissue to digestive enzymes [20]. The isolated islet tissue is returned to the operating room where islets are infused into the portal vein. Significant recent advances have been made in use of tailored enzyme preparations to enhance optimized islet isolation [21].

Unsurprisingly, there are far fewer facilities that have the manufacturing resources to perform islet isolation than there are that have skilled pancreatic surgeons. To address this issue, a number of centers have explored distant processing of the pancreas at a core facility with return of the isolated islets for infusion to the operative site. While time from removal of pancreas to infusion of islet is typically 8–10 hours longer, graft function results in these studies have been roughly comparable to those where pancreas was processed locally [22,23].

The Operation: Unique Features

The operation of total pancreatectomy with islet autotransplant is essentially a total pancreatectomy with duodenectomy (plus/minus distal gastrectomy) with a splenectomy. Although some institutions advocate a splenic-preserving procedure, because of the concern for affecting blood flow to the pancreas during surgery and the concern for postoperative sinistral portal hypertension with resultant gastric varices, we typically perform a splenectomy at the same setting. Patients should therefore be vaccinated preoperatively against *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis* to minimize the likelihood of developing potentially lethal post-splenectomy sepsis. Appropriate vaccination strategies for these organisms change on a regular basis, with the most current guidelines typically available on the Centers for Disease Control and Prevention website [24]. Vaccination has been shown to significantly reduce the risk of post-splenectomy sepsis [25].

Another variation in patients undergoing pancreatectomy for islet cell isolation is the approach to preserve pancreatic blood supply to decrease warm ischemia time. In this case, the splenic artery and vein and gastroduodenal artery are identified, isolated, and preserved until the final dissection is complete. Typically these vessels are then ligated along with the common bile duct and uncinate process to complete the resection. The pancreas is immediately placed in a basin with iced saline where the duodenum is excised, excess peripancreatic

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tissue is removed, and the gland is exsanguinated to facilitate enzymatic digestion. The gland is then sent to the islet cell laboratory for processing.

One controversy is whether to perform pylorus preserving or a standard distal gastrectomy during the resection. It is argued that delayed gastric emptying is shorter in those undergoing a classical resection, and that the risk of postoperative dumping syndrome is lower in those with pylorus-preserving resection. One of the outcomes awaited in the POST trial (a prospective, multicenter observation trial of outcomes after TPIAT) is related to this variation in care [26].

Islet processing can take from 5 hours for an islet laboratory co-located with the patient to up to 24 hours in a setting where islets are processed at a distant site. Another variation is how to manage the delay. There are a number of management techniques described. A common approach is to keep the patient in the operating room under anesthesia for the period of time that islets are being processed, infusing islets, then completing closure. Other described approaches include temporary cannulation and closure with removal of the catheter after infusion, percutaneous placement of catheter by IR into the portal system with infusion, or a return to OR for operative infusion of islets (the typical approach for centers utilizing remote processing of islets).

In most cases, the islet preparation is infused into the portal vein or one of its major branches. The authors' technique is to use a 5-French micropuncture kit to place a catheter into the anterior portal vein or splenic vein. Anticoagulation of the patient is necessary as the islet preparation includes injured tissue that will induce a hypercoagulable state [27] and 70 units of heparin per kg body weight administered intravenously is typically utilized. Portal pressures are measured at the beginning and throughout infusion of islets, with infusion held if pressures increase by greater than 25 cm H_2O. Portal pressure increase is expected, as the islet preparation volume is embolizing within the portal venous system, which has a limited capacity for tissue [28] of about 0.25 mL of tissue per kg body weight. In the situation where portal pressures remain elevated during infusion, islets can be safely placed within an omental pouch or other extraportal site [29].

Laparoscopic-assisted, laparoscopic, and robotic total pancreatectomy with islet autotransplant have been described [30–32]. In a case-control series of laparoscopic-assisted total pancreatectomy compared to an open procedure in children (21 patients in each group), perioperative morbidity, operative time, length of stay and outcomes were similar between laparoscopic and open groups, with a higher use of opioids at 2 years post-procedure in the laparoscopic group [30]. Other case series demonstrate the feasibility of both laparoscopic and robotic approaches to TPIAT [31,32]. One issue continues to be the inflammation and scarring associated with CP and the potential effect of this state on the ability to safely perform the dissection via laparoscopy or robotically.

Postoperative Care

Many of the postoperative complications associated with total pancreatectomy and islet autotransplant are common with other similar procedures such as a Whipple procedure. These include anastamotic leak from GI tract or bile duct, postoperative abscess, and postoperative bleeding. Other complications are related to and unique to the islet autotransplant portion of the procedure. Postoperative management of these patients includes close monitoring for these complications and care supportive of the unique features of this operation. In a large, multicenter prospective study of patients after TPIAT [6], complications included need for reoperation for bleeding, portal vein thrombosis, intra-abdominal abscess, and wound infection (Table 66.3).

A common feature in this operation is delayed gastric emptying. In this population of patients this seems to be present for 3–6 weeks after surgery. There is some evidence that laparoscopic or robotic procedures may reduce the duration of this problem, but this has not yet undergone careful study. Current protocol in our institution is to place a gastrojejunostomy tube at the time of surgery, with initiation of tube feedings the morning

Table 66.3 Postoperative complications in a multicenter study of 279 patients after total pancreatectomy with islet autotransplantation [6].

	Incidence: Adults	Incidence: Pediatrics
Complication	***n*** **= 195**	***n*** **= 83**
Reoperation within 30 days	11%	7%
Abdominal infection requiring drainage	9%	3%
Bile duct obstruction/leak	2%	2%
Portal venous thrombosis	10%	2%
Mechanical ventilation >24 hours postoperative	3%	1%
Vasopressor use >24 hours postoperative	3%	6%
Pulmonary embolus/deep venous thrombosis	4%	0%

Source: Nathan et al. 2022 [6]/With permission of Elsevier.

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after surgery. The patient can be transitioned to oral intake and the gastrojejunostomy tube can be removed several weeks postop. Pancreatic exocrine insufficiency is common in patients with CP in the preoperative state, with nearly 50% of patients on pancreatic enzyme supplementation. Of course, after removal of the pancreas all patients have a lifelong requirement for pancreatic enzyme supplementation. During tube feeds, this deficiency is addressed using an immobilized lipase cartridge in line with the tube feeds (Relizorb R). Pancreatic enzymes are initiated as the patient transitions to oral intake and adjusted as necessary.

Anticoagulation is important in the operating room and postoperatively due to infusion of the hypercoagulable islet tissue. Various regimens include low-dose heparin infusions or moderate doses of low-molecular weight heparin. Patients should be imaged 4–6 days postoperatively for presence of portal vein thrombosis and if this condition is identified, patients should be fully anticoagulated for 3 months postoperatively [33].

Pancreatic islets are routinely cultured for presence of bacterial contamination prior to infusion. If these cultures return positive (this occurs in 40–60% of cases), appropriate tailored antibiotic therapy is initiated and continued for 7 days to treat the positive cultures. In one series of more than 250 patients, this approach resulted in no concordant bacterial infections [34].

Pain management after TPIAT is a vexing problem. Essentially every patient is habituated to narcotics, and appropriate control of pain without oversedation is challenging. An epidural catheter is contraindicated, due to the need for intraoperative anticoagulation. Typical therapy includes a multimodal management approach that can include i.v. narcotics, adjuncts such as ketamine or dexmetatomidine, and local therapies including paravertebral catheters or long-acting abdominal wall blocks. A key component of this management is in counselling of the patient and their support persons on the difficulty of achieving adequate pain control for the first several days following surgery. As the patient recovers from surgery, transition to long-acting narcotics to treat both the narcotic dependency and postop pain is appropriate, with weaning of narcotics over the months following surgery.

Glycemic Management

The important concept to preserve islet function after autotransplantation is maintainance of normoglycemia. Hyperglycemia can lead to both poor engraftment of cells in the perioperative period, and loss of islet cells after TPIAT [35,36]. Management of blood glucose to promote optimal islet function begins in the operating room. Solutions containing dextrose should be minimized in the intraoperative period as this has been shown to be associated with sustained intraoperative and postoperative hyperglycemia. Insulin should be administered to maintain blood glucose levels between 80 and 120 mg/dL and postoperatively an insulin infusion should be maintained to keep blood glucose within this range. Patients are typically transitioned to long-acting insulin preparations as enteral nutritional requirements are met. Most patients are maintained on insulin for the first 3 months after islet autotransplant with gradual weaning of insulin as tolerated.

Outcomes after Total Pancreatectomy and Islet Autotransplantation

The major outcome of interest in patients receiving TPIAT is relief of pain, with other outcomes including need for insulin and quality of life. Studies from multiple centers have recently been evaluated in a meta-analysis from the Dutch Pancreatitis Study Group [37] where outcomes from 14 studies that included 1255 patients were evaluated. In this meta-analysis, at 1 year after total pancreatectomy with islet cell autotransplantation, opioid-free rate had improved from between 0% and 15% to 63% (95% CI: 46–77), and the insulin-free rate had decreased from between 89.5% and 100% to 30% (95% CI: 20–43). Alcohol as the cause of pancreatitis was associated with lower insulin-free rate. Quality of life significantly improved after TPIAT.

In one of the largest single center studies published to date, Chinnakotla and coauthors reported long-term outcomes in adults ($n = 490$) and children ($n = 91$) after TPIAT [38]. They reported 10-year survival of 90%, with 1 year narcotic-free rates of 67% and insulin-free rates of 18% (adults) and 31% (children) (Fig. 66.2). Pediatric patients had significantly improved outcomes compared to adults. Other larger series have shown comparable results [39,40] An ongoing prospective multicenter trial is actively enrolling patients from nearly a dozen institutions to evaluate postoperative outcomes and relationship to preoperative findings [6,41].

There have been two long-term studies examining the durability of TPIAT for resolution of pain, glycemic control, and quality of life. In a 5-year follow-up study, Wilson and coauthors report their results in 195 patients [40]. Annual visits and hospitalizations decreased from 6 and 4, respectively, to 0 for each of years 1, 2, and 5 after surgery. Postoperative quality of life scores significantly improved with a durable improvement at 5 years for both physical and mental well-being. Finally, median oral morphine equivalents were significantly reduced and remained significantly lower than preop (214 mg/kg before surgery, 69 mg/kg at 5 years postoperatively). A second study, reporting 10-year

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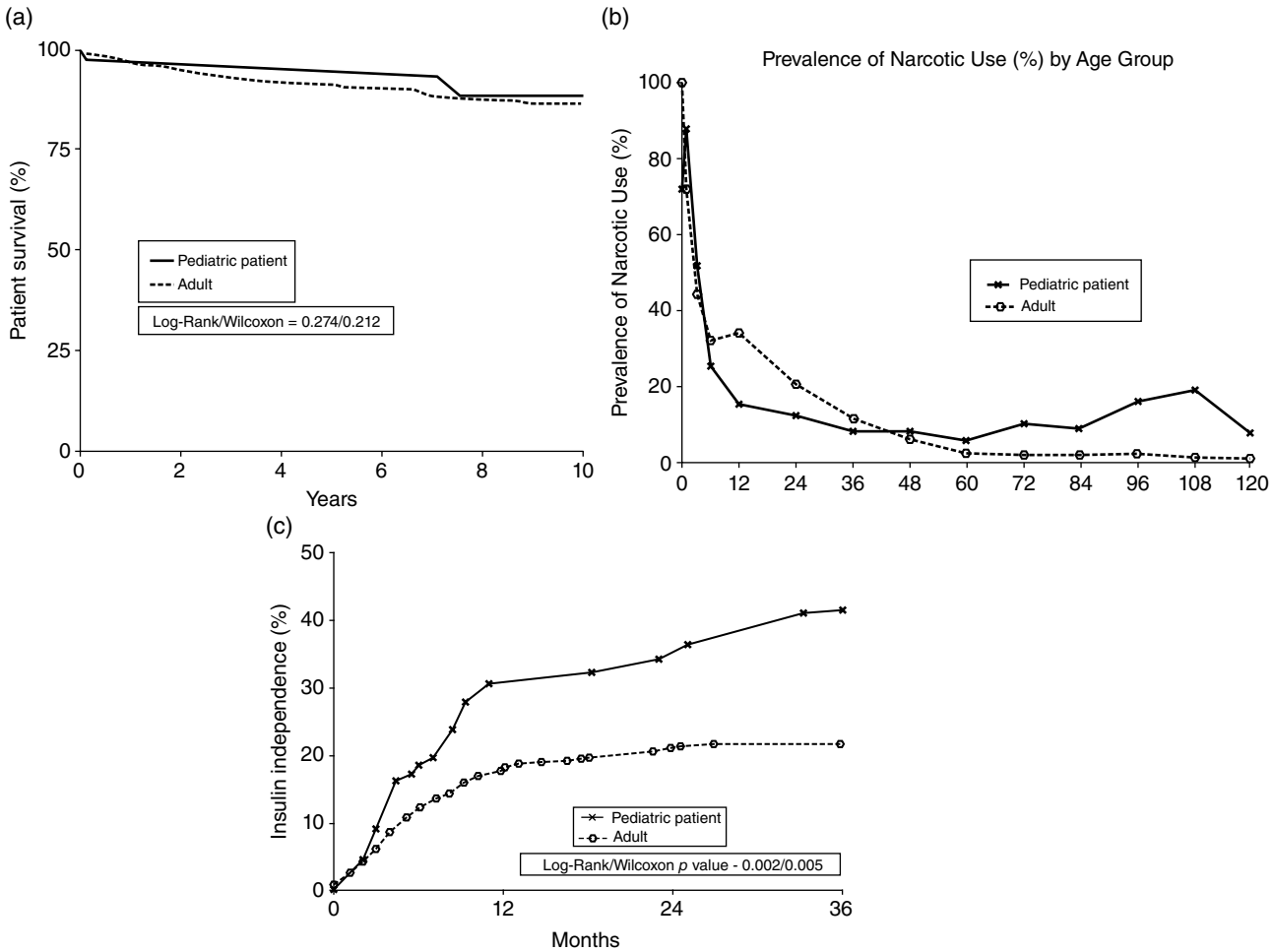


Figure 66.2 Outcomes after total pancreatectomy with islet autotransplant (TPIAT) in 581 patients at a single center [38]. (a) Ten-year actuarial survival in adults and children after TPIAT. (b) Narcotic-free percent in adults and children after TPIAT. (c) Insulin-independence in adults and children after TPIAT. *Source:* Chinnakotla et al. 2015 [38]. Reproduced with permission.

outcomes in 215 patients [42], noted a 10-year actuarial survival rate of 72%. Narcotic use declined with time: the rates were 50% at 5 years and 37% at 10 years. At 10 years, the rate of insulin independence was 20%; the rate of partial graft function, 32%. Transplantation of islet equivalents/kg >4000 was the strongest predictor of islet graft function at 10 years. Health-related quality of life continued to improve at 10 years, even in patients on narcotics.

In conclusion, total pancreatectomy with islet autotransplantation has become a viable option for selected patients with painful chronic pancreatitis, with long-term success in terms of pain relief and glycemic control.

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Minimally Invasive Surgical Management of Chronic Pancreatitis

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Introduction

The introduction of laparoscopy, and more recently robotics, into abdominal surgical practice has revolutionized the approach to complex surgical conditions. The first laparoscopic procedure for chronic pancreatitis (CP) was reported in 1994 by Gagner and Pomp who successfully performed a pylorus-preserving pancreaticoduodenectomy (PD) on a 30-year-old woman [1]. In 1996, Cuschieri et al. described a series of five laparoscopic distal pancreatectomies (LDP) with splenectomy in patients with CP, with good perioperative outcomes [2]. Due to concerns of excessive morbidity, the expansion of laparoscopic, and robotic pancreatic surgery was initially met with resistance. Over the past two decades, however, minimally invasive approaches have slowly been integrated into the repertoire of high-volume centers, with rates of mortality and morbidity equivalent to those of open procedures [3]. In addition, with the advent of robotic assistance, surgeons can now benefit from binocular three-dimensional vision, scaling, stabilization of tremor, reduced operator fatigue, and improved ergonomics from the console–surgeon interface. As the technology continues to evolve, and surgeons progress through their learning curve, minimally invasive approaches and indications for pancreatic pathology are continuing to expand.

Traditionally, the majority of surgical interventions for CP are performed through an open approach. The literature continues to grow supporting the safety and comparable efficacy of minimally invasive versus open pancreas surgery; however, most data combines both benign and malignant indications as well as laparoscopic and robotic interventions. As only a few studies have focused solely on benign indications, it may be reasonable to infer that outcomes of larger laparoscopic and/or robotic series can be used to provide insight into the applicability of minimally invasive approaches to CP. This chapter, therefore, will summarize the current data on the safety, feasibility, and efficacy of minimally invasive procedures for CP, but also draw on the broader available literature on minimally invasive pancreatic surgery performed for other indications.

Generally, surgical strategies for CP can be categorized into resection-type procedures, drainage-type procedures, and combination-type procedures involving resection and drainage (Table 67.1). In addition, minimally invasive surgery can be broadly defined as laparoscopic or robotic assisted.

Patient Selection

Laparoscopic and robotic pancreatic resection, drainage, or combination procedures offer the advantages of minimally invasive surgery to appropriately selected patients. Initially it was believed that patient factors such as age, comorbidities, body habitus, and prior operations were useful in selecting which patients should be candidates for minimally invasive operations. Recently the Miami Consensus Guidelines sought to provide evidence-based recommendations on the role and appropriate use of minimally invasive pancreatic resection [4].

Within the consensus guidelines, neither patient factors nor operative plan were found to impact patient outcomes and thus should not be used to guide patient selection for laparoscopic or robotic interventions. In general, robotic PD (RPD), with or without vascular resection, should only be performed in high-volume centers with experienced surgeons; however, the need for vascular resection itself should not preclude patients from minimally invasive options [5]. Moreover, the Miami Consensus states that patients should not be

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Table 67.1 Clinical outcomes following minimally invasive treatment for chronic pancreatitis.

Author	Study design Indication	Pts	Approach	Operating room time (min)	Open conversion	EBL (mL)	Complications	Mortality	LOS	Follow-up	Outcome
Resection											
Total pancreatectomy with islet autotransplantation (TPIAT)											
Galvani et al. 2014 [11]	Retrospective CP	6	Robot(1 with AIT)	712	0	630	2 (33%)	0	12.6	1 mo	All 5 patients weaning narcotics; 2 required splenectomy
Zureikat et al. 2015 [10]	Retrospective 3/10 CP	10	Robot	560	1 (10%)	650	2 (20%)[a]	0	10	NR	1 (10%) reoperation
Pancreaticoduodenectomy (PD–Whipple)											
Zureikat et al. 2021 [7]	Retrospective 17% Benign	500	Robot	391	26 (5.2%)	~250	24%[a]	1.4%	8	36.7 mo	5% reoperation; 35% readmission
Zureikat et al. 2013 [14]	Retrospective 8% Benign	132	Robo	527	11 (8%)	~250	28 (22%)[a]	1.5%	10	NR	3% reoperation; 28% readmission
Boggi et al. 2015 [15]	Systematic review 17% Benign	746	52% PL 16% LA 31% Robot 1% hand	464	64 (9.1%)	321	41%	1.9%	13.6	NR	NR
Distal pancreatectomy (DP)											
Esposito et al. 2022 [16]	Retrospective 0 CP	300 101	Lap Robot	235	31 (8%)	NR	45 (11%)[a]	0	8	NR	9% reoperation; 10% readmission
Cuschieri et al. 1996 [2]	Retrospective CP	5	Lap	240–360	0	400	1 (20%)	0	6	3–22 mo	Substantial pain relief in all, complete in 2 patients
Fernandez-Cruz et al. 2002 [17]	Retrospective CP	5 41	Lap Open	240	NR	450	1 (20%) 20 (48%)	0	4.512	13 mo 5 years	100% lap patients pain-free, 80% open patients pain-free
Venkat et al. 2012 [18]	Meta-analysis Benign + malignant	780 1034	Lap Open	MD 10.2	NR	MD 355*	OR 0.73*	OR 0.63	MD 4.1*	NR	2.1% reoperation in lap, 12.6% readmission
Drainage											
Lateral pancreaticojejunostomy (LPJ-Puestow)											
Kirks et al. 2017 [19]	Retrospective CP	7 19	Robot Open	268 236	2	75 250	1 (14.3%)[a] 6 (31.5%)[a]	0%	5 7	24 mo	Reduced LOS offset cost of robotic platform
Khaled et al. 2011 [20]	Systematic review CP	37	Lap	218	5 (13.5%)	NR	5 (13.5%)	0%	5.5	5–84 mo	89% pain-free; 2.7% reoperation rate
Meehan et al. 2011 [21]	Case report CP	1	Robot	390	0	NR	NR	0	8	2 yrs	Pain-free

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Khaled et al. 2014 [22]	Retrospective CP	5	Lap	278	0	150	1 (25%)	0	5	14 mo	4/5 (80%) patients pain-free
Cyst gastrostomy or jejunostomy (CG/CJ)											
Al Masri et al. 2021 [23]	Case report	1	Robot	180	0	25	0	0	7	NR	Resolution of complex bilobed WON
Khaled et al. 2014 [24]	Retrospective Sterile pseudocyst	30 10	Lap Open	62 95	0 -	NR	3 (10%)* 6 (60%)	0 1 (10%)	6.2* 11	13 mo 18 mo	97% resolution in lap 100% resolution in open
Worhunsky et al. 2014 [25]	Retrospective 2/3 sterile necrosis	21	Lap	170	0	50	12 (57%)	1 (5%)	5	11 mo	10% reintervention 6% long-term complications
Khreiss et al. 2015 [26]	Retrospective	20	14 Robot	167	0	30	4 (20%)	0 (0%)	7	NR	15% reintervention
	Sterile necrosis		6 Lap								0.42 months to resolution
Video-assisted retroperitoneal debridement (VARD)											
Horvath et al. 2010 [27]	Prospective	9 25 6	Perc VARD Open	135	10 (40%)	NR	0 9 (36%) 3 (50%)	1 (11%) 0 0	48 64 54	6 mo 6 mo 6 mo	11% pancreatic fistula 20% pancreatic fistula 33% pancreatic fistula
Drainage											
LPJ-Puestow García-Ureña et al. 2013 [28]	Retrospective Necrotizing pancreatitis (1 CP)	7	Lap	63	0	NR	4 (57%)	0 (%)	50	NR	2 (29%) requiring second VARD
Combination											
Frey procedure											
Cooper et al. 2014 [29]	Case report CP	1	Lap	NR	0	NR	0	0	6	NR	No narcotics on discharge
Tan et al. 2015 [30]	Case seriesCP	9 37	Lap Open	323 NR	2 (22%) –	57 293	1 (14%) 4 (11%)	0 0	7 NR	3 mo NR	100% lap patients had decreased VAS pain score
Beger procedure											
Khaled et al. 2014 [22]	Case report CP	1	Lap	285	0	NR	0	0	5	16	Mild pain; 1/3 of preop opioid dose

CP: chronic pancreatitis; AIT: auto-islet transplantation; WON: walled-off necrosis; Lap: conventional laparoscopy; robot: robotic approach; Pts: number of patients; LOS: length of stay, median days; NR: not reported; VAS: visual analog scale; PL: pure laparoscopy; LA: laparoscopic-assist; MD: mean difference; OR: odds ratio.

[a] Clavien–Dindo grades III or IV.

* $P < 0.05$.

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excluded from RPD based on obesity, patient age, or previous abdominal surgery [6].

Girgis et al. actually found a decrease in operative time, estimated blood loss, and POPF rate when compared to open PD for obese patients undergoing robotic pancreatic resection [6]. In an updated series of the University of Pittsburgh's first 500 cases of RPD, expanding patient selection criteria to include higher Charlson comorbidity scores, patients who received neoadjuvant therapy for PDAC, and vascular resections did not impact operative time, conversion rates, blood loss, or clinically relevant POPF [7]. Additionally, Kim et al. investigated whether anatomic variation of the right hepatic artery led to differences in pre- and postoperative outcomes and finding no difference, concluding that these variations should not be considered contraindications to the robotic approach [8]. In the hands of appropriately trained surgeons who are through their learning curve, robotic and other minimally invasive pancreatic surgery is comparable in efficacy to open approaches with the added benefits of improved postoperative recovery associated with MIS.

When managing CP, the specific procedure performed will continue to remain dependent on anatomic considerations such as the presence of a mass in the head of the pancreas, peripancreatic fluid collections, and pancreatic ductal involvement. A flow diagram for decision-making is depicted in Fig. 67.1. Importantly, given the infrequent indication for surgical interventions in CP, minimally invasive pancreatic operations for CP are best delivered at high-volume tertiary centers, by experienced pancreatic surgeons, in the context of multidisciplinary assessment. The operative approach to such patients (open, laparoscopic, or robotic assisted) must be dictated by surgeon experience and comfort level.

Resection Procedures

Total Pancreatectomy with Islet Autotransplantation

Total pancreatectomy with islet autotransplantation (TPIAT) is a rare procedure that is performed in only a

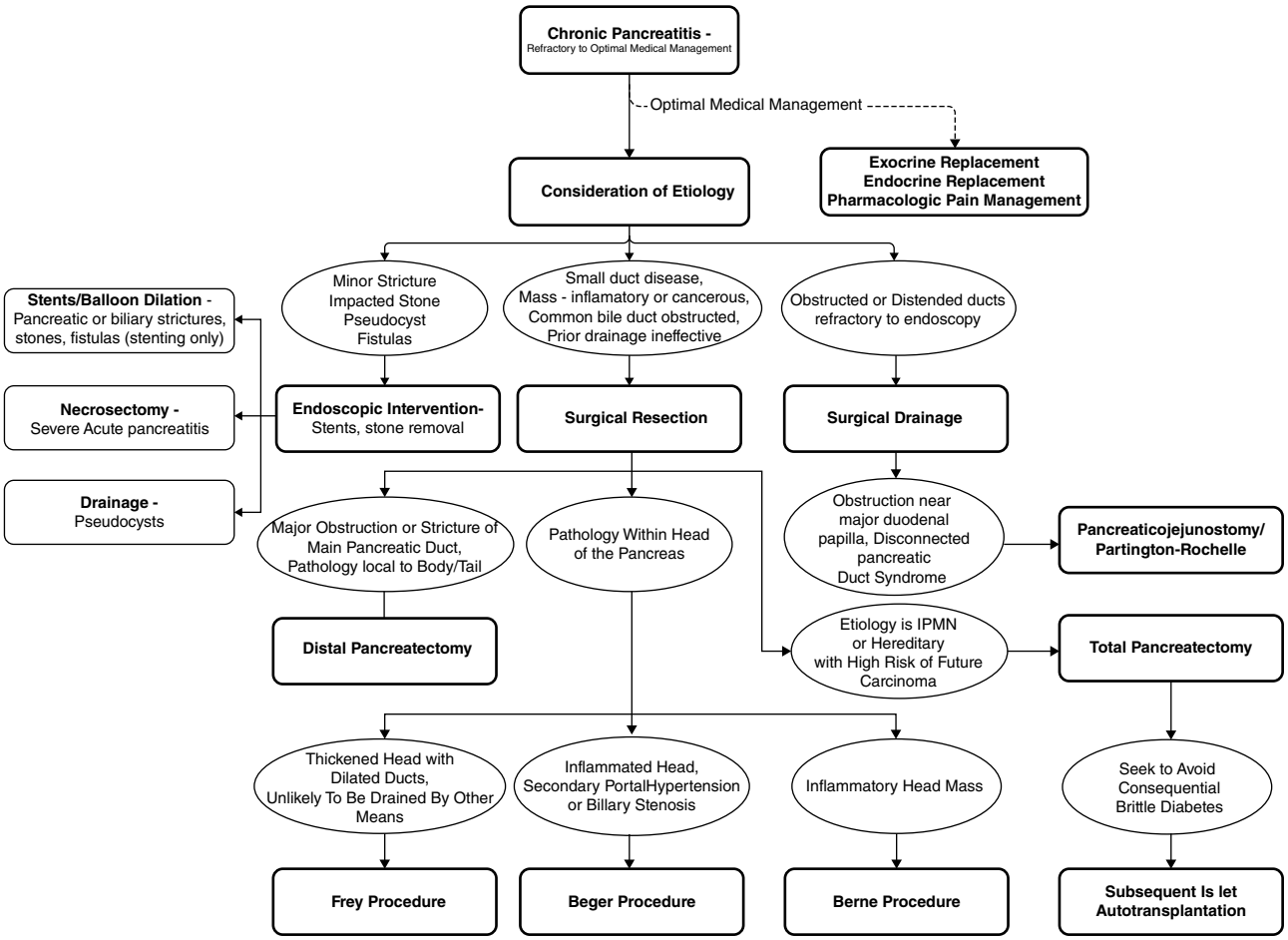


Figure 67.1 Flow diagram for determining the appropriate operative management for chronic pancreatitis sequelae [9] With permission of Elsevier.

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few specialized centers across the United States, with mortality and morbidity up to 16% and 70%, respectively [10]. As expected, the majority of such procedures are completed through an open approach, with laparoscopic or robotic-assisted approaches infrequently reported (Fig. 67.2). A single-center retrospective review of six patients with CP who underwent fully robotic-assisted TPIAT reported a mean operative time of 712 minutes and mean estimated blood loss (EBL) of 630 mL and no mortality [11]. At 1 month follow-up, all five patients who initially presented with intractable chronic pain syndrome were in the process of weaning off narcotics.

As early as 2009, cases of robotic-assisted laparoscopic distal pancreatectomy with autologous islet transplantation for CP were being reported [12]. The largest reported case series of robotic-assisted laparoscopic total pancreatectomy includes 10 patients with both benign and malignant pathology [10]. One of three patients with CP underwent AIT; seven patients had concomitant splenectomy while two were spleen-preserving. Median operative time was 560 minutes and median EBL was 650 mL. There was no 90-day mortality, and two Clavien–Dingo grade III complications were reported in two patients, including pleural effusion and fascial dehiscence. The median length of stay (LOS) was 10 days. These results are comparable to a more recent series of 12 TPIAT perfomed through an open approach [13].

Pancreaticoduodenectomy (Whipple)

The last two decades have witnessed an increasing number of single-institution reports of minimally invasive PD, but the efficacy of either laparoscopic or robotic PD for CP still requires larger series and a more robust assessment of outcomes. It can be inferred from studies that include benign and malignant indications that the minimally invasive PD is a safe and feasible procedure for patients treated at high-volume centers. A recent systematic review, for example, comparing laparoscopic and open PD (17.5% for benign disease) found similar rates of postoperative morbidity [15]. The study included 25 articles encompassing 746 cases of laparoscopic PD: 386 (52%) were pure laparoscopy, 121 (16%) with laparoscopic assistance, 231 (31%) with robotic assistance, and

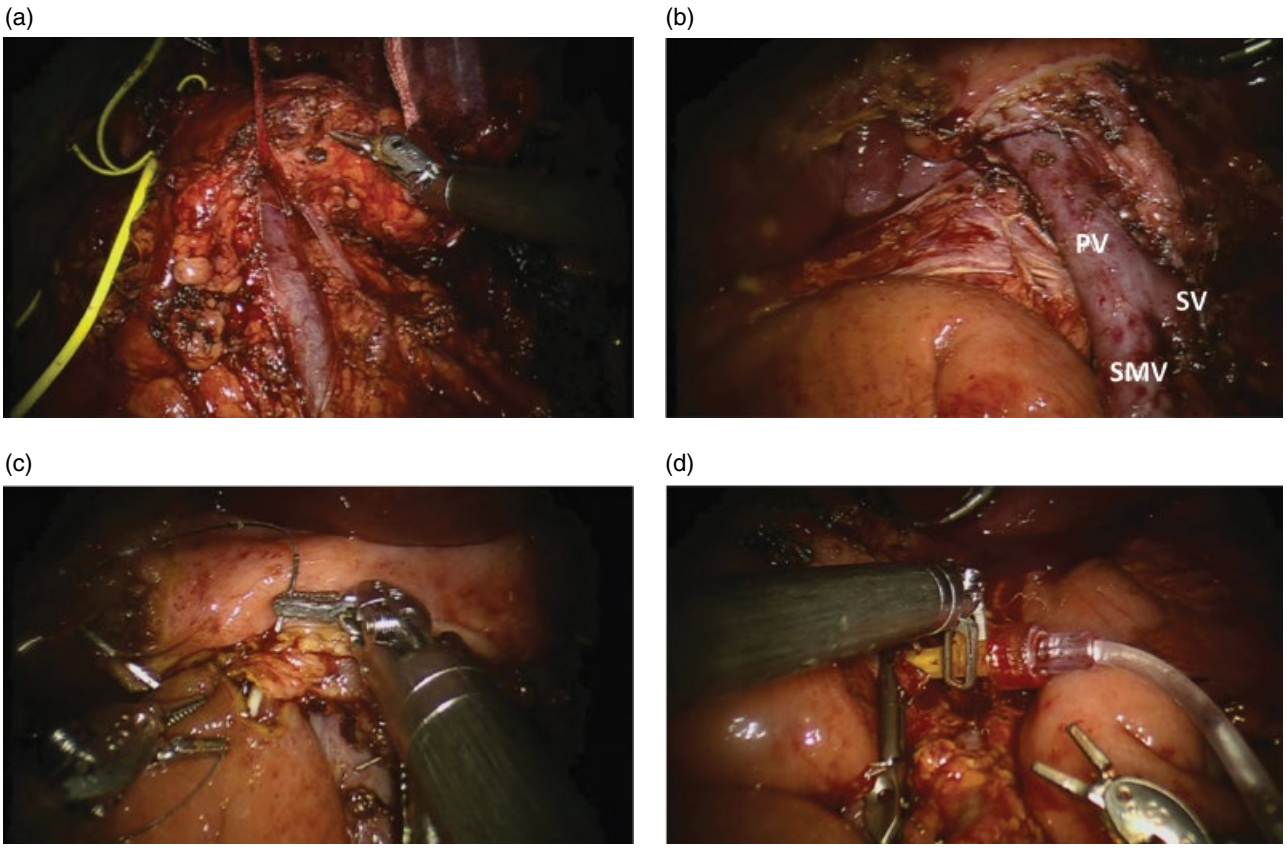


Figure 67.2 Robotic-assisted total pancreatectomy with auto-islet transplantation. (a) Pancreatic neck is freed from the superior mesenteric vein (SMV), splenic vein (SV), and portal vein (PV). (b) Resection of entire pancreas from the retroperitoneum. (c) Creation of hepaticojejunostomy over a stent. (d) Angiocatheter introduced through the SV stump for islet cell infusion.

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5 (1%) with hand assistance. Overall, open conversion was necessary in 9.1% of all cases. Mean operative time was 464 minutes and EBL 321 mL. The morbidity rate was 41%, including 22% patients developing pancreatic fistula, and mortality 1.9%. Mean LOS was 13.6 days. Pure laparoscopy was associated with shorter operative times, less blood loss, and lower rates of pancreatic fistula. Laparoscopic assistance had shorter operative times than robotic assistance, but higher rates of blood loss and pancreatic fistulas. The largest available single-institution review of robotic PD (500 cases) performed for various indications reported outcomes comparable to open historic controls with only a 6% rate of conversion in the most recent 100 cases despite broad indications and expanded patient selection [7]. As institutions and individual surgeons progress futher past their learning curves, outcomes appear to remain consistent despite increasing complexity of operations performed.

Distal Pancreatectomy (DP)

Similar to pancreatic head resections, the majority of studies comparing laparoscopic with open distal pancreatectomy do not stratify between benign and malignant indications. Specifically, data on minimally invasive distal pancreatectomy for CP are lacking and limited to a handful of small series such as that by Fernandez-Cruz et al., who reported a series of five CP patients who underwent LDP with spleen preservation, compared to 41 open pancreaticoduodenectomies with or without splenectomy [17]. This early study suggested that LDP for CP was feasible with acceptable outcomes.

LDP appears to be a safe and feasible approach for the treatment of left-sided pancreatic pathology. A systematic review of 18 studies by Venkat et al. (1814 patients) comparing laparoscopic (43%) and open (57%) distal pancreatectomies for all indications found that the laparoscopic technique was associated with decreased intraoperative blood loss by 355 mL, surgical site infections (3% vs. 8%), postoperative complications (34% vs. 44%), and decreased length of hospital stay by 4 days [18], with no differences in operative time, postoperative pancreatic fistula, or mortality. In addition, two single-institution retrospective series also suggest the robotic approach to distal pancreatectomy may have lower rates of open conversion, and higher rates of splenic preservation compared to conventional laparoscopy [31,32]; this latter benefit, however, may not be translatable in the setting of adhesive CP. In a Dutch series of 401 consecutive minimally invasive DP, 25% were performed robotically, and similar to the effect seen in RPD, outcomes remained consistent as surgeons progressed further beyond their learning curve despite expansion of indications and relaxed patient selection [16]. Splenic preservation, performed in 27% of patients, also reduced operative time and eliminated conversion to open in this study, which notably did not include any patients with CP [16]. Contemporary series of high-volume surgeons performing this operation in the setting of CP are thus needed to better characterize outcomes in this patient population.

Drainage Procedures

Lateral Pancreaticojejunostomy (Puestow)

The conventional open lateral pancreaticojejunostomy (LPJ) can be associated with high morbidity rates of up to 25% and mortality <5% [20]. Limited case reports of laparoscopic LPJ have shown it to be feasible, safe, and effective [20,22]. In 2014, Khaled et al. described five laparoscopic LPJ for CP with a median operative time of 278 minutes and EBL of 150 mL with no mortality and 5-day LOS. At a follow-up of 14 months, four out of the five patients were pain-free [22]. These results are comparable to a recent literature review of 37 laparoscopic LPJ that reports a mean operative time of 218 minutes, 0% mortality, and mean 5.5 day LOS. There was a 13.5% rate of open conversion and 13.5% complication rate. Importantly, at variable rates of follow-up between 5 and 84 months, 89% of patients were pain-free [20].

The first case report of a robotic-assisted LPJ in a 14-year-old child with idiopathic CP was reported in 2011. Operative time and LOS were 390 minutes and 8 days, respectively, with the patient remaining asymptomatic and pain-free at 2 years postoperatively [21]. Subsequently two new cases with satisfactory outcomes have been reported including a video demonstrating one group's approach to robotic-assisted LPJ [33,34]. These cases highlight the potential for high-volume centers to safely expand minimally invasive, and particularly robotic approaches to traditionally open interventions for CP as surgeon comfort with minimally invasive techniques increases.

Cyst Gastrostomy

Complications of pancreatitis such as pseudocyst, walled-off necrosis (WON), and infected WON are increasingly being managed by minimally invasive techniques. Although WON historically has been treated with open cyst gastrostomy (or cyst jejunostomy if the WON is not retrogastric in location) and necrosectomy, the associated operative morbidity of this approach has spawned the application of endoscopic and minimally invasive surgical alternatives (Fig. 67.3) [24,26].

Deciding between an endoscopic versus minimally invasive approach to cyst gastrostomy and necrosectomy should take several factors into consideration. Endoscopic

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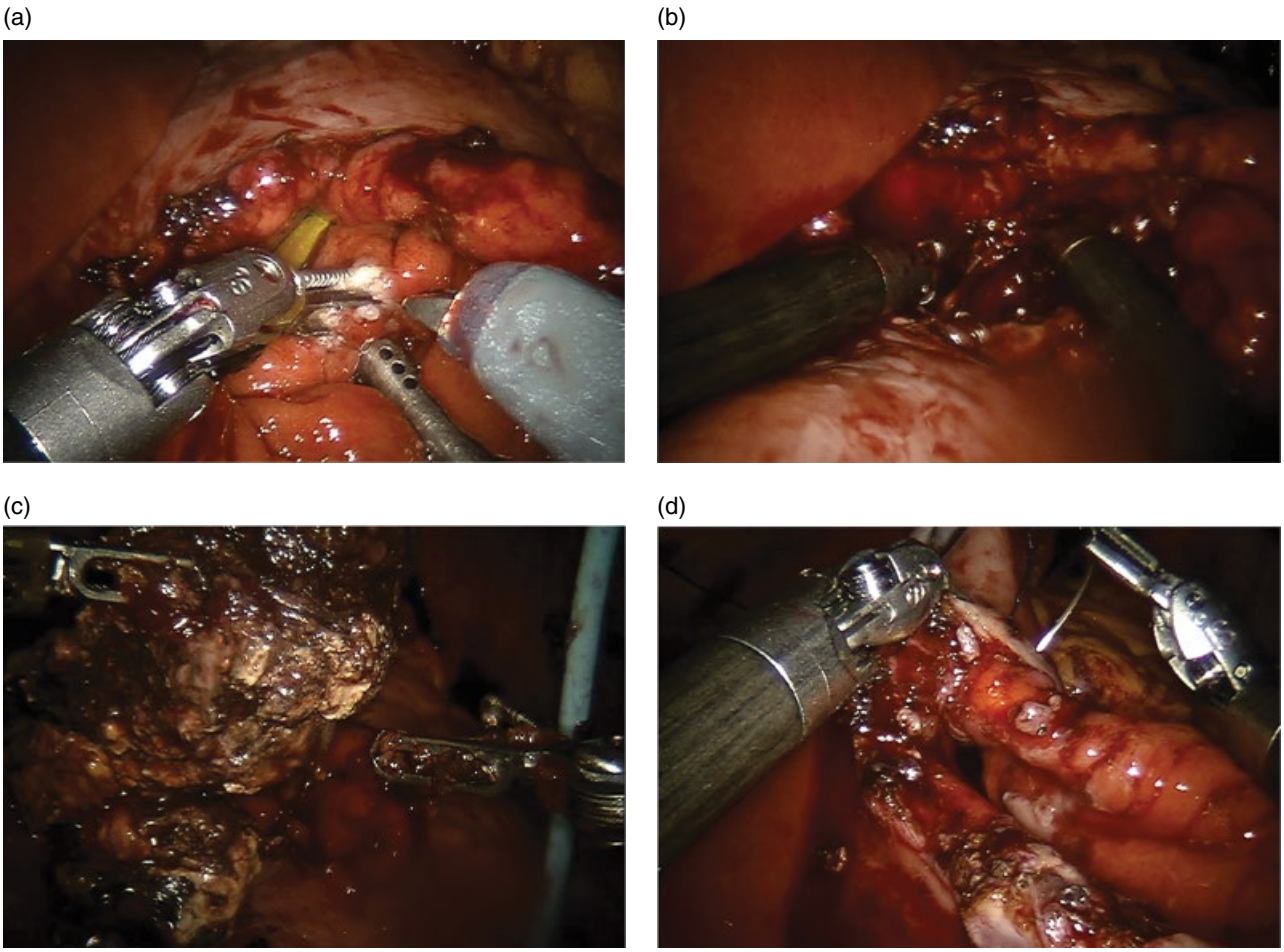


Figure 67.3 Robotic-assisted laparoscopic cyst gastrostomy. (a) Anterior cyst gastrostomy. (b) Posterior cyst gastrostomy. (c) Pancreatic debridement. (d) Gastrostomy closure.

and laparoscopic cyst gastrostomy have been shown to have comparable mortality and morbidity, but the reintervention rate is usually higher using the endoscopic route [26]. Khreiss et al. compared 20 patients with sterile WON undergoing minimally invasive surgical drainage with 20 patients undergoing endoscopic drainage. In the laparoscopic group, the median operating room time was 167 minutes with 30 mL EBL. There were no open conversions, reoperations, or periprocedural mortality, and both groups had equal complication rates (20%). Forty-five percent of the endoscopic patients, however, required reintervention for residual WON, compared to 15% in the minimally invasive surgical group. Despite a shorter LOS in the endoscopic group (2 days vs. 7 days), surgical patients had a faster time to resolution (mean 0.42 months vs. 3.6 months). The authors concluded that minimally invasive cystgastrostomy and debridement for WON can be advantageous, especially if a concomitant cholecystectomy is needed at the time of the WON drainage. A similar retrospective review of 21 patients with pancreatic necrosis (14/21 with sterile necrosis) by Worhunsky et al. reported that 19 of 21 patients (90%) were successfully debrided in a single operation without requiring additional interventions [25]. Recently, robotic cyst jejunostomy with RNY reconstruction has been reported for resolution of two simultaneous, complex WON with operative time of 180 minutes, EBL of 25 mL, and 7-day LOS [23]. Again, although reports are still rare, high-volume surgeons at centers routinely performing minimally invasive pancreatic surgery are able to safely translate these new approaches to classic operations for the management of CP.

Video-Assisted Laparoscopic Retroperitoneal Debridement

Video-assisted retroperitoneal debridement (VARD) is a minimally invasive technique that allows debridement of WON via a retroperitoneal route. The presence of a retroperitoneal drain—especially on the left side—is a

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requirement for a VARD procedure, since it provides a direct unimpeded route to the necrosum, thereby avoiding associated peritoneal inflammation and adhesions. Briefly, the procedure entails placing a laparoscopic port into the retroperitoneal cavity with the guidance of a percutaneous drain. Irrigation, suction, and direct debridement are gently conducted under direct visualization. A large sump drain is left in the cavity at the conclusion of the operation. Postoperatively, scheduled lavage using normal saline or dilute hydrogen peroxide is repeated until the effluent is clear.

Horvath et al. analyzed 40 patients with pancreatic necrosis across six tertiary care centers; 9 of whom were treated with drains alone, 25 with VARD, and 6 with planned open surgery [27]. Patients already treated with a percutaneous drain were enrolled, and received an additional retroperitoneal drain (within 48 hours of enrollment) that was upsized every 3–4 days until a 20-F catheter was reached. Patients underwent a computed tomography (CT) scan on postdrain day 10–14; those exhibiting >75% reductions in collection size were treated with drains alone. Out of 25 patients requiring VARD, 10 (40%) required an open conversion and 19% required a second VARD. The most common cause of open conversion was a centromedial collection with extension into the mesenteric root that was not accessible from the flank. The mean operative time was 135 minutes. There were four (16%) primary VARD-related complications including bleeding and enteric fistula, and nine secondary complications (pneumonia, deep vein thrombosis, respiratory failure, bacteremia, pseudocyst, pancreatic fistula). The median LOS was 64 days, and there were no 30-day mortalities, though there was one death (4%) between 3–6 months following discharge.

Overall, low reported rates of morbidity and mortality for VARD compare favorably to open necrosectomy. As 23% of 40 patients in the Horvath study were successfully treated with percutaneous drainage alone, and in accordance with the "step-up approach," it is reasonable to begin with percutaneous or endoscopic drainage [27,32]. Of note, 75% size reduction of the necrotic collection at 10–14 days on CT scan in the Horvath study predicted success of percutaneous drains alone with 100% accuracy [27]. If patients fail to progress clinically, treatment may be escalated to additional drains, or a VARD.

Combination Procedures (Resection and Drainage)

Frey Procedure

The surgical tenets of the minimally invasive Frey procedure are closely modeled after the open technique, as depicted in Fig. 67.4. Data from Europe and the United

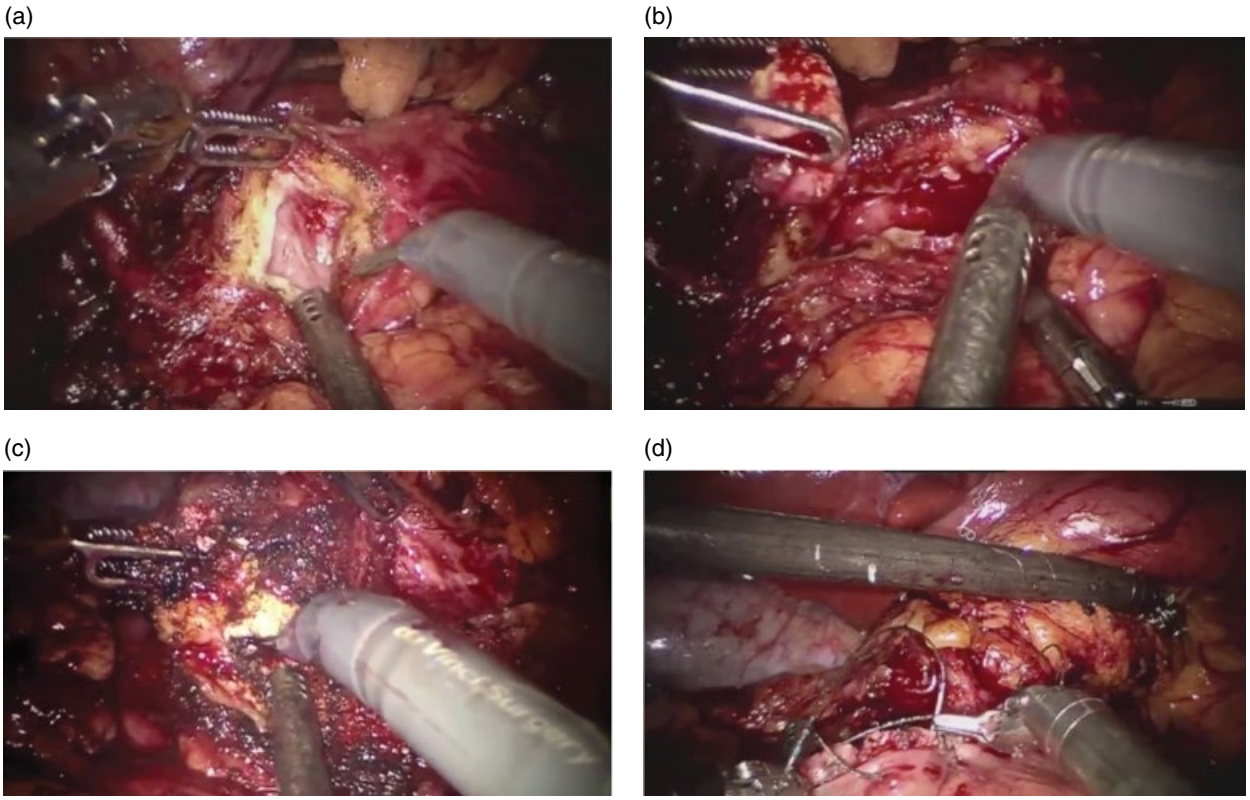


Figure 67.4 Robotic-assisted Frey procedure. (a) Opening of pancreatic duct. (b) Removal of pancreatic duct stones. (c) Enucleation of pancreatic head. (d) Lateral pancreaticojejunostomy.

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States on outcomes following laparoscopic Frey procedure for CP are limited and exclusively comprise case reports [29].

A single-institution experience in China described 9 laparoscopic and 37 open Frey procedures for CP [30]. In two (22%) laparoscopic cases, open conversion was necessary due to inability to locate the pancreatic duct. In the seven laparoscopic completions, mean operating room time was 323 minutes with 57 mL of blood loss. There was one postoperative complication of post-pancreatectomy hemorrhage, with no mortality. Average LOS was 7 days. At 3-month follow-up, all seven patients had significantly decreased visual analog scale (VAS) scores for pain. Outcomes were comparable to the open cohort. The authors recommended a minimum pancreatic duct width of >8 mm for successful laparoscopic intervention.

Beger Procedure

Available data on the minimally invasive Beger procedure is scarce. A case report of a laparoscopic Beger procedure with "Berne modification" in a patient with an inflammatory head mass causing an intrapancreatic common bile duct stricture documented an operative time of 285 minutes [22]. The patient was discharged after 5 days without complications and at 16-month follow-up reported mild pain, controlled with one-third of the preoperative oral opioid dose.

Conclusion

Although the data for minimally invasive approaches for chronic pancreatitis continues to be limited to small retrospective studies and case reports, there is sufficient evidence from mixed indication studies to demonstrate that laparoscopic and robotic interventions for the pancreas are safe and feasible in highly specialized centers. Analogous to the open approach, a myriad of resection-, drainage-, and combination-type procedures can be performed for CP and surgeon comfort and expertise rather than patient factors should determine the appropriate role for minimally invasive approaches. Nevertheless, further comparative studies on the efficacy of these approaches and their impact on quality of life for patients with CP are needed. The data for malignant indications as it currently stands is promising and points to increasing uptake of the robotic approach.

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Section 5

Autoimmune Pancreatitis

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Epidemiology of Autoimmune Pancreatitis

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Introduction

There are two histologic types of autoimmune pancreatitis (AIP): (i) lymphoplasmacytic sclerosing pancreatitis (LPSP), which is called type 1 AIP; and (ii) idiopathic duct-centric pancreatitis (IDCP), which is called type 2. Type 1 AIP is recognized as a pancreatic manifestation of IgG4-related disease [1,2].

Since 2002, several diagnostic criteria for AIP have been identified worldwide, and international consensus diagnostic criteria (ICDC) have been developed to incorporate the diagnostic strategies used in the different criteria [3].

Four nationwide epidemiologic surveys of AIP have been conducted in Japan [4–7], as well as three international multicenter surveys [8–10]. In this chapter, the epidemiology of AIP is described based on the findings of these surveys.

Nationwide Surveys of Autoimmune Pancreatitis in Japan

The first nationwide survey in Japan analyzed patients who visited selected hospitals during 2002 [4], the second survey was conducted in 2007 [5], and the third survey was conducted in 2011 [6]. The estimated total number of AIP patients was 1700 in 2002, 2790 in 2007, and 5745 in 2011. The rapid increase in the number of AIP patients might be explained by increased recognition of the AIP concept and development of diagnostic criteria in Japan.

The fourth nationwide survey was conducted in 2016 according to the Japanese diagnostic criteria 2011 [11]. The estimated number of AIP patients was 13,436, with an overall prevalence rate of 10.1 per 100,000 population. The number of newly diagnosed AIP patients was estimated to be 3984, with an annual incidence rate of 3.1 per 100,000 population. The male to female ratio was 2.94, and the patients' mean age was 68.1 years. At diagnosis, 63% patients were asymptomatic and nearly half presented with jaundice. Among the 1449 patients, 84.5% presented with high serum IgG4 levels (≥135 mg/dL), and serum IgG4 levels were significantly higher in patients who developed extrapancreatic lesions (612.2 ± 577.0 mg/dL) than in those who did not (406.4 ± 405.4 mg/dL) ($P < 0.01$). Nearly 50% of patients showed localized enlargement of the pancreas. Pancreatic cysts were found in 9% and calcifications in 6%. Pancreatic tissues were obtained in 64%, and tissue samples were obtained mainly by endoscopic ultrasound-guided fine-needle aspiration. Extrapancreatic lesions were detected in 873/1456 (60%) patients as follows: 357 intrapancreatic sclerosing cholangitis, 291 sialadenitis/dacryoadenitis, 149 retroperitoneal fibrosis, 113 hilar sclerosing cholangitis, and others. Steroid treatment was given to 84%, and it was effective in 98.6%. The most common daily prednisolone dose was 30 mg (64%). Maintenance steroid treatment was given in 85% and the relapse rate was 23.4%. The mortality rate was favorable, but malignant tumors were detected in 242 (16%) patients including 18 patients with pancreatic cancer. Pancreatic cancer accounted for death in one-quarter of fetal cases.

First International Survey of Autoimmune Pancreatitis

The first international multicenter survey of AIP was carried out in 2009 and involved 10 centers in 5 Asian countries (Japan, Korea, Taiwan, China, and India) [8].

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A total of 327 AIP patients (258 males, 69 females; average age 60.0 years) diagnosed according to the Asian diagnostic criteria [12] were enrolled.

The most common initial symptom was obstructive jaundice, followed by weight loss and abdominal pain. Diffuse swelling of the pancreas was frequent in Japan (64%) and Korea (81%), but segmental swelling of the pancreas was more frequent in Taiwan (70%) and China (72%) ($P < 0.01$). Increased serum IgG4 levels were seen in 58–100% of patients in Japan, Korea, and Taiwan. Pathologically, almost all AIP patients in Asia were diagnosed as LPSP. Steroid therapy was the major and effective therapeutic strategy, but the rate of resection or bypass operation was higher in Taiwan and China ($P < 0.01$).

Japan, Korea, Taiwan, and China are geographically adjacent, and their populations appear to share a common genetic background. The features of AIP patients were fundamentally similar and most of them were type 1 AIP in these countries. Differences in the clinical and pathophysiologic characteristics of AIP in these areas might be due to differences in the rates of recognition of this disease.

Second International Survey of Autoimmune Pancreatitis

The second international multicenter survey of AIP in 2010 involved 15 institutes in 8 countries (Japan, Korea, Taiwan, India, the United States, Germany, Italy, and the United Kingdom) [9]. A total of 731 AIP patients were enrolled, with 204 cases confirmed histologically as LPSP and 64 cases confirmed as IDCP. The AIP patients were diagnosed according to various diagnostic criteria.

LPSP patients were approximately 16 years older than IDCP patients (61.6 years vs. 44.8 years). No sex difference was observed between the two groups. Obstructive jaundice was a more frequent presentation in LPSP than in IDCP (75% vs. 47%, $P < 0.01$), whereas abdominal pain (41% vs. 68%, $P < 0.01$) and acute pancreatitis (5% vs. 34%, $P < 0.01$) were more frequent presentations in IDCP patients. Compared to IDCP patients, LPSP patients were more likely to have diffuse pancreatic swellings (40% vs. 25%, $P < 0.05$), increased serum IgG4 levels (63% vs. 23%, $P < 0.01$), retroperitoneal fibrosis (7% vs. 0%, $P < 0.05$), and salivary gland swelling (12% vs. 0%, $P < 0.01$), but they were less likely to have ulcerative colitis (1% vs. 16%, $P < 0.01$). IDCP patients more frequently underwent surgery (60% vs. 78%, $P = 0.01$). Good therapeutic responses to steroid treatment were seen in both groups, but IDCP patients had a significantly lower relapse rate (36% vs. 5%, $P < 0.01$).

In nonhistologically confirmed AIP patients, the most common initial symptom was obstructive jaundice in six countries, but it was less frequent in Italy (44%) and Germany (13%). Abdominal pain was the most frequent initial symptom in India (86%) and Germany (63%). Acute pancreatitis was seen frequently in Germany (66%) and Italy (32%). Increased serum IgG4 levels were detected in 85–100% of AIP patients in Japan, Taiwan, India, and the United States, but only in 50–61% in other countries. Italian AIP patients frequently had ulcerative colitis (30%). Steroids were given in 69–100% of AIP patients. The initial prednisolone dose was 1 mg/kg/day in three countries, 0.6 mg/kg/day in two countries, and 30–40 mg/day in the remaining three countries. This dose was tapered by 5 mg every 1–2 weeks. The time from initiation to cessation of steroid therapy ranged from 3 months to 2 years. All patients showed good responses to steroid treatment. The relapse rate in steroid-treated patients ranged from 15% to 64% (Table 68.1).

The clinical profiles of patients in six countries were similar to those of LPSP patients. However, Italian and German AIP patients had different clinical profiles, which appeared to include a mixture of LPSP and IDCP.

Third International Survey of Autoimmune Pancreatitis

The third international multicenter survey of AIP in 2012 involved 23 institutes in 10 countries (Japan, Korea, Taiwan, the United States, Germany, Italy, the United Kingdom, Hungary, Sweden, and France) [10]. The patients were diagnosed using the ICDC [3], and the survey focused on long-term outcomes, including organ involvement, treatments, relapse frequency, and long-term sequelae.

A total of 1064 patients who met the ICDC [3] for type 1 ($n = 978$) or type 2 ($n = 86$) were included. Average ages of type 1 and type 2 patients were 61.4 and 39.9 years, respectively. The proportion of males was 77% among type 1 patients and 55% among type 2 patients ($P < 0.01$). The proportion of patients diagnosed with type 2 AIP was lower in Asian countries (3.7%) than in both Europe (12.9%, $P < 0.01$) and North America (13.7%, $P < 0.01$) (Fig. 68.1).

In type 1 patients, jaundice was the most common indication (63%), followed by abdominal pain, but in type 2 AIP, it was abdominal pain and inflammatory bowel disease. The majority (74%) of type 1 patients were treated initially with steroids, while only 62% of type 2 patients were treated with steroids ($P = 0.01$).

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Table 68.1 Clinical, radiologic, and serologic features of nonhistologically confirmed AIP patients in the second international survey.

Country	Japan	Korea	Taiwan	India	USA	Germany	Italy	UK
Number of pts	127	86	33	36	28	38	87	28
Average age, years	64.7	59.0	66.4	NA	64.1	45.5	43.4	57.6
Gender (% male)	106 (83%)	61 (71%)	29 (90%)	25 (69%)	22 (79%)	17 (45%)	54 (62%)	23 (82%)
Initial symptom								
Jaundice	77 (61%)	43 (50%)	23 (70%)	20 (56%)	22 (79%)	5 (13%)	38 (44%)	18 (64%)
Abdominal pain	16 (13%)	20 (23%)	6 (18%)	31 (86%)	14 (50%)	24 (63%)	17 (20%)	5 (18%)
Acute pancreatitis	3 (2%)	11 (13%)	6 (18%)	8 (22%)	7 (25%)	25 (66%)	28 (32%)	0
Diffuse pancreatic swelling	74 (58%)	73 (85%)	13 (39%)	15 (41%)	16 (57%)	18 (47%)	32 (37%)	5 (18%)
Elevation of serum IgG4	102/112 (91%)	32/62 (52%)	28/28 (100%)	36/36 (100%)	22/26 (85%)	19/31 (61%)	28/56 (50%)	15/28 (54%)
OOI								
Total involvement	80 (63%)	35 (41%)	(33%)	11 (31%)	21 (75%)	17 (44%)	13 (15%)	23 (82%)
Proximal bile duct	13 (10%)	9 (10%)	(25%)	7 (19%)	13 (46%)	10 (26%)	rare	22 (79%)
Renal lesions	11 (9%)	9 (10%)	(4%)	0	7 (25%)	0	2 (2%)	5 (18%)
Retroperitoneal fib.	5 (4%)	14 (16%)	(4%)	2 (6%)	4 (14%)	0	2 (2%)	2 (7%)
Salivary/lacrimal	27 (21%)	7 (8%)	(17%)	1 (3%)	2 (7%)	1 (3%)	4 (5%)	3 (11%)
Extensive LN	27 (21%)	6 (7%)	(17%)	1 (3%)	2 (7%)	0	NA	5 (8%)
Ulcerative colitis	4 (3%)	3 (3%)	0	2 (6%)	3 (11%)	0	26 (30%)	4 (14%)
Initial therapy								
Steroid	84%	85%	100%	100%	89%	71%	69%	93%
Response rate	100%	100%	100%	100%	100%	100%	100%	100%
Relapse rate	15%	26%	18%	25%	64%	15%	37%	54%

NA: not available; OOI: other organ involvement.

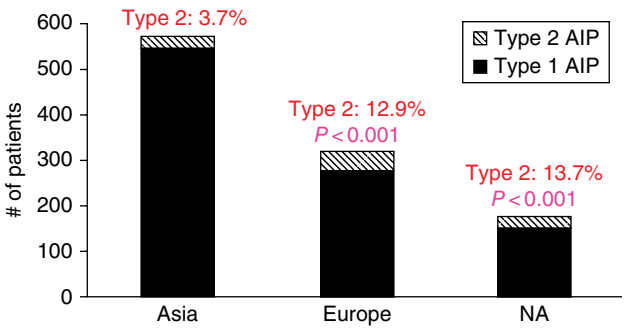


Figure 68.1 Regional distribution of type 1 and 2 AIP based on the country of diagnosis. *Source:* [10] / BMJ Publishing / CC BY.

Almost all patients with type 1 and 2 AIP achieved remission. A total of 302 (31%) type 1 patients experienced at least one disease relapse, compared to 8 (9%, $P < 0.01$) of type 2 patients. Most relapses occurred in the biliary system or pancreas for type 1 patients, while relapses in type 2 patients were limited to the pancreas. Several relapses occurred in type 1 AIP, but only one in type 2 AIP (Table 68.2). Steroid retreatment remained effective for inducing remission with or without alternative treatment, such as azathioprine.

Conclusions

With increased recognition of the AIP concept and development of diagnostic criteria, the number of AIP patients has rapidly increased in Japan. The estimated number of AIP patients in the recent nationwide survey in Japan was 13,436, with an overall prevalence rate of 10.1 per 100,000 population.

International surveys of AIP showed the regional and ethnic differences in the pathologic and clinical features of AIP as well as the quite different profiles of type 1 and type 2 AIP patients. To improve our understanding of this disease, further multinational collaborations are required.

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Table 68.2 Initial treatment strategies and relapse in type 1 and type 2 AIP patients in the third international survey.

	Type 1 AIP (*n* = 901)		Type 2 AIP (*n* = 85)	
Initial treatment:	**Successful remission**	**Relapse rate**	**Successful remission**	**Relapse rate**
Steroids	681/684 (99.6%)	35.8%	48/52 (92.3%)	15.3%
Surgical resection	125/127 (98.4%)	30.2%	17/25 (68.0%)	0%
Palliative surgical bypass	22/23 (95.7%)		1/2 (50.0%)	
Conservative	37/67 (55.2%)		4/6 (66.7%)	

	Type 1 AIP (*n* = 724)	Type 2 AIP (*n* = 53)	*P* value
Indications for steroid treatment:	***n***	***n***	
Jaundice	458 (63%)	13 (25%)	**<0.01**
Pancreatitis/abdominal pain	198 (27%)	34 (64%)	**<0.01**
Inflammatory bowel disease	1 (0.1%)	23 (48%)	**<0.01**
Location of relapse following steroid treatment:	***n* = 245 episodes**	***n* = 8 episodes**	
Biliary system	124 (50.6%)	–	
Pancreas	107 (42.9%)	8	
Salivary	18 (7.3%)	–	
Frequency of relapse per subject:			
1 relapse	189 (77.1%)	8	
2 relapses	39 (15.9%)	–	
3 relapses	13 (5.3%)	–	
≥4 relapses	4 (1.6%)	–	

Source: Adapted from Hart et al. 2012 [10]. Reproduced with permission of BMJ Publishing.

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Molecular Immunology and Pathogenesis of Autoimmune Pancreatitis

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Introduction

Similar to many other immune-mediated conditions, a likely pathogenetic mechanism for autoimmune pancreatitis (AIP) is the exposure of genetically susceptible individuals to environmental or intrinsic factors that results in orchestral immune reactions. Among the two distinct subtypes of AIP, type 1 has been the main target of pathogenetic studies [1]. Therefore, this chapter focuses on the prototypic type of AIP. Although the molecular features of type 2 AIP are currently unclear, recently obtained findings on the less common form of AIP are also briefly introduced in the last section.

Type 1 Autoimmune Pancreatitis

Genetic Predisposition

The strongest genetic risk is related to human leukocyte antigens (HLA), with the subtypes DRB1*0405 and DQB1*0401 known to increase the susceptibility of Japanese populations to type 1 AIP [2]. The absence of aspartic acid at HLA DQβ1 57 has also been correlated with disease relapse in Koreans [3]. A genome-wide association study of 835 Japanese patients with IgG4-related disease (IgG4-RD) identified *HLA-DRB1* and *FCGR2B* regions as susceptibility loci [4]. Rs1340976 in *FCGR2B* showed an association with increased FCGR2B expression, the number of involved organs in diagnosis, and high serum IgG4 concentrations [4]. Other potential disease-susceptible genes encode cytotoxic T lymphocyte-associated protein 4 (*CTLA4*), tumor necrosis factor-α (*TNFA*), Fc receptor-like protein 3 (*FCRL3*), and cationic trypsinogen (*PRSS1*) [5–8].

Parallel Immune Response

Two parallel immunological responses are suspected to underlie the pathophysiology of type 1 AIP; one is a proinflammatory, tissue-destructive process characterized by the expansion of particular subsets of lymphocytes, while the other is an anti-inflammatory feedback response (Fig. 69.1) [9].

Autoantigen

The proinflammatory process is supposedly triggered by autoantibodies against autoantigens. Recent nonbiased global analyses identified annexin A11, laminin 511-E8, galectin-3, and prohibitin as potential autoantigens in type 1 AIP and IgG4-RD [10–13]. Other possible autoantigens identified by earlier targeted studies include carbonic anhydrase II, lactoferrin, pancreatic secretory trypsin inhibitor, and trypsinogens PRSS1 and PRSS2 [14,15].

T cells

Among the T-cell subsets, T helper 2 (Th2) cells and regulatory T cells (Tregs) are activated in this condition, with the Th1/Th2 balance shifting in favor of Th2 [16,17]. However, the Th1 reaction is not fully suppressed [18]. The expression of IFN-γ in the tissues of type 1 AIP is similar to that in those of primary sclerosing cholangitis and primary biliary cholangitis, while the expression of Th2 cytokines (e.g., IL-4, IL-5, IL-13, and IL-21) is markedly stronger in type 1 AIP, with a large number of IL-4+ lymphocytes infiltrating the pancreas [16]. The proportions of Tregs are also increased in both tissue-infiltrating lymphocytes and peripheral blood mononuclear cells [16,19].

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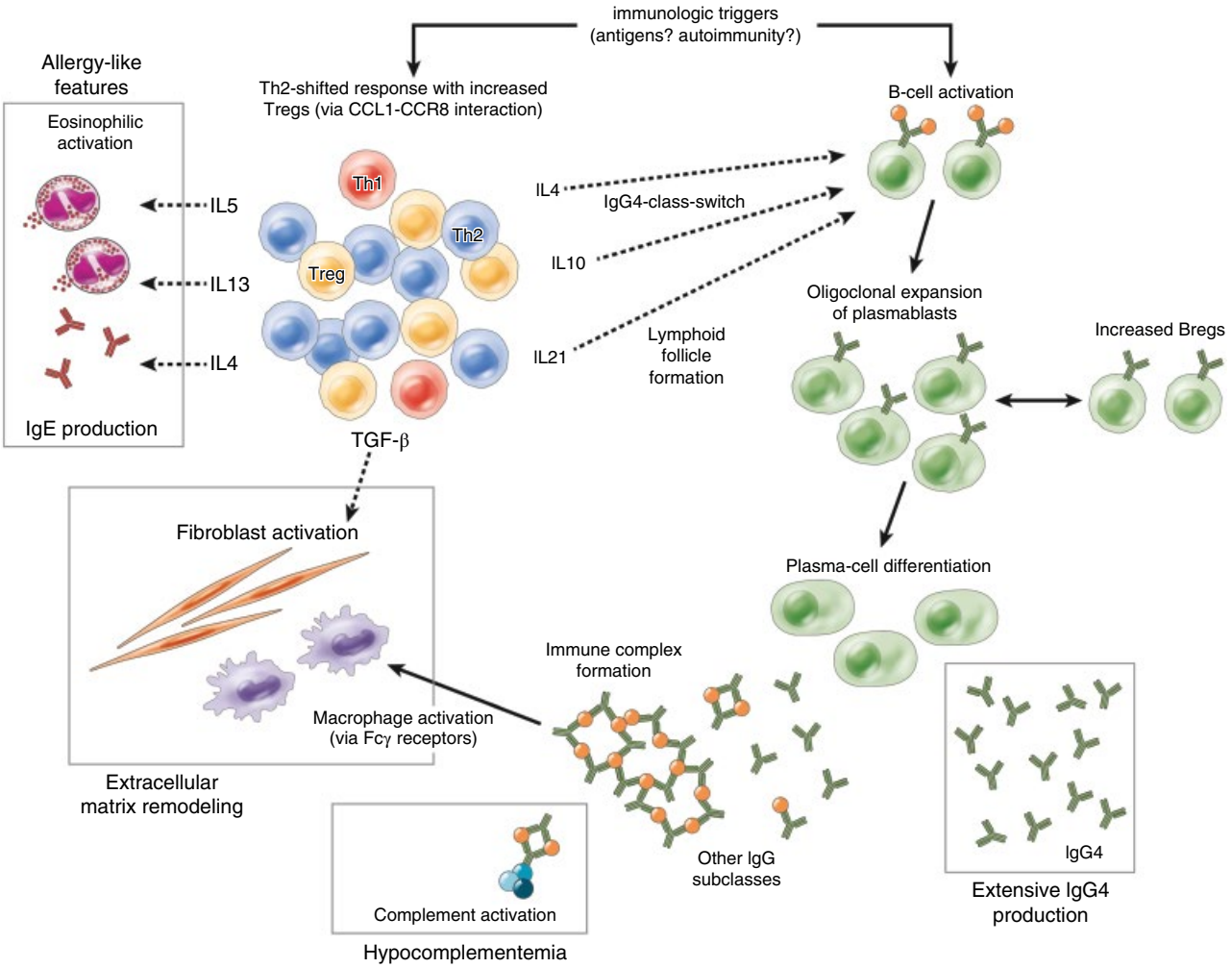


Figure 69.1 Proposed immunologic interactions in type 1 AIP. *Source:* Adapted from [9].

A T-cell subset involved in maturation and class-switching of B cells in germinal centers is known as T follicular helper (Tfh) cells. In IgG4-related disease, Tfh type 2 (Tfh2) cells are particularly expanded with the circulating Tfh2 cell counts positively correlated with the number of affected organs, disease activity, and serum IgG4 concentrations [20,21]. An *in vitro* study demonstrated that B cells co-cultured with patient-derived Tfh cells produce IgG4 [20]. Corticosteroid therapy decreases serum concentrations of IgG4 and IL-4, but does not affect the total number of circulating Tfh2 cells, which may initiate immune reactions at the time of relapse [20].

The potential involvement of CD4+ cytotoxic T lymphocytes (CTL) in IgG4-RD has been examined mainly in extrapancreatic organs. CD4+ CTL express granzyme A, IFN-γ, IL-1β, and TGF-β1. Next-generation sequencing of the T-cell receptor β chain gene revealed prominent clonal expansions of CD4+ CTL but not CD4+ memory Th2 cells in patients with IgG4-RD [22]. Infiltration of CD4+ CTL was also demonstrated by multi-color immunohistochemistry [23]. The ratio of CD4+ CTL among infiltrating lymphocytes in IgG4-RD is higher than that in other conditions; the ratio is also correlated with serum IgG4 concentrations and the number of affected organs. Another tissue study revealed that an increased number of HLA-DR-positive mesenchymal cells undergo apoptotic cell death in IgG4-RD [24]. Taken together, the expanded CTL may target the mesenchymal cells, leading to fibrosis and tissue remodeling.

Cytokines and Chemokines

Various types of cytokines are known to be expressed in type 1 AIP and IgG4-RD. Th2 cytokines such as IL-4, IL-5, and IL-13 supposedly contribute to tissue or serum

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eosinophilia and elevated serum IgE levels, which are sometimes observed in patients with type 1 AIP [25,26]. IL-10, a cytokine produced by Tregs or macrophages, is also strongly expressed in type 1 AIP (Fig. 69.2) [16,17]. The combination of IL-4 and IL-10 may be relevant to the production of IgG4 because IL-4 induces the production of IgE and IgG4 from B cells and plasma cells, while IL-10 in addition to IL-4 suppresses the production of IgE, but selectively enhances that of IgG4 [27]. IL-21 is supposed to promote the interaction between B cells and Tfh2 cells at germinal centres [28]. TGF-β, another regulatory cytokine, may play a central role in the fibrosing process of type 1 AIP.

The CCL1–CCR8 interaction appears to be crucial for the recruitment of Th2 cells and Tregs because 50% of Th2 lymphocytes and 60% of FOXP3+ Tregs express CCR8 [29]. CCL1 is expressed in the duct epithelium and endothelial cells, including those involved in obliterative phlebitis, in type 1 AIP [30]. CCL1+ sites are infiltrated by CCR8+ lymphocytes (Fig. 69.2). The CCL1–CCR8 interaction may create a microenvironment in which Th2 cells and Tregs are abundant, leading to the IgG4 class switch through IL-4 and IL-10. This immunologic reaction is also probably responsible for the characteristic histologic changes observed in type 1 AIP such as periductal inflammation and obliterative phlebitis.

B Cells

B-cell depletion therapy with anti-CD20 antibodies is effective for type 1 AIP, which highlights the crucial involvement of B cells in its pathogenesis [31]. The proportion of circulating plasmablasts increases in type 1 AIP, and decreases rapidly upon treatment. Expanded plasmablasts are mainly of the IgG4 type and oligoclonal in nature, with dominant clones varying among

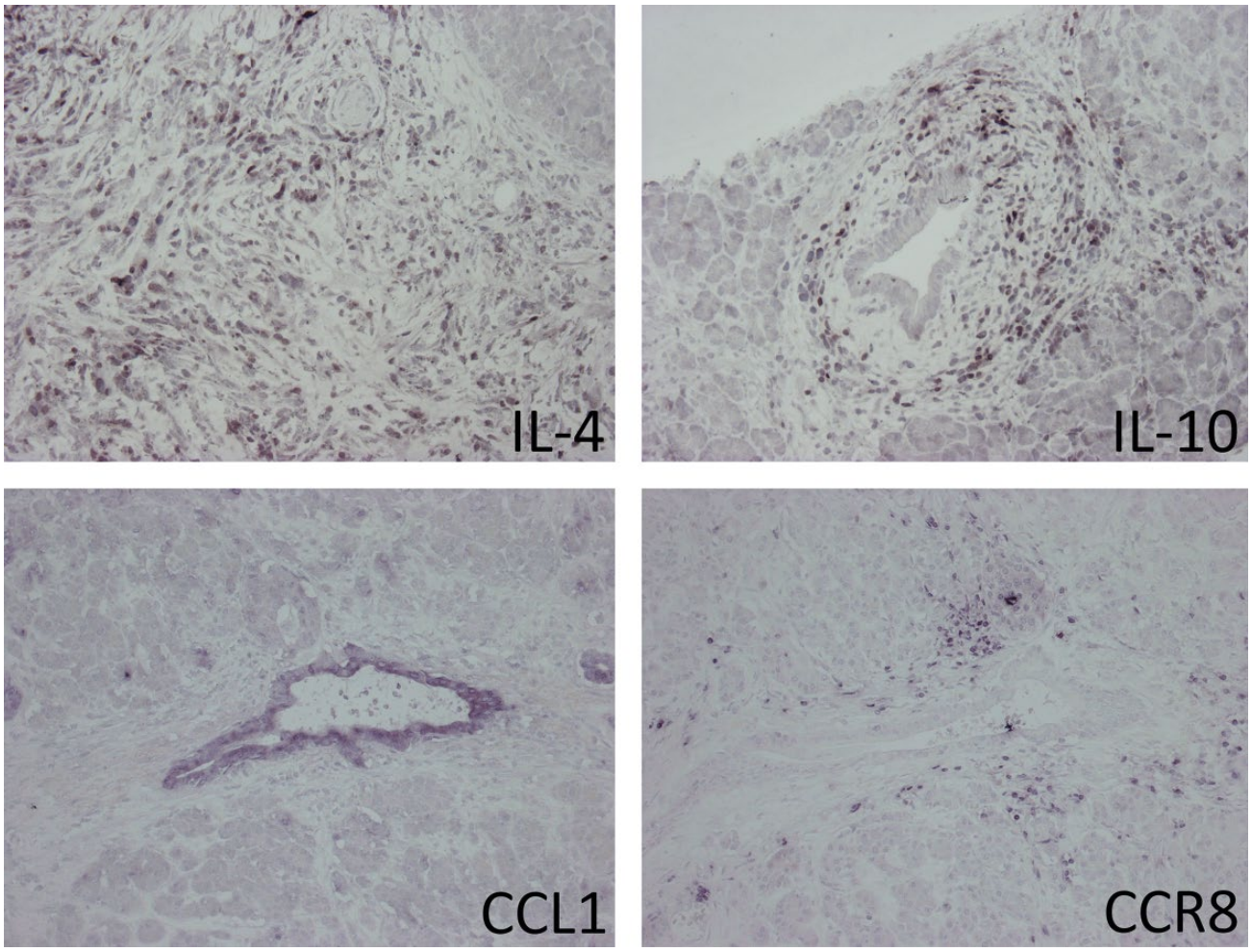


Figure 69.2 Immunologic factors expressed in type 1 AIP (*in situ* hybridization). Lymphocytes expressing IL-4 or IL-10 are observed. The pancreatic duct positive for CCL1 is surrounded by CCR8+ lymphocytes. *Sources:* (Upper panels) Zen et al. (2013) / Reproduced with permission of Elsevier. (Lower panels).

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patients [32]. Similarly, tissue-resident and circulating IgG4-switched B cells in type 1 AIP are oligoclonal [33].

Role of IgG4

IgG4 generally has an anti-inflammatory property because of its relative inability to fix complement and its poor capacity to bind to Fc receptors [34]. This minor IgG subclass also has the unique ability to exchange a pair of heavy and light chains (the "Fab-arm exchange") [35]. This immunologic process causes IgG4 molecules to lose their antigen cross-linking ability, behave as monovalent antibodies, and become incapable of forming large immune complexes. Based on these anti-inflammatory characters of IgG4 molecules, the disease may be driven by other immunoglobulin subclasses, while IgG4 is secondarily induced in order to suppress inflammatory reactions in type 1 AIP.

A similar discussion will also be applied to hypocomplementemia, which is observed in ~40% of patients, particularly those with renal involvement [36]. Among the three complement activation systems, the classical pathway is predominantly activated in type 1 AIP. Since IgG4 cannot efficiently activate the classical pathway, complement fixation may be activated by other IgG subclasses, particularly IgG1, which fix complements more efficiently.

In a recent study, circulating IgG1 and IgG4 isolated from patients with type 1 AIP were subcutaneously injected into neonatal mice aiming to demonstrate the tissue reactivity of patient-derived immunoglobulins [37]. Injection of either IgG1 or IgG4 led to pancreatic injury with histologic evidence of stromal edema, acinar necrosis, hemorrhage, and the infiltration of polymorphonuclear leukocytes. The degree of tissue damage was higher with IgG1. Interestingly, the tissue injury led by IgG1 was suppressed by the simultaneous injection of patient-derived IgG4. It is the first objective finding indicating that IgG4 may behave in an anti-inflammatory manner in type 1 AIP [37].

Fibrosis

Fibrosis is persistently observed across the early and late phases of type 1 AIP. A characteristic pattern of fibrosis in type 1 AIP is referred to as storiform fibrosis. A unique feature of storiform fibrosis is the presence of abundant M2-type macrophages among collagen fibres. The number of myofibroblasts highlighted by immunohistochemistry is smaller in storiform fibrosis than in nonspecific granulation tissue or scarring fibrosis [38]. Therefore, storiform fibrosis represents a macrophage-rich, fibroblast-poor tissue reaction. This unique composition may explain the dramatic response to corticosteroids despite the fibrotic appearance.

Immune reactions underlying the macrophage induction in type 1 AIP remain unknown. Innate immunity (e.g., toll-like receptor) or cytolines are known to induce various types of macrophages. In addition, interaction between immune complexes and Fc receptors is another potential inducer of macrophages. A robust proteomic study with phosphopeptide enrichment methods identified that the immunologic pathway activated most significantly in type 1 AIP compared to primary sclerosing cholangitis is Fc-γ receptor-mediated phagocytosis [39]. This signal cascade occurring inside macrophages is initiated by the interaction between IgG molecules and Fc-γ receptors on the cell membrane. Since the capacity of IgG4 to bind to Fc receptors is poor [34], this signal pathway may be activated by IgG subclasses other than IgG4. However, several studies indicated that IgG4 molecules are capable of inducing M2 macrophages [40]. Although fibrosis in chronic inflammatory conditions is generally regarded as a consequence of the proinflammatory process, storiform fibrosis may be induced by IgG4 and therefore potentially represents an anti-inflammatory property in type 1 AIP.

Type 2 Autoimmune Pancreatitis

The rarity of this condition as well as the lack of serologic and immunologic biomarkers has restricted our investigations on the pathogenesis of type 2 AIP. A single potential clue is that one-third of patients have inflammatory bowel disease, particularly ulcerative colitis [41,42].

In our previous study, the immunopathologic features of type 2 AIP were compared with those of type 1 AIP and ulcerative colitis [43]. Quantitative PCR using mRNA extracted from pancreatic tissues revealed the markedly higher expression of IL-8 in type 2 AIP than in type 1 AIP. The expression of other cytokines (e.g., IFN-γ, IL-4, IL-10, and TNF-α) was similar in types 1 and 2 AIP or weaker in type 2 AIP. Immunostaining revealed that IL-8 was mainly expressed in the damaged duct epithelium, infiltrating neutrophils, and lymphocytes, with its expression being particularly strong around injured ducts (Fig. 69.3). This expression pattern of IL-8 was not observed in other forms of pancreatitis. Since IL-8 is a chemotactic factor for neutrophils, its aberrant expression in pancreatic ducts may underlie pathognomonic duct-centered, neutrophil-rich inflammation, known as granulocytic epithelial lesions (GEL), in type 2 AIP [42].

A similar expression pattern of IL-8 was also observed in colonic biopsies of active ulcerative colitis. IL-8 appeared to be aberrantly expressed in the crypt epithelium, particularly at sites of cryptitis and crypt abscesses [43]. The colonic epithelium was largely

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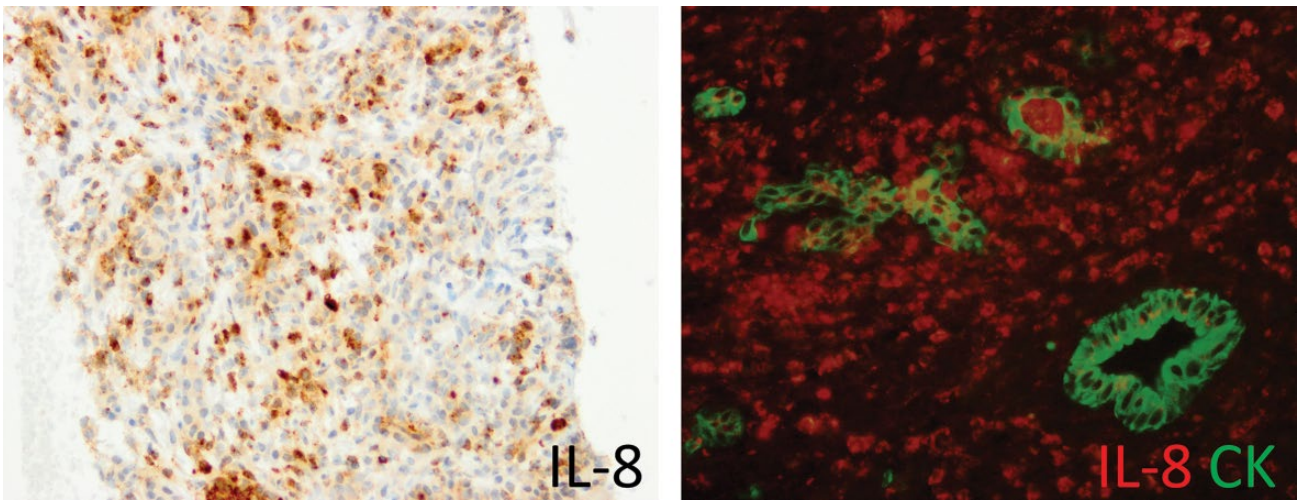


Figure 69.3 IL-8 expression in type 2 AIP. Single immunostaining shows the extensive expression of IL-8 in pancreatic tissue. On double immunostaining, IL-8 (red) appears to be expressed in infiltrating inflammatory cells and pancreatic ducts that are also positive for cytokeratin (CK, green).

negative for this immunologic marker in infectious colitis, another form of neutrophil-rich enteritis. These findings indicate that IL-8 is one of the key molecules involved in the pathogenesis of type 2 AIP, and also suggest a pathogenetic link between type 2 AIP and ulcerative colitis.

The pancreatic duct epithelium in type 2 AIP was also demonstrated to aberrantly express programmed death-ligand 1 (PD-L1) [44]. The positive immunoreactivity was identified in 70% of cases of type 2 AIP, while it was not observed in type 1 AIP or other forms of pancreatitis [44]. This finding was observed in not only damaged ducts but also nonaffected epithelium. Although this unique finding has a diagnostic value, the immunologic significance remains unclear. The expression of PD-L1 did not correlate with the number of immune cells positive for programmed death 1 (PD-1) or CD8 [44].

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70

Clinical Manifestation of Type 1 Autoimmune Pancreatitis

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What Is Autoimmune Pancreatitis?

Autoimmune pancreatitis (AIP) is a type of chronic pancreatic inflammation; its pathogenesis is suspected to involve immune mechanisms [1]. Two subtypes are presumed; one is pathologically defined by lymphoplasmacytic sclerosing pancreatitis (LPSP) [2], and the other by idiopathic duct-centric pancreatitis (IDCP)/granulocytic epithelial lesion (GEL) [3,4]. Considering the clinically distinct features of each type, the Honolulu consensus in 2009, defined the former as type 1 and the latter as type 2 [5]. Since AIP type 1 is characterized by the elevation of serum immunoglobulins, especially IgG4, and by the infiltration of IgG4-positive plasma cells in the pancreas and the various extrapancreatic lesions, this type is regarded as a manifestation of pancreatic involvement in the systemic disorder called "IgG4-related disease (IgG4-RD)," which is characterized by an overproduction of IgG4 due to some sort of immune abnormality [6].

In contrast, as AIP type 2 lacks biomarkers, including immunoglobulins, and shows unique pathologic findings in the pancreas characterized by the infiltration of granulocytes, there is a need for continued discussion on whether or not type 2 is truly caused by an autoimmune mechanism [7]. AIP type 1 corresponds to the concept of autoimmune pancreatitis proposed by Yoshida et al. in 1995 [8], and resembles chronic inflammatory sclerosis of the pancreas introduced by Sarles et al. in 1961 [9]. AIP type 1 is reportedly the dominant type of AIP in East Asia, whereas AIP type 2 is more frequently observed in Western countries [5,10].

The Clinical Features of AIP Types 1 and 2

Herein, I summarize the clinical features of AIP types 1 and 2, which were presented chiefly in the reports published before the third edition of *The Pancreas* [11–19].

Patients Profiles and Symptoms

AIP type 1 tends to develop in elderly male subjects with painless jaundice or mild abdominal pain, but acute pancreatitis is rare or less frequent at the onset compared to AIP type 2. Occasionally, asymptomatic patients are incidentally diagnosed based on characteristic findings on imaging, serology and the presence of extrapancreatic lesions. AIP type 2 presents more frequently with acute pancreatitis in younger populations, with no gender predilection. Obstructive jaundice is seen less frequently in type 2 AIP than in type 1 AIP. Approximately 30–50% of patients with type 1 AIP develop diabetes mellitus (DM) as a complication, but this percentage is lower in type 2 patients.

Imaging

Characteristic imaging findings in AIP types 1 and 2 include enlargement of the pancreas and irregular narrowing of the main pancreatic duct (MPD), which are common features of both types. The pancreas shows diffuse (>2/3 of the entire pancreas), segmental (1/3–2/3), or focal (<1/3) enlargement. Care should be taken when differentiating atypical AIP cases that show mass-like

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lesions, as in cases of focal pancreatic swelling, from pancreatic cancer.

A typical finding on abdominal ultrasound (US) is a diffusely swollen, hypoechoic "sausage-like" pancreas (Fig. 70.1a). Focal swelling or a tumor-like appearance was observed as a homogeneous hypoechoic mass with distinct margins. The characteristic feature of contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) is a delayed enhancement of the pancreas, which denotes gradual enhancement of the pancreatic parenchyma in the late phase on dynamic CT/MRI. A low-density or low-signal intensity peripheral band-shaped structure called "capsule-like rim" is sometimes seen on dynamic CT/MRI, which is considered highly specific to AIP (Fig. 70.1b). The inflammatory lesion in the pancreas showed a strong signal intensity on diffusion-weighted MRI. Positron emission tomography (PET) scans demonstrate the heavy accumulation of ^{18}F-fluorodeoxyglucose in the pancreas in both types of AIP and extrapancreatic lesions in AIP type 1, making it easy to understand the pathological extension.

Endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) showed diffuse, segmental, focal, or occasionally multiple narrowing of the MPD (Fig. 70.2). MPD narrowing in AIP can be differentiated from the short and severe stricture seen in pancreatic cancer by long-segment irregular narrowing in the AIP. In addition, AIP demonstrates slight dilatation of the duct upstream from the narrowed segment, which may help differentiate its duct stricture from that of pancreatic cancer, which usually shows severe dilatation in the upstream MPD.

Serological Findings

Most patients with AIP type 1 show elevated serum γ-globulin, IgG, and IgG4 levels, and high serum IgG4 levels are characteristic features of AIP type 1. Antinuclear antibody (ANA) and rheumatoid factor are often positive, and various autoantibodies such as carbonic anhydrase II, lactoferrin, pancreatic secretory trypsin inhibitor, lipase, and amylase α-2A occasionally present nonspecific positive results. A recent study suggested that laminin 511-E8 may be a specific autoantigen in some patients with AIP type 1 because patients' serum IgG binds to laminin in the diseased area of the

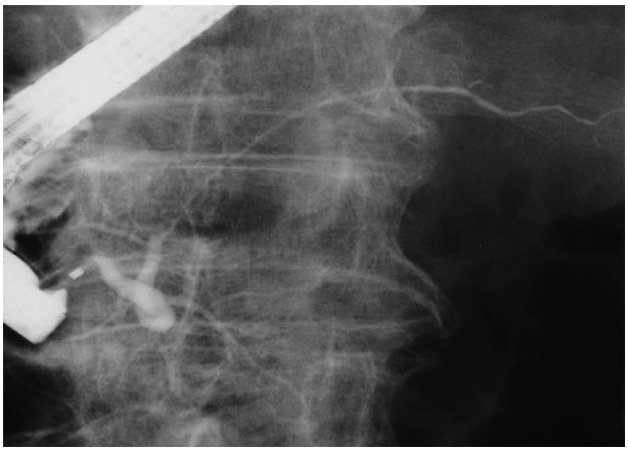
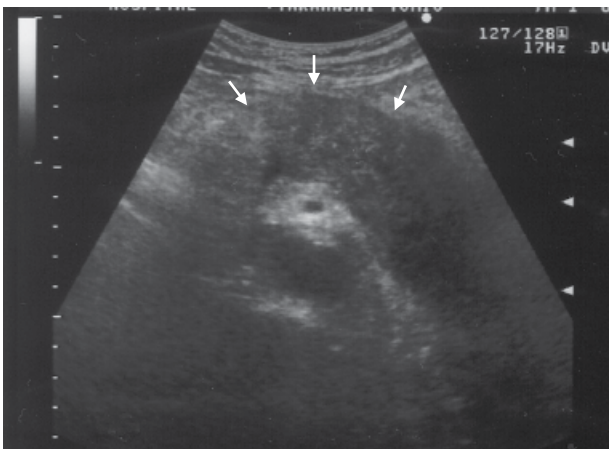


Figure 70.2 The patient showed diffuse and irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography (ERP).

(a)



(b)

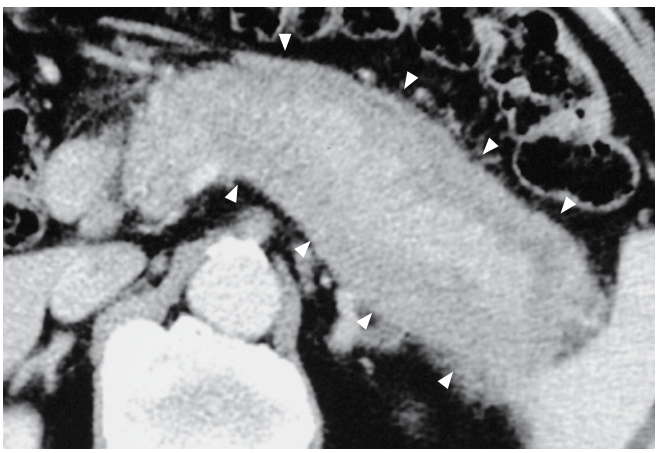


Figure 70.1 (a) Typical US imaging of the "sausage-like" pancreas observed in a patient with type 1 AIP. The entire pancreas swells diffusely (white arrows) and shows internal hypoechoic pattern with scattered hyperechoic spots. (b) The late-phase imaging of swollen pancreas of the same patient on CECT. The pancreas shows diffuse enlargement called "sausage-like" and the parenchyma of swollen pancreas demonstrates characteristic delayed enhancement with a low-density rim-like structure in the periphery of the pancreas (capsule-like rim: white arrowheads).

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pancreas [20]. Anti-laminin 511-E8 antibody can be detected in approximately 50% of Japanese patients with AIP. The presence or absence of the antibody may be related to the phenotype of type 1 AIP, such as the location of pancreatic involvement and the association with malignant or allergic diseases [20]. Serum complements show low titers in some patients with AIP type 1, especially when they are complicated with renal lesions. In contrast, no specific biomarkers have been identified for AIP type 2, including elevated serum γ-globulin and immunoglobulins.

Histopathology of the Pancreas

The histopathologic definition of AIP type 1 is LPSP [2]. Abundant lymphocytes and IgG4-positive plasma cells infiltrate the pathological lesion of the pancreas, which is especially dense around medium and small ducts. These infiltrates compress the ducts while keeping the epithelium intact. LPSP is also characterized by severe and characteristic fibrosis called storiform fibrosis and obliterative phlebitis (Fig. 70.3a, b). Eosinophil infiltration can be seen in some patients, but granulocytes are principally absent.

AIP type 2 is pathologically defined as IDCP/GEL [3,4]. It is characterized by the infiltration of granulocytes around ducts and in acini, sometimes associated with GEL [4], infiltration of granulocytes into the duct lumen, and duct epithelium with the destruction of the epithelium. These findings are considered more specific if present in and around the interlobular ducts.

Extrapancreatic Lesions

AIP type 1 is characterized by the presence of various extrapancreatic lesions. The pathologic characteristics of the extrapancreatic lesions resemble the lesions in the pancreas, including the infiltration of numerous IgG4-positive plasma cells. Representative extrapancreatic lesions include sclerosing cholangitis (involvement of intrahepatic or hilar hepatic bile duct, and/or intrapancreatic bile duct), sclerosing dacryosialoadenitis (symmetrically swollen upper eyelid lacrimal glands and/or submandibular glands, which are painless, smooth-surfaced, elastic hard nodules or masses), retroperitoneal fibrosis (marked fibrosis in retroperitoneal tissue), and renal lesions (tubulointerstitial nephritis with various imaging findings on contrast-enhanced CT (CECT) such as multiple enhancement defects in the renal cortex, mass-like appearance, or swelling of the kidney). Less frequent or rare lesions reported to date include pulmonary diseases (nodular lesions or interstitial pneumonitis), aortitis (inflammatory aneurysms in the abdominal or thoracic aorta), inflammatory pseudotumors, hypophysitis, chronic thyroiditis, mediastinal or abdominal lymph node swelling, swollen duodenal papilla, prostatitis, autoimmune thrombocytopenia, autoimmune neurosensory hearing loss, uveitis, Henoch-Schönlein purpura. In addition, irritable bowel disease (IBD) can be a complication even in patients with type 1 AIP; however, it is rare or less frequent compared with type 2 AIP. In contrast, IBD, especially ulcerative colitis (rather than Crohn's disease), complicates approximately 30% of type 2 AIP cases, whose patients usually

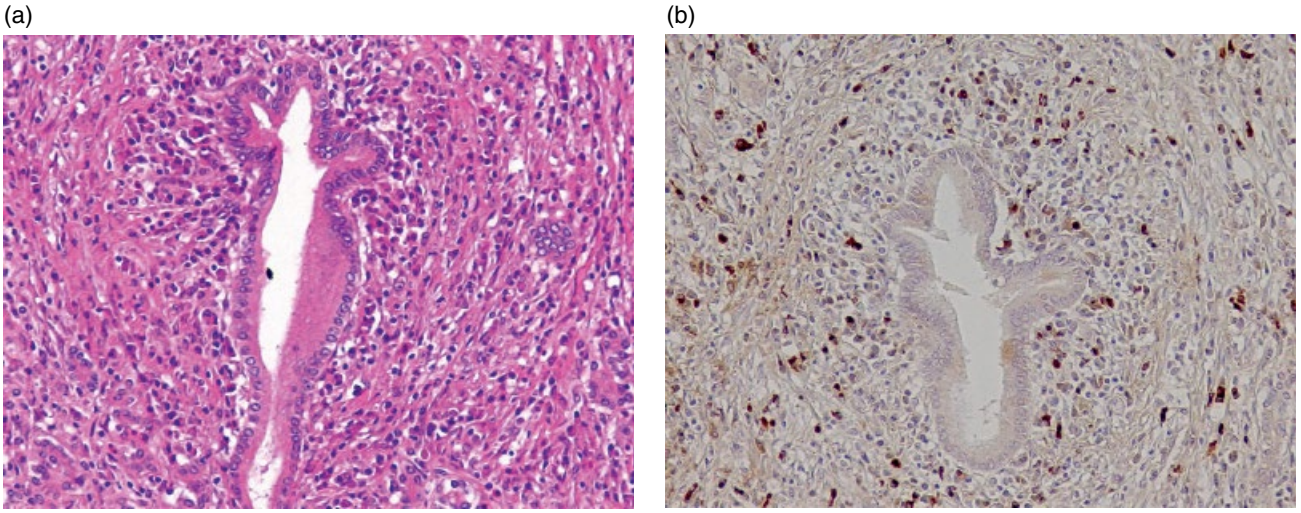


Figure 70.3 (a) Hematoxylin-eosin stained tissue section showed dense lymphoplasmacytic infiltration and strong fibrosis called "storiform fibrosis" around the duct while preserving the duct epithelium intact. (b) Immunostaining for IgG4 revealed aggregation of numerous IgG4-positive plasma cells chiefly around the duct.

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lack the wide array of extrapancreatic lesions seen in patients with type 1 AIP.

Response to Steroids and Relapses

Although patients with both AIP types 1 and 2 show excellent responses to steroids and clinical symptoms, signs, imaging findings, and pathologic findings improve quickly and remarkably, the high rate of relapse is a problematic feature of type 1 AIP. Relapse typically does not occur or is present less frequently in type 2 AIP than in type 1 AIP.

Long-Term Prognosis

The long-term prognosis of patients with type 1 AIP is relatively good, and it has been reported that their 5-year survival rate is not different from the background population [11]. Patients with type 2 AIP also show a fairly good prognosis, and their 5-year survival rate is similar to that of patients with type 1 AIP. However, it is also known that patients with type 1 AIP develop intraductal stones, parenchymal atrophy, and frequent pancreatic exocrine insufficiency during long-term follow-up, showing clinical findings similar to those seen in advanced chronic pancreatitis [21–23]. In addition, some reports suggest higher rates of malignant diseases, including pancreatic cancer, during the clinical course of type 1 AIP [24–27].

Typical Features of AIP Type 1 (Example of Japanese AIP Patients)

Japanese people are roughly of a single race and are considered ethnically homogeneous. It is well known that AIP type 1 is the dominant type in Japanese patients with AIP, whereas type 2 is extremely rare. Recently, a nationwide survey of patients in 2016 diagnosed using the clinical diagnostic criteria for AIP 2011 (JPS 2011) was conducted in Japan [28,29]. The diagnostic criteria used in the study were modified from the ICDC [30] to diagnose type 1 AIP specifically and more concisely [31]. Here, we summarize the results of the latest nationwide survey in Japan and introduce the clinical features of Japanese patients with AIP as a typical example of type 1 AIP.

According to the results [29], the estimated number of Japanese patients with AIP was 13,436 annually (prevalence rate of 10.1/100,000 population), and the estimated number of new patients was 3984 annually (incidence rate of 3.1/100,000 population). The nationwide survey was conducted three times (in 2002, 2007, and 2011), and the number of patients increased in every survey. The estimated number of patients with AIP in 2016 was 7.9 times higher than the 1700 patients identified in the 2002 nationwide survey.

In the survey, 1474 patients with AIP were identified by a secondary survey, and their clinical features were examined in detail (Table 70.1). The male-to-female ratio was male-dominant at 2.94, and the average age was 68.1 years. Most male patients were aged in their seventies, whereas female patients were in their sixties.

Among the patients examined, 62.8% were symptomatic, with jaundice observed in nearly half of the patients (48.6%), followed by abdominal pain (25.6%), and weight loss (3%); however, acute pancreatitis was rare (0.9%). Pancreatic enlargement was observed in 96.5% of the patients, among which diffuse enlargement was observed in 47.2%, segmental swelling in 28.0%, and focal swelling in 19.7%; however, atypical findings such as a tumor-like appearance were noted in only 0.8% of patients. MPD narrowing was observed in 87.5% of the patients, with diffuse, segmental, focal, and multiple narrowing in 34.4%, 30.9%, 17.8%, and 2.6%, respectively. Calcification of the pancreas was detected in 5.9% of patients. Elevation of serum IgG4 (≧135 mg/dL) was seen in 84.5% of the patients, the elevation of serum IgG in 58.5%, ANA-positivity in 32.6%, and rheumatoid factor in 18.3% of the patients.

Extrapancreatic lesions were complications in 60% of the patients, most frequently observed as sclerosing cholangitis in 48.6% (hepatic hilum, 12.9%; intrapancreatic bile duct, 40.9%), sclerosing dacryosialadenitis in 33.3%, retroperitoneal fibrosis (RF) in 17.1%, renal involvement in 8.4%, lung lesions in 8.4%, IBD in 2.5%, and inflammatory pseudotumors in 1.6%. Steroids were administered to 84.4% of the patients, and 98.6% showed good responses. However, relapse occurred in 23.4% of the patients, with accumulating relapse rates of 14% at 3 years, 25% at 5 years, 40% at 10 years, and 50% at 15 years after the commencement of steroids. Although malignant tumors, including gastric, colon, and prostate cancers developed during the clinical course in some patients, the overall prognosis was fair, and the survival rate was 97.3%, at 2 years after the start of the survey.

Global AIP Type 1

The results of a multicenter study on patients with AIP conducted by 15 centers in 8 countries were reported in 2011 [12]. In this study, the clinical features of 204 patients with histologically confirmed LPSP and 64 with IDCP were compared. As shown in (Table 70.1), the patients with LPSP, the histologic definition of AIP type 1, had a mean age of 61.6 years, with a male-dominant

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Table 70.1 Comparisons of clinicopathologic features of AIP patients around the world.

	Japan [29]	8 countries [12]		Korea [14]		China [36]		USA [11]		Netherlands [37]		Spain [38]		Italy [39]		Germany [40]		Sweden [41]	
	2020	2011		2012		2015		2010		2015		2016		2020		2016		2018	
AIP types	**type 1**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**	**type 1**	**type 2**
Diagnosis	JPS 2011	LPSP	IDCP	LPSP	IDCP	Asian, JPS, HISORt, ICDC		LPSP HISORt	IDCP	ICDC, HISORt		ICDC		ICDC		ICDC		ICDC, histology	
Case number	1,474	204	64	37	15	673	33	50	19	96	11	45	5	106	48	33	20	62	9
Age	68.1	61.6	44.8	61*	34	48.6–67.0		62*	48	72*	48	60.2*	44.4	62.5*	48	63*	32.5	49.6	46.9
Male/female	2.94	2.84	2.7	11.3	2.8	4.47		3.34	2.84	8.6*	1.75	2.75	5	2.03	1.18	3.1	0.8	1.06	0.5
Jaundice	48.6%	75%*	47%	67.6%*	33.3%	63.4%						51.1%	60.0%	49%*	25.0%			35%	
Abdominal pain	25.6%	41%*	68%	13.5%*	60.0%	62.3%						66.7%	60.0%	24.5%					
Acute pancreatitis	0.9%	5%*	34%	2.7%*	40.0%			15%	32.0%			31.1%	20.0%	19.8%	25.0%	27.3%*	60%	22%	
Pancreatic enlargement	96.5%					94.4%								85%					
Diffuse	47.2%	40%*	25%	62.2%	73.3%	53.8%		40%*	16%	57.9%		60.5%	50.0%					27%	
Focal	19.7%			37.8%	26.7%	46.2%		60.0%	84%	19.6%		32.5%	0.0%			39.4%*	5.0%	76%	
MPD narrowing	87.5%					68.1%													
Diffuse	34.4%			42.4%	60.0%							12.5%							
Segmental	30.9%																		
Focal	17.8%											75.0%							
Multiple	2.6%			21.2%	20.0%							12.5%							
Serum IgG4	84.5%	63%*	23%	70.3%*	0.0%	86.0%		80%*	17%	84%*	0%	76.7%*	20.0%	73.8%*	27.5%	50.0%		43.5%*	0%
Extrapancreatic lesions	60.0%	45%	38%	45.9%*	0.0%			60%*	0%	69.8%	54.5%	55.6%	100.0%	57.5%		24.2%*	0.0%	84%	
Sclerosing cholangitis	48.6%					65.9%				58%				39.6%				66.2%	
Hepatic hilum	12.9%	29%	23%	21.6%	0.0%	3.6%						17.8%	20.0%						
Intrapancreatic	40.9%			71.6%		62.3%													
Dacryosialadenitis	33.3%	12%*	0%	8.1%	0.0%	14.7%						6.7%	0.0%	7.5%				7.0%	
Retroperitoneal fibrosis	17.1%	7%*	0%	10.8%	5.0%	3.4%						6.7%	0.0%	1.9%				4.2%	
Renal lesions	8.4%	8%	3%	13.5%	0.0%	4.6%						6.7%	0.0%	11.3%				18.3%	
IBD	2.5%	2%*	18%	0%*	33.3%	1.6%		6%	16%	0%*	36.4%	4.4%	100.0%	1.9%*	27.1%	6.1%	15.0%	15.5%	
DM	18.8%			59.5%	26.7%	26.9%						35.6%	40.0%	37.7%	25.0%	24.2%	5.0%	22.6%	11.1%
Steroids	84.4%	44%	33%	67.6%	93.3%	78.4%		42%	32%	84.0%	72.7%	80.0%	80.0%	67.9%	70.8%	72.7%		79%	
Effectiveness	98.6%	100%	100%	100.0%	100.0%	96.2%								90.4%	97.0%	84.8%		100%	
Resection				32.4%	6.6%	29.7%		32%*	68%	32.0%	27.3%	17.8%	20.0%	12.2%	4.2%	48.5%*	6.1%	16%	
Relapses	23.4%	36%*	5%	32.4%*	0.0%	13.8%		47%*	0.0%	54.1%	27.3%	44.4%	0%	30.2%*	6.3%	39.4%	15.0%	27%	

* Significant difference compared with type 2 AIP.

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male-to-female ratio of 2.84, and had symptoms including jaundice in 75% of the patients, abdominal pain in 41%, and acute pancreatitis in only 5%. In addition, diffuse enlargement of the pancreas was noted in 40% of the patients, elevated serum IgG4 in 63%, association of extrapancreatic lesions in 45%, sclerosing cholangitis at the hepatic hilum in 29%, sclerosing dacryosialadenitis in 12%, and IBD in only 2%. Steroids were administered to 44% of the patients, showing good responses in all patients, but relapse occurred in 36%.

The clinical features of the patients with LPSP shown in this study resembled those of 1474 patients analyzed in the Japanese nationwide survey in 2016 [29], but differed from those of the patients with IDCP in the same study (Table 70.1) [12]. In that report, the clinical features of 463 AIP patients without histologic confirmation were also studied according to their respective nations [12]. As a consequence, the clinical features of the patients in Asian countries diagnosed by the Asian criteria [32] and those of the patients in the United States, India, and the United Kingdom diagnosed by the HISORt criteria [33] showed characteristics similar to those of patients with histologically confirmed LPSP. In contrast, the German patients diagnosed by the Mannheim criteria [34] and the Italian patients diagnosed by the Italian criteria [35] showed clinical features partly resembling type 2 AIP, suggesting the influence of diagnostic criteria employed on the clinical features of AIP.

By country, 52 histologically confirmed Korean patients with AIP types 1 and 2 in 2012 [14], and 706 Chinese patients with AIP diagnosed by various criteria in a multicenter study in 2015 were evaluated [36]. The clinical features of AIP patients clarified in these studies resembled those of the histologically confirmed LPSP patients reported in an international multicenter study [12], suggesting the dominance of AIP type 1 in both countries (Table 70.1). In addition, the clinical features of AIP type 1 (LPSP) and type 2 (IDCP) patients diagnosed by the ICDC or histology were studied in the United States [11] and in various European countries, including the Netherlands [37], Spain [38], Italy [39], and Germany [40], confirming that the clinical features of AIP type 1 (LPSP) patients in the Western countries were fundamentally not different from those of Asian patients (Table 70.1). A report from a single institute in Sweden [41] showed somewhat different results from the typical clinical features of AIP type 1, even in patients diagnosed with type 1 by the ICDC or histology, such as younger age, no sex difference, greater frequency of acute pancreatitis onset, and lower rates (less than half) of serum IgG4 elevation. Therefore, a prospective multicenter study involving various countries may be required to clarify whether the differences originate from ethnicity or other factors.

AIP Type 1 and IgG4-RD

Kamisawa proposed a new disease concept, "IgG4-related sclerosing disease," in 2003 [42].

He considered AIP type 1 a systemic fibrous disease characterized by the overproduction of IgG4 and infiltration of abundant IgG4-positive plasma cells in various organs. Various nomenclatures have been proposed for the disease, such as "systemic IgG4-related plasmacytic syndrome (SHIPS)" [43] by a group of researchers who considered sclerosing dacryosialadenitis, which used to be called Mikulicz disease, as its representative, and "IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS)" [44] considering it as an IgG4-positive plasma cell proliferative disease. Thereafter, the name was unified as "IgG4-related disease (IgG4-RD)" [45], which is now commonly used worldwide. IgG4-RD includes IgG4-related sialadenitis (IgG4-Mikulicz), IgG4-related ophthalmic disease, IgG4-related pachymeningitis, IgG4-related hypophysitis, IgG4-related pulmonary diseases, AIP type 1, IgG4-related sclerosing cholangitis (IgG4-SC), IgG4-related kidney disease, RF, inflammatory pseudotumor, inflammatory periaortitis, and periarteritis [45].

Comprehensive diagnostic criteria for IgG4-RD were proposed in 2011 [46], partly revised in 2020 [47], and they have been used to screen patients to diagnose IgG4-RD. However, as the comprehensive criteria, both original and revised, depend heavily on histologic findings for the diagnosis, it is necessary to use other criteria that are more specific to AIP [30], IgG4-SC [48], IgG4-Mikulicz [49], IgG4-related ophthalmic disease [50], IgG4-related kidney disease [51], IgG4-related respiratory disease [52], and IgG4-related periaortitis/periarteritis and RF [53] when the acquisition of histologic specimens is difficult or confirmation of the diagnosis is required.

Recently, it has been suggested that IgG4-RD could be categorized into three groups according to the distribution of diseased organs on either side of the diaphragm [54]: head and neck IgG4-RD (HN IgG4-RD), pancreatobiliary IgG4-RD (PB IgG4-RD), and diffuse IgG4-RD. In comparison with PB IgG4-RD, HN IgG4-RD showed manifestations more frequently on the rostral side of the diaphragm, including the orbital, lacrimal gland, submandibular, parotid gland, asthma, and sinusitis, whereas lung manifestations were similar. When compared with HN IgG4-RD, PB IgG4-RD showed manifestations more frequently on the caudal side of the diaphragm, represented by the pancreas and biliary manifestations, whereas renal lesions were similar. Interestingly, compared with HN IgG4-RD, PB IgG4-RD patients were older, more frequent in males, and showed a shorter duration of follow-up.

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These findings suggest that IgG4-RD tends to develop a cluster of involved organs on either side of the diaphragm and extend from there to systemic manifestations with increased disease activity. It is interesting to study whether HN and PB IgG4-RD are different subsets of IgG4-RD and whether the difference in the phenotypes is caused by genetic background or by immunologic response to heterogeneous autoantigens.

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Clinical Manifestation of Type 2 Autoimmune Pancreatitis

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Introduction

Autoimmune pancreatitis (AIP) is a fibroinflammatory disease of the pancreas that has attracted increasing interest [1]. Two distinct entities, type 1 and type 2, have been defined histologically under the unifying term AIP [2]; the subtypes share symptoms, radiologic appearance, and a dramatic response to steroids. However, the subtypes clearly differ in terms of their pathologic features, the involvement of other organs, and clinical outcomes [3,4]. A histologic diagnosis of AIP subtypes is not always achievable. The introduction of the International Consensus Diagnostic Criteria (ICDC) [3], based on the combination of five cardinal criteria (imaging, serology, other organ involvement, histology, and response to steroids), classified into level 1 (more reliable) and level 2 (less reliable), has enabled the diagnosis of disease subtype even in the absence of histology. ICDC introduced another type of disease, AIP not otherwise specified (NOS), if diagnosis of type 1 or 2 AIP cannot be achieved. Since there is no serologic marker for type 2 AIP, the diagnosis of this subtype remains much more difficult. This may explain why almost all the literature on AIP is focused on type 1 AIP, which is a part of IgG4-related disease and represents between 80% and 95% of all AIP cases [4]. Few studies have been published on type 2 AIP, and most of the available data have been extrapolated from small subgroups in studies focused on type 1 AIP.

Type 2 AIP remains an undefined, underestimated, and debated clinical entity. Consensus is lacking and controversies still surround this subtype of AIP [5].

Pathology

The first pathologic distinction of subtypes of AIP was published at the beginning of the twenty-first century [6,7]. Initially, descriptive pathologic terms were used to describe the subtypes of the disease, such as lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric chronic pancreatitis (IDCP) [6]. Zamboni et al. [7] introduced the term "granulocytic epithelial lesion" (GEL) to identify patients with ICDP. The terms LPSP and ICDP were definitively replaced with type 1 and type 2 AIP, respectively [2], following the publication of the Honolulu consensus document in 2010.

Type 2 AIP is characterized by an inflammatory infiltrate mainly involving the pancreatic ductal system with a predominant neutrophilic component [2]. The most distinctive feature is the presence of GEL in medium- and small-size ducts, characterized by neutrophilic infiltrate in the epithelial layer of the pancreatic ducts (ICDC level 1), changes that may lead to the destruction and obliteration of the duct lumen (Fig. 71.1). GEL often also involve the acini (ICDC level 2). Intraductal clusters of neutrophils resembling crypt abscesses in IBD often coexist. Diffuse inflammation, obliterative phlebitis and storiform fibrosis, which are characteristic of type 1 AIP, are less prominent in type 2 AIP. The other distinctive feature of type 2 AIP is the scant presence (<10 cells/high-power field) or complete absence of IgG4-positive plasma cells on immunostaining.

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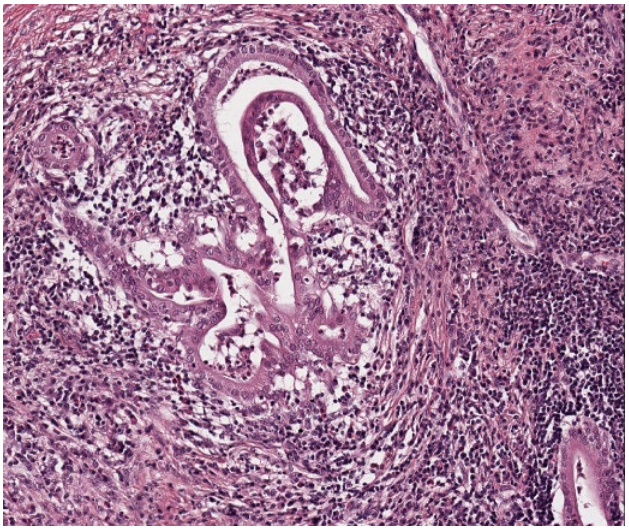


Figure 71.1 Histologic features of type 2 AIP: periductal lymphoplasmacytic cells infiltration with granulocytic epithelial lesion, characterized by the invasion of the ductal structures by neutrophilic granulocytes, with destruction of the duct epithelium (hematoxylin-eosin). *Source:* Image courtesy of Giuseppe Zamboni, Verona, Italy.

Epidemiology

The epidemiology of type 2 AIP is undefined, and no data are available about its incidence and prevalence.

Type 2 AIP is estimated to be a rare disease with a prevalence of 0.5/100,000 [5]. However, the probability of type 2 AIP might be higher in the pediatric population or in young patients (<40 years) with a previous history or synchronous diagnosis of IBD presenting with acute pancreatitis without etiologic factors (gallstone, alcohol, hypertriglyceridemia, genetics) [8,9]. Patients with type 2 AIP are generally in the third to fourth decade of life, with no gender preference, and they are significantly younger than patients with type 1 AIP, who are usually in the sixth or seventh decade of life and are predominantly male [10–15].

Type 2 AIP represents less than 10% of all AIP patients. The proportion of type 2 AIP is lower in Asia (3.7%) [16] and China (4.7%) [17] than in Europe (12.9%) [16], Italy (18%) [11], and North America (13.7%) [16]. However, the proportion of type 2 AIP is higher (28.8%) when considering patients with a histologic diagnosis of AIP [18].

The association with inflammatory bowel disease (IBD) as a diagnostic criterion [3] strengthens the relation between type 2 AIP and IBD. The concomitant presence of IBD has been described in 40–84% of patients with type 2 AIP [10–12]. Lorenzo et al. [19] published a retrospective case series of 91 patients with type 2 AIP and IBD, reporting ulcerative colitis (UC) and Crohn's disease in 58 (64%) and 33 patients (36%), respectively. Hart et al. [10] reported a higher proportion of UC (74%) compared to Crohn's disease (16%) among 19 patients with concomitant IBD and type 2 AIP.

In most cases, the clinical onset of IBD precedes or is concomitant with AIP. However, the development of IBD after AIP has also been described [10,20]. The diagnosis of IBD after diagnosis of AIP switches the diagnosis of AIP subtype from type NOS to type 2 [20].

Despite the high frequency of IBD in patients with type 2 AIP, the prevalence of type 2 AIP in patients with IBD seems to be quite low. A Korean study estimated a prevalence of AIP to be approximately 0.54% in 1106 patients with UC [21]. In a Japanese study, type 2 AIP was found in 5 out of 961 patients with UC (0.5%) and in 2 out of 790 patients with Crohn's disease (0.2%) [22]. However, a diagnosis of type 2 AIP was made in 52 out of 138 patients with IBD and pancreatitis (37.7%), histologically confirmed in 15 patients (10.8%), and based on Japanese criteria, "probable" in an additional 37 patients (26.8%) [23]. The prevalence of type 2 AIP in patients with IBD is probably underestimated, and the diagnosis of AIP needs to be considered in IBD patients with acute pancreatitis.

Clinical Profile and Symptoms

The clinical profile of type 2 AIP significantly differs from that of type 1 AIP [11,14,16,18]. Type 2 AIP is an organ-specific pancreatic inflammatory process, while type 1 AIP is one part of a systemic IgG4-related disease [24]. Therefore, symptoms correlated with the involvement of other organs might be observed in patients with type 1 AIP (e.g., retro-ocular infiltration) but not in patients with type 2 AIP. Acute pancreatitis is the most frequent presentation at clinical onset in patients with type 2 AIP (50–65%), while jaundice is less frequent (7–30%) [10,15]. Jaundice is related to biliary involvement (single biliary stenosis, distal) secondary to direct compression of the inflamed pancreatic tissue on the distal (intrapancreatic) common bile duct; this is in contrast to type 1 AIP, where biliary involvement (multiple stenoses, distal and proximal) is related to the direct involvement of the biliary tree wall by the IgG4-related inflammatory process. Other clinical manifestations of type 2 AIP are abdominal pain and, uncommonly, diabetes and steatorrhea.

A significant proportion of patients with type 2 AIP have concomitant IBD, mainly UC. Type 2 AIP generally develops in patients with a known history of IBD, but AIP might occur simultaneously with IBD or before the clinical onset of IBD [20]. However, the histologic and clinical features of UC associated with type 2 AIP seem to be quite different from "classical" UC [25].

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Diagnosis

The diagnosis of type 2 AIP is based on the ICDC [3], and it is more difficult to achieve compared to the diagnosis of type 1 AIP because of the lack of a serologic marker.

The distinction between "definitive" and "probable" type 2 AIP was proposed by the ICDC to underline the strength of the diagnostic criteria and to overcome the need for histology for the diagnosis of type 2 AIP [3].

According to the ICDC, a "definitive" diagnosis of type 2 AIP based on histology is achieved only if GEL are detected at histology (Fig. 71.2). Indeed, the diagnostic criteria include the evidence of disease at imaging (typical – level 1; atypical – level 2) and the presence of GEL in the pancreatic ductal system (level 1) or GEL in the acini (level 2) together with an association with IBD and a response to steroids at imaging (Fig. 71.3). A definitive diagnosis of type 2 AIP is easily achieved on surgical specimens in patients who are improperly resected. In nonresected patients, histology might be achieved with EUS-guided tissue acquisition, but the detection of GEL is limited. Very few case reports have been published on the role of EUS-guided fine-needle biopsy (FNB) for the diagnosis of type 2 AIP, reporting rare cases of GEL identification in tissue specimens of the fork-tip needle [26].

If histology with GEL identification is lacking or inconclusive, a "probable" diagnosis of type 2 AIP can be achieved with evidence at imaging (typical – level 1; atypical – level 2) and an association with IBD and a response to steroids, that is, without histology (Fig. 71.2).

Radiologically, patients with type 2 AIP might have a typical diffuse (level 1) (Fig. 71.4) or atypical focal (level 2) (Fig. 71.5) involvement of the pancreatic gland, similar to patients with type 1 AIP. Indeed, it is not possible to distinguish between type 1 AIP and type 2 AIP by imaging [3,27]. The concomitant involvement of other organs at imaging, such as the kidney, retroperitoneum, lung, and proximal biliary tree, is suggestive of an IgG4-related disease and, therefore, of type 1 AIP.

The most specific radiologic appearance of type 2 AIP on CT and MRI scans (detectable in approximately 30–50% of patients) is a diffuse enlargement of the pancreas with loss of the normal lobulated contour (Fig. 71.4) [28,29]. The pancreas typically appears hypoenhanced in the early phase and hyperenhanced in the late phase after contrast medium (c.m.) administration. Moreover, a hypoenhanced capsule-like rim surrounding the pancreatic gland in the early phase after c.m. has been described in less than one-third of patients. Unfortunately, some patients present an atypical focal involvement of the pancreatic gland (ICDC level 2) with the detection of a hypodense (at CT-scan images) or hypointense (at T1-weighted MRI images) pancreatic mass that is hypoenhanced in the arterial phase [28–30]. The pancreatic mass is generally slightly hyperenhanced in the late portal phase in AIP, in contrast to pancreatic cancer. However, EUS-guided tissue sampling is strongly suggested in these patients, considering that the risk of pancreatic cancer is 10 times higher [31]. The introduction of new end-cutting forward-acquiring needles seems to increase the

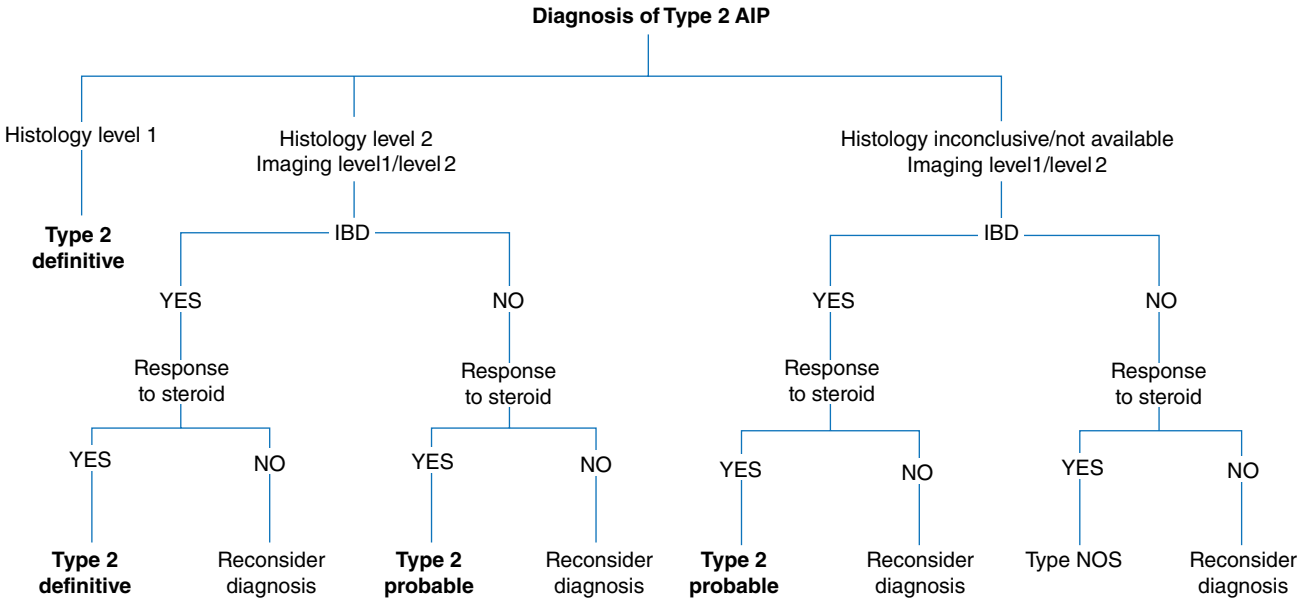


Figure 71.2 Diagnostic algorithm for diagnosis of type 2 AIP based on ICDC [3]. For an explanation of levels 1 and 2 (specific for type 2 AIP), see Adapted from [3].

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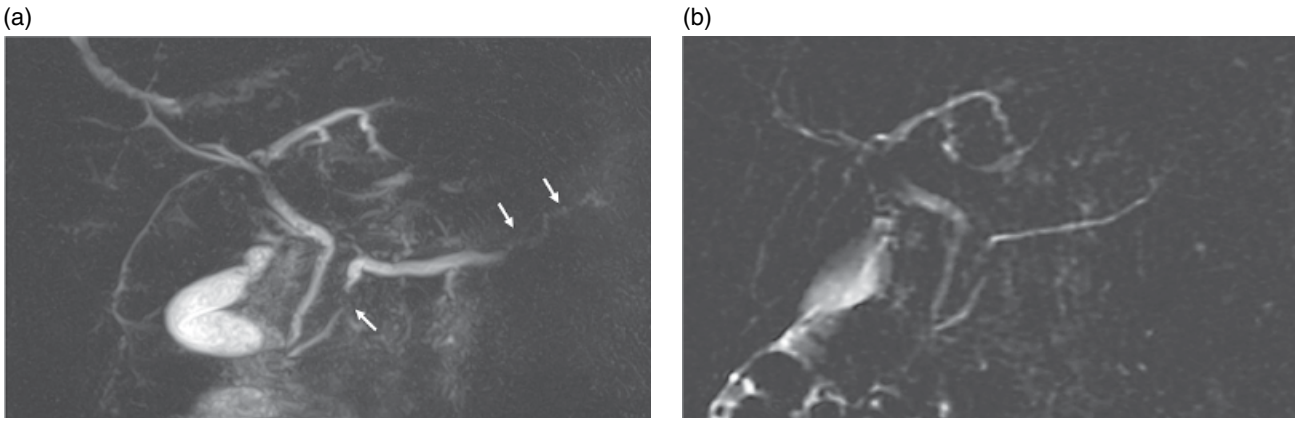


Figure 71.3 Magnetic resonance cholangiopancreatography (MRCP) of a patient with type 2 AIP. Before steroid treatment: (a) a short stricture of the main pancreatic duct in the pancreatic head (single arrow) with upstream dilation, with a second long stricture in the pancreatic tail (arrows). After steroid treatment (b) the main pancreatic appearance is normal.

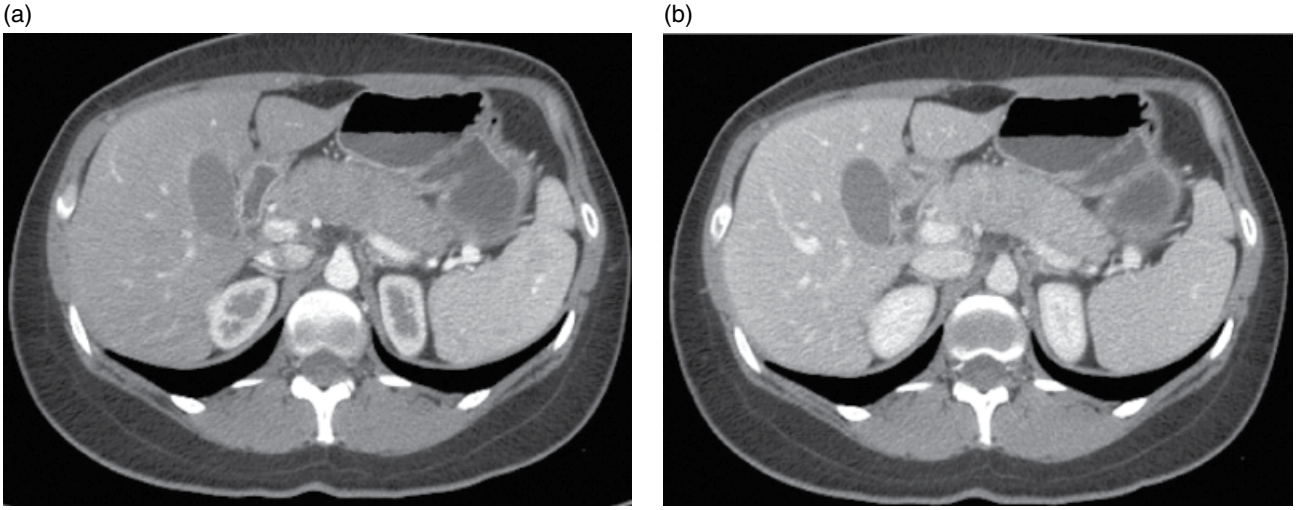


Figure 71.4 Contrast-enhanced computed tomography (CT) of a patient with diffuse type 2 AIP involving the body and tail of the pancreas. In the "early" arterial phase (a) the involved pancreas is hypoenhancing. In the "late" portal phase (b) it appears isoenhancing or slightly hyperenhancing. The main pancreatic duct is not visible in both images.

sensitivity and specificity of EUS-guided pancreatic biopsies in the diagnosis of pancreatic masses [31] Therefore, the new needles allow not only the exclusion of a cancer diagnosis, similar to what is possible with fine-needle aspiration cytology, but also the diagnosis of AIP.

Hart et al. [10] showed that patients classified as having "definitive" or "probable" type 2 AIP have similar clinical profiles and disease-related outcomes. Therefore, the distinction between "definitive" or "probable" type 2 AIP is not necessary in clinical practice.

Finally, considering that the presence of IBD allows for a diagnosis of type 2 AIP, and UC associated with type 2 AIP is often asymptomatic [25], the dosage of fecal calprotectin has been suggested as a screening test to select patients for colonoscopy with biopsy, even if asymptomatic [32].

Therapy and Risk of Relapse

The aim of AIP treatment is to relieve pancreatic pain and resolve jaundice by reducing inflammation, and treatment can possibly prevent disease relapse and progression toward chronic pancreatitis. Spontaneous remission of type 2 AIP has been described, even though further episodes of pancreatitis have been later observed in these patients [10,14]. Therefore, if a lot of time has

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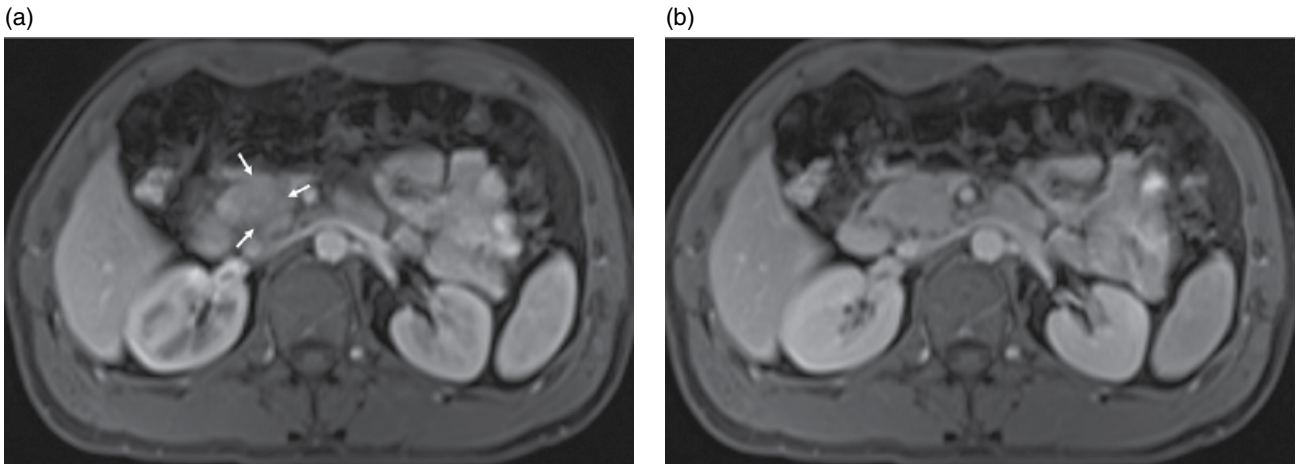


Figure 71.5 Contrast-enhanced magnetic resonance image (MRI) of a patient with focal type 2 AIP involving the head of the pancreas. In the "early" arterial phase (a) the presence of a hypoenhanced mass in the head of the pancreas (arrows). In the "late" portal phase (b) the involved pancreas appears isoenhancing.

elapsed from the last imaging (CT or MR), it is advisable to repeat the diagnostic investigation before starting therapy to avoid treating patients in spontaneous remission.

Medical treatment of type 2 AIP is based on steroids at the same dosage (0.6–1 mg/kg/day or 30–40 mg/day) proposed for the treatment of type 1 AIP [33]. Response rates to steroids are close to 100% but may reflect the need for "response to steroids" as a criterion for the diagnosis when histology is lacking. Steroids induce a quicker remission more consistently, and they reduce the probability of relapse compared to a conservative approach [34]. Differently from type 1 AIP, no alternative treatments have been proposed to induce remission in patients with type 2 AIP, even if responses to antitumor necrosis factor agents [19] and colchicine [35] have been reported in a few cases.

Response to treatment should be assessed within 2–4 weeks from initial steroid administration. In atypical focal forms of AIP, an absent or incomplete response is suggestive of an alternative diagnosis, and surgery is recommended if pancreatic cancer cannot be safely excluded [36].

After remission, steroid dosage can be reduced by 5 mg every 1–2 weeks up to suspension.

Relapse in patients with type 2 AIP is rare (<10%) [10,12]. Therefore, in contrast to type 1 AIP treatment, no upfront maintenance therapy is considered. However, in cases of relapse, a new steroid treatment is effective. Azathioprine (2–2.5 mg/kg/day) may be considered maintenance therapy in relapsing disease, particularly in patients with active IBD [37].

Long-term complications, including pancreatic exocrine insufficiency, the onset of pancreatic calcifications, and malignancy, seem to be uncommon in patients with type 2 AIP [14–16].

Conclusion

Type 2 AIP is a rare disease that is difficult to diagnose because of the lack of serologic markers and, therefore, it is largely underestimated in clinical practice. It clearly differs from type 1 AIP in terms of histology, the clinical profile of patients, and the risk of relapse, despite their similar radiologic appearance and common response to steroids. A strong association with IBD, particularly ulcerative colitis, has been identified, and the concomitant presence of IBD is often necessary to achieve diagnosis of type 2 AIP in clinical practice if a definitive histology is lacking. The clinical onset of IBD generally precedes AIP, but AIP might precede IBD onset in some cases. The incidence of type 2 AIP might be higher in young patients with IBD and acute idiopathic pancreatitis. The clinical outcome of the disease is more favorable, in terms of disease relapse and pancreatic exocrine and endocrine insufficiency, compared to type 1 AIP.

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72

Clinical Diagnostic Criteria for Autoimmune Pancreatitis

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Historical View of the Diagnostic Criteria for AIP

The Japan Pancreas Society (JPS) was the first in the world to have proposed the diagnostic criteria for AIP in 2002 [1]. Subsequent efforts to improve the prototype produced multiple diagnostic criteria, including the criteria of Asan Medical Center in 2006 [2], the revised criteria of Japan in 2006 [3], and the revised criteria of Asan Medical Center in 2006 [4]. Rapid progress in the understanding of this disease necessitated multiple revisions within a short time, such as atypical cases presenting with focal swelling or tumor-like appearance of the pancreas, besides the typical diffuse enlargement of the pancreas, the discovery of serum IgG4 as a specific biomarker for AIP, and the recognition of AIP as a systemic disease because of the association with various extrapancreatic lesions showing characteristic pathologic findings similar to those observed in the pancreas. Repeated discussions by Japanese and Korean experts over the differences in the criteria proposed by the respective countries led to the postulation of unified criteria in 2008, known as the Asian criteria [5–7]. Meanwhile experts from the Mayo Clinic searched their past database to examine the clinical features of patients with histologically confirmed AIP, and proposed the HISORt criteria in 2006 based on their findings, which consisted of five items, namely, histology (H), pancreatic imaging (I), serology (S), other organ involvement (O), and response to steroids (Rt) [8]. Furthermore, they meticulously compared the characteristics of patients with AIP and those with pancreatic cancer and proposed the revised HISORt criteria in 2009, which categorized the respective diagnostic findings into three groups depending on the strength of the association with AIP or pancreatic cancer [9]. Both the Asian and HISORt criteria were compiled on the assumption that they would diagnose a subtype of AIP that was histologically defined by lymphoplasmacytic sclerosing pancreatitis (LPSP) [10]. However, the first scheme to integrate the two criteria was unsuccessful because of the difference in the diagnostic approaches: while the Japanese and Korean experts considered the unique MPD narrowing judged on ERP as an essential factor for the diagnosis of AIP, the HISORt criteria prioritized the pathologic findings of the pancreas acquired from tissue specimens collected by resection or core biopsy [11,12]. Another newly emerged serious issue was the possibility of another type of AIP that was histologically distinct from LPSP. Idiopathic duct-centric pancreatitis (IDCP)/granulocytic epithelial lesion (GEL) proposed by Western pathologists was characterized by the infiltration of granulocytes into the duct epithelial tissues with destruction of the epithelium, and the clinical features of patients with IDCP/GEL were distinct from those of patients with LPSP [13–15]. It was essential to discuss the true nature of the two distinct subtypes and stipulate diagnostic parameters for each type in order to devise universal diagnostic criteria. Therefore, an international symposium was organized on the sidelines of the joint meeting celebrating the 40th anniversary of the American Pancreatic Association and the JPS in Honolulu in November 2009 to discuss these matters. The final consensus obtained after intense discussions among experts from the East and West was called "the Honolulu consensus," which defined AIP characterized by histologic LPSP as type 1, and that characterized by IDCP/GEL as type 2, and proposed the need for

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continued efforts to clarify the pathologic condition of the respective type of AIP, especially the autoimmune nature of type 2 [16]. The proposal of the Honolulu consensus enabled the initiation of the process for establishing universal diagnostic criteria for AIP. The Eastern and Western panelists proposed a draft of the ICDC, the final version of which was published after revision in 2011 [17], following discussions at the consensus symposium conducted at the 14th meeting of the International Association of Pancreatology in Fukuoka in July 2010.

International Consensus Diagnostic Criteria for AIP (ICDC)

The ICDC were formulated with the objective of providing a high level of sensitivity and specificity for the identification of AIP, with special focus on its differentiation from pancreatic cancer, after scrutinizing the various diagnostic criteria for AIP formulated and used in various countries and regions [18–21], in addition to the Japanese [1,3,7], Korean [2,4,7], and Mayo Clinic's criteria [8,9]. The ICDC were devised to facilitate accurate diagnosis by various diagnostic approaches, to ensure universal application, even if the preferred diagnostic methods or tests varied according to country or region [17]. The fundamental concept underlying the creation of the ICDC was to combine the merits of the Asian criteria [7] and the HISORt criteria [8,9]: the ICDC was designed to possess high diagnostic ability by virtue of the combinations of various findings other than duct imaging and pancreatic histology, even if ERP and/or pancreatic tissue sampling were not available [22]. Moreover, the ICDC were formulated to diagnose AIP type 1 and 2 separately and clarify the clinicopathologic features of the respective types of AIP prevalent in the world. Even now, the ICDC are the sole diagnostic criteria that can diagnose AIP with differentiation between types 1 and 2.

The ICDC are composed of five cardinal features, namely, parenchymal imaging (P), ductal imaging (D), serology (S), other organ involvement (OOI), and histology of the pancreas (H), whose findings are graded into levels 1 and 2 according to their specificity to AIP, so that the diagnosis of AIP can be made flexibly by collating multiple findings [17]. The response to steroids (diagnostic steroid trial) was provisioned as an option that could be used as a supplementary parameter for diagnosis after thorough examination to eliminate the possibility of biliary and pancreatic cancers (Tables 72.1a and 72.2a). The ICDC consider parenchymal imaging (P), i.e., enlargement of the pancreas, which is easily detectable on CT/MRI, to be an essential finding (akin to the Asian criteria) and classified it in Level 1 (Typical: diffuse enlargement with delayed enhancement) and Level 2 (Indeterminate (including atypical): segmental/focal enlargement with delayed enhancement). Minimum collateral evidence of the other cardinal features is required for the diagnosis of AIP in patients with Level 1 (P). Conversely, the diagnosis of patients with Level 2 (P), in whom the differential diagnosis from pancreatic cancer is important, entails meticulous diagnostic examinations that combine multiple other cardinal findings. The diagnosis of type 1 and 2 AIP can be definitive or probable (Tables 72.1b and 72.2b), and in some cases, the distinction between the subtypes may not be possible (AIP-Not Otherwise Specified) (Table 72.2c). The ICDC reportedly possess the highest sensitivity, specificity, and accuracy for the diagnosis of AIP compared to other diagnostic criteria for AIP reported in the past [22–24].

Table 72.1a Level 1 and level 2 criteria for type 1 AIP Adapted from [17].

Criterion		Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargment with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value	IgG4, 1–2× upper limit of normal value

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Table 72.1a (Continued)

Criterion		Level 1	Level 2
OOI	Other organ involvement	a or b	a or b
		a) Histology of extrapancreatic organs Any three of the following: 1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration 2) Storiform fibrosis 3) Obliterative phlebitis 4) Abundant (>10 cells/HPF) IgG4-positive cells	a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct[#] Both of the following: 1) Marked lymphoplasmacytic infiltration without granulocytic infiltration 2) Abundant (>10 cells/HPF) IgG4-positive cells
		b) Typical radiological evidence At least one of the following: 1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture 2) Retroperitoneal fibrosis	b) Physical or radiologic evidence At least one of the following: 1) Symmetrically enlarged salivary/lachrymal glands 2) Radiologic evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection): At least 3 of the following: 1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2) Obliterative phlebitis 3) Storiform fibrosis 4) Abundant (>10 cells/HPF) IgG4-positive cells	LPSP (core biopsy): Any 2 of the following: 1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2) Obliterative phlebitis 3) Storiform fibrosis 4) Abundant (>10 cells/HPF) IgG4-positive cells
Response to steroid (Rt)*		Diagnostic steroid trial Rapid (≦2wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

* Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats only after negative workup for cancer including endoscopic ultrasound-guided fine-needle aspiration.
† Atypical: some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative.
# Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla often is involved pathologically in AIP.
Source: Adapted from [17].

Table 72.1b Diagnosis of definitive and probable type 1 AIP using ICDC [17].

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/Indeterminate	Histologically confirmed LPSP (Level 1 H)
	Imaging	Typical	Any non-D Level 1/Level 2
		Indeterminate	Two or more from Level 1 (+ Level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or Level 1 D + Level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

Source: Adapted from [17].

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Table 72.2a Level 1 and level 2 criteria for type 2 AIP Adapted from [17].

Criterion[#]		Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargment with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical †): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
OOI	Other organ involvement		Clinically diagnosed inflammatory bowel disease
H	Histology of the pancreas	IDCP (core biopsy/resection): Both of the following: 1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation 2) Absent or scant (0–10 cells/HPF) IgG4-positive cells	IDCP (core biopsy/resection): Both of the following: 1) Granulocytic and lymphoplasmacytic acinar infiltrate 2) Absent or scant (0–10 cells/HPF) IgG4-positive cells
Response to steroid (Rt) *		Diagnostic steroid trial Rapid (≦2wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

* Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats only after negative workup for cancer including endoscopic ultrasound-guided fine-needle aspiration.
† Atypical: some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative.
# For the diagnosis of type 2 AIP, criterion "S" is removed because no serologic marker is identified.
Source: Adapted from [17].

Table 72.2b Diagnosis of definitive and probable type 2 AIP using ICDC [17].

Diagnosis	Imaging evidence	Collateral evidence
Definitive type 2 AIP	Typical/ Indeterminate	Histologically confirmed IDCP (Level 1 H) *or* Clinical inflammatory bowel disease + Level 2 H + Rt
Probable type 2 AIP	Typical/ Indeterminate	Level 2 H/Clinical inflammatory bowel disease + Rt

Source: Adapted from [17].

Table 72.2c Diagnosis of AIP-Not Otherwise Specified (AIP-NOS) using ICDC Adapted from [14].

Diagnosis	Imaging evidence	Collateral evidence (cases with only D/2)
AIP-NOS	Typical/Indeterminate	D 1/2 + Rt

Source: Adapted from [14].

Clinical Features of Type 1 and 2 Patients Diagnosed by the ICDC

A multinational study conducted at 23 facilities located in 10 Asian and Western countries recruited 1064 patients with AIP diagnosed using the ICDC (978 patients with type 1 AIP and 86 patients with type 2) and analyzed their clinical features [25]. The results demonstrated that the proportion of type 2 disease was 3.7% in Asian countries, considerably lower than the 12.9% prevalence in European countries and 13.7% in North America; however, it was also evident that AIP type 1 was the dominant manifestation even in Western countries, accounting for over 85% of all patients. The clinical features of patients with AIP types 1 and 2 analyzed in the study coincided with those of previously reported patients with histologic LPSP and IDCP, respectively [26]. Thus, patients diagnosed as AIP type 1 by the ICDC showed a tendency to develop jaundice, especially elderly men, and presented with various extrapancreatic lesions, but only 0.1% had inflammatory bowel disease (IBD). In contrast, patients diagnosed as type 2 were younger than their type 1 counterparts (39.9 years vs. 61.4 years,

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respectively), without any sex-specific predilection, developed pancreatitis/abdominal pain (64% vs. 27%) more frequently, and nearly half of the patients (48%) developed IBD, but did not present with the various extrapancreatic lesions seen in type 1. Steroids were highly effective for both types, but relapse occurred significantly more frequently in type 1 patients (31%) compared to type 2 patients (9%) [25].

Recent reports from European countries showed similar results with respect to the clinical features of patients with AIP diagnosed by the ICDC with differentiation between types 1 and 2 (see Table 70.1) [27–31]. Studies conducted in the Netherlands [27], Spain [28], Italy [29], Germany [30], and Sweden [31] reported that patients with type 1 AIP tended to be older, predominantly male, and exhibited a greater proportion of serum IgG4 elevation and higher relapse rate compared to those with type 2. Sclerosing cholangitis was the most frequent extrapancreatic lesion in type 1, whereas the incidence of complications such as IBD was significantly higher in type 2. Most patients with types 1 and 2 were treated with steroids, which elicited an excellent response. These findings more or less correspond to those reported by previous multinational studies [25,26], suggesting phenotypic uniformity with AIP types 1 and 2, even in different European countries when the ICDC are used for the diagnosis.

Issues to Be Discussed on the ICDC

Magnetic Resonance Cholangiopancreatography (MRCP)

The ICDC designated the use of ERP-based duct imaging for the diagnosis of AIP [17] because of the insufficient resolution of MRCP for precise judgment of MPD narrowing (especially multiple narrowing), as determined during the compilation of the criteria [7]. Therefore, the perspective of the Japanese and Korean experts who deemed ERP-based identification of MPD narrowing to be mandatory for the diagnosis of AIP was respected and this parameter was incorporated into the ICDC. However, recent advancements, such as the availability of high-resolution MRCP imaging (especially with 3T-weighted MRI), have made it acceptable for the diagnosis of AIP, since the improvement in the MRI apparatus has rendered it almost equivalent to ERP imaging. Japan proposed unique diagnostic criteria for AIP in 2011 (JPS 2011), which were a modification of the ICDC, to render them more convenient and highly specific for the diagnosis of AIP type 1, the exclusively dominant type of AIP in Japan [22,32,33]. Recently, the JPS 2011, which have been used domestically for 7 years were revised partially, and new criteria, i.e., the JPS 2018, were proposed [34]. The JPS 2018 included MRCP imaging for the diagnosis of AIP under the caveat that proper MRI apparatus and suitable conditions would be used for the imaging process, in addition to conventional ERP imaging. The inclusion of MRCP as a diagnostic tool may facilitate the use of the slightly complicated ICDC in daily clinical practice. Therefore, it is important to discuss whether MRCP imaging can be employed for "ductal imaging (D)" of the ICDC in order to promote greater global awareness of AIP.

Endoscopic Ultrasound-Guided Fine-Needle Biopsy (EUS-FNB)

AIP types 1 and 2 are pathologically defined as LPSP and IDCP/GEL, respectively [10,12–14].

The definitive diagnosis of type 1 or 2 AIP can be made by histology alone if Level 1 findings of the "histology of the pancreas (H)" in the ICDC are confirmed. Level 2 findings of (H) also could be extremely helpful for the accurate diagnosis of AIP. The ICDC specify the use of pancreatic tissues obtained by core-biopsy or resection [17], because an adequate amount of tissue samples is required for detailed histologic examination to facilitate precise diagnoses of LPSP and IDCP/GEL. At the time of devising the ICDC, core-biopsy of the pancreas was performed only at a limited number of institutes in the world using the TruCut needle with a long tip [35,36]. However, the long tip and needle stiffness confer several disadvantages, such as difficulty in maneuvering the EUS device when used for the puncture, restriction of the site of the needle insertion only from the stomach (it does not function properly when used in the duodenum apex and the second portion of the duodenum), and restriction of the site of specimen collection to the swollen body of the pancreas [35]. However, several recent studies have suggested that sufficient tissue specimens can be collected by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) using fine 22-G needles for the diagnosis of LPSP [37,38]. Even more satisfactory results have been reported recently with the use of small-caliber core biopsy needles; the shape and sharpness of the needle tips were refined in order to achieve smooth and safe needle insertion and acquisition of well-shaped samples with preservation of the tissue structure [39–41]. Moreover, the recently published guidance for the diagnosis of AIP by biopsy samples [42] may promote the use of EUS-FNB for the diagnosis of AIP. Therefore, the adequacy of EUS-FNB as a tool for "histology of the pancreas (H)" in the ICDC should be deliberated upon.

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Laboratory Diagnosis of Autoimmune Pancreatitis

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Introduction

Autoimmune pancreatitis (AIP) is an enigmatic disease and has stirred up the field of pancreatology and gastroenterology as a whole. After the rediscovery of an autoimmune form of pancreatitis in the 1990s, the pivotal paper described the presence of elevated IgG and IgG4 in this form of pancreatitis (then called "sclerosing" pancreatitis). From histology (see Chapter XX), it became clear that there are two forms of AIP. Just the AIP type 1 was associated with IgG4, both in the serum and tissue. It became further apparent that AIP type 1 is part of a larger syndrome that is now known as IgG-related diseases (IgG-RD). With two types of AIP that may look similar upon imaging (see Chapter XX), but differ in their response to treatment and complications, the need for further serum markers became obvious.

Serum Markers

Generic Markers

The conventional markers of inflammation, namely, erythrocyte sedimentation rate (ESR), leucocytes—white blood cells (WBC), C-reactive protein (CRP), and procalcitonin, are of no use in establishing the diagnosis of AIP. Depending on the character of the respective disease form, stage, and time point, these may or may not be elevated.

Pancreatic Enzymes

Ninety-three years ago, it was stated that "elevated amylase has become a cornerstone in the diagnosis of pancreatitis" [1]. Although the specificity of both serum amylase and lipase for chronic pancreatitis (CP) is acceptable, in the range of 90–95%, their sensitivity is extremely low, oscillating around 10%. Consequently, serum markers can neither be used for establishing the diagnosis of CP nor for the diagnosis of AIP. Serum elastase-1 is useful in acute pancreatitis [2] but has no better performance in CP or AIP [3].

While we could not demonstrate significant differences for absolute values of cationic (PRSS1) and anionic trypsinogen (PRSS2) [4] in AIP, CP, and healthy controls, we found a change in the PRSS1-PRSS2 ratio in healthy individuals (ratio 1 : 3). In AIP (ratio 1 : 2) PRSS2 dominates [4], and in non-AIP CP the ratio was shifted toward PRSS1 (ratio 2 : 1).

If one reflects on how amylase, like any other enzyme, reaches the circulation (serum) [5], its low specificity and sensitivity are not surprising. After massive damage of exocrine pancreatic tissue, that is, leakage through dead cells, serum levels rise significantly; however, this condition is not chronic (autoimmune) pancreatitis, but acute pancreatitis. Other promising markers such as pancreatic stone protein [6] and procarboxypeptidase B [7] have also not fulfilled expectations as sensitive markers for CP and neither are of use in diagnosing AIP.

Taken together, neither a generic marker nor serum levels of pancreatic enzymes can be used to establish the diagnosis of AIP.

Markers of Autoimmunity

Generic markers of autoimmune disease are certain immunoglobulin classes and some other markers. Elevated IgG and especially IgG4 has been the first marker for AIP [8], later found to be related to the type 1 (lymphoplasmacytic sclerosing pancreatitis, LPSP) that

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later was determined to be part of the IgG syndrome, immunoglobulin G4-related disease (IgG-RD) [9]. As a result of many studies in AIP, elevated levels of both IgG and/or IgG4 have been determined to be one of the diagnostic criteria for AIP type 1 in the international consortium for diagnostic criteria (ICDC) for AIP [10].

However, serum IgG4 concentrations can be normal in up to 40% of patients with histologically proven IgG4-RD. Several groups have reported a lack of sensitivity and specificity of elevated serum IgG4 levels to establish the diagnosis of IgG4-RD or to distinguish from primary sclerosing cholangitis (PSC) or cholangiocarcinoma [11,12]. Even not good correlation between tissue and serum levels of IgG4 was reported [12]. IgG4 serum levels seem to have diagnostic value when the level is higher than four times the upper level of normal, which is the case in only a minority of patients [11]. This is the reason why IgG4 serum levels should be put in the right context in the diagnostic workup of suspected AIP type 1, and combine with other diagnostic criteria (histology, organ morphology at imaging, search for other organ involvement, and response to glucocorticoid treatment).

Other measures of autoimmunity, i.e., nonspecific markers that can be found are: antinuclear antibodies (ANA = 54–69%), rheumatoid factor (RF = 23–33%), and autoantibodies against smooth muscles (ASMA = 15%) [13,14]. In an attempt to define a serum marker profile, we could not describe a set specifically for AIP [15], even if this was successful for pancreatic cancer [16].

Autoantibodies against specific target tissue-related antigens are the hallmark of any autoimmune disease. Autoantibodies can be divided into two categories: consisting of nonorgan and organ-specific autoantibodies. Shortly after the initial description of IgG4, the first autoantibodies against pancreatic antigens were described in AIP: antibodies against lactoferrin and antibodies against carbonic anhydrase type II, the lead enzyme of the pancreatic duct epithelial lining producing bicarbonate [17]. However, only a small subset of patients seem to be positive [18] (Table 73.1). The third autoantibody described was against SPINK1 [13], a protein known to be disease-facilitating once mutated in some forms of hereditary pancreatitis [19]. These autoantibodies against SPINK1 could be confirmed in an independent patient group by another investigator [4]. Of the autoantibodies described above, only those against carbonic anhydrase type II and lactoferrin are commercially available; however, sensitivity is low and thus their clinical use is limited. Therefore, these autoantibodies cannot be recommended for the diagnosis of AIP [12].

Another autoantibody requires mentioning because it could suggest a link to the possible etiology or causing agent/precipitating event: the ubiquitin-protein ligase E3 component n-recognin 2 (UBR2), is an enzyme highly expressed in acinar cells of the pancreas [20]. There is a certain degree of homology to the plasminogen-binding protein (PBP) of *Helicobacter pylori*—an agent that has been suggested to be linked to AIP for another homology between *Helicobacter pylori cag-A* and human carbonic anhydrase type II in a molecular mimicry fashion [21–23]. However, no confirmatory studies have been performed with URB2. We were also unable to detect *Helicobacter pylori* DNA in pancreatic tissue samples from AIP [24].

Another antibody against the acinar compartment, amylase α2A, was described with good sensitivity and reasonable specificity [25] (Table 73.1); however, this has not been confirmed in larger cohorts.

None of the autoantibodies could be correlated with the expression levels of IgG or IgG4 and when investigated, the autoantibodies were not of the IgG4 class [14]. None of these antibodies are absolutely disease-specific and this is one of the distinct features of AIP compared to other gastrointestinal and liver autoimmune disease characterized by disease-specific autoantibodies such as anti-mitochondrial antibodies (AMA) in PBC and anti-liver kidney microsomal-1 (LKM1) in AIH [14].

Table 73.1 Disease-specific autoantibodies and immunoglobulins in autoimmune pancreatitis.

Antigen	% pos all AIP	AIP 1	AIP 2	Sensitivity	Specificity	% pos in PDAC	References
CA II	53.8					n.d.	[13,17]
Lactoferrin	73			73		0	[13,17]
SPINK1	42			79*		n.d.	[13, 4]
Trypsinogens	79					0	[4]
UBR2	95					10	[20]
Amylase α2A	79	67	75			0	[25]
IgG, IgG4	40	80	<5	41	99	10	[8]

CA-II: carbonic anhydrase II; *: SPINK1 and ALF together; n.d.: not determined; PDAC: pancreatic ductal adenocarcinoma.

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Preliminary studies have reported promising results for new diagnostic biomarkers for IgG4-RD that might be more accurate than serum IgG4 levels. Next-generation sequencing identified class-switched IgG4+ clones in blood and affected tissue, predominantly in the IgG B cell receptor repertoire [12,26]. The presence of these IgG4+ clones could differentiate active IgG4-RD of the bile ducts and pancreas from other types of hepatopancreatobiliary disease. In a similar way, circulating plasmablasts and CC-chemokine ligand 18 (CCL18) levels seem to have value in the diagnosis of IgG4-RD and in monitoring the disease course [27]. However, confirmation of these preliminary results in larger cohorts is certainly warranted for these markers.

By contrast, blood IgG4 to IgG RNA ratio, previously described as a promising diagnostic marker, lacked specificity for IgG4-RD of the pancreas and bile ducts in a prospective cohort study of patients with suspicion of pancreatobiliary malignancies [12,28]. Of interest, antibodies against prohibitin, annexin A11, and laminin 511-E8 have been found in only a small portion of patients with IgG4-RD [12].

We propose a possible pathomechanism, based on the RNA expression profiling and proteomics data in conjunction with the findings in the blood explaining the occurrence of these antibodies, at least against the acinar antigens (Fig. 73.1). It is based on the fine description of IgG-RD elsewhere [9].

Other Markers

For the diagnosis of (chronic) pancreatitis, especially AIP, some other body fluids could be used. One would be pancreatic juice collected during ERCP or in the duodenum, stimulated after secretin injection. In an attempt to describe markers from pancreatic juice samples, we could not detect any with high-resolution 2D-PAGE [29]. The cytologic analysis will not reveal anything diagnostically relevant for establishing the diagnosis of AIP.

Fecal elastase-1 (FE-1), a marker of pancreatic exocrine insufficiency (PEI), can also be measured. It is a rather crude marker, which if positive (below 200 µg/g) constitutes the diagnosis of PEI and in so doing would

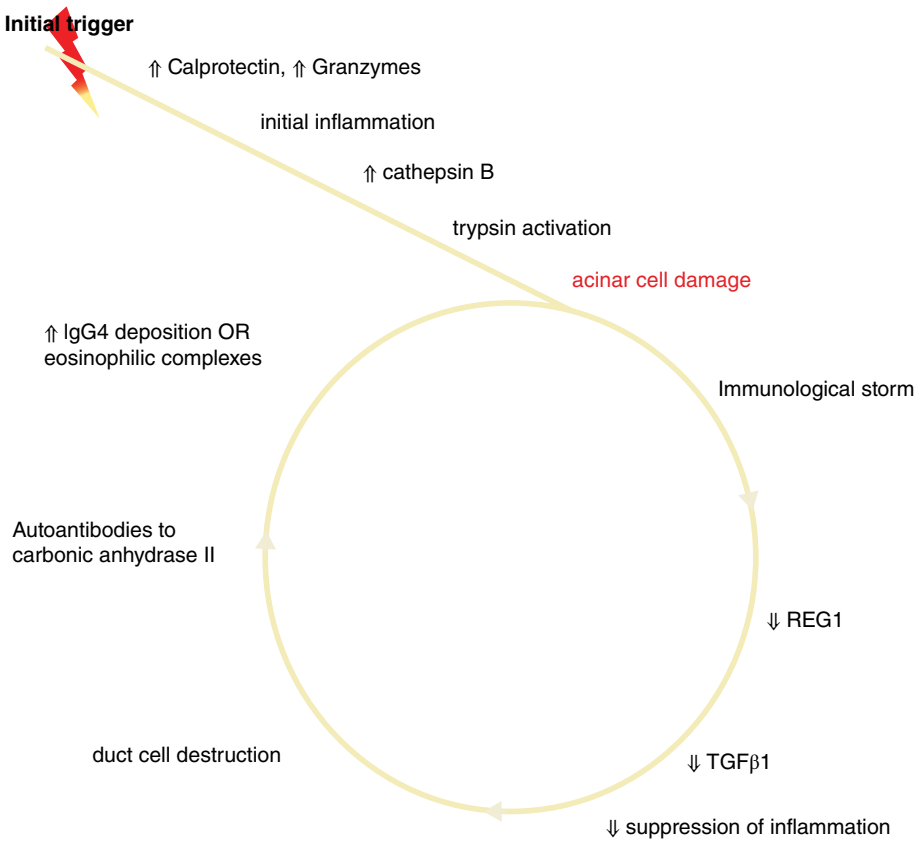


Figure 73.1 Pathomechanism explaining the occurrence of autoantibodies in AIP. *Source:* Using expression profiling data from Löhr et al. 2010 [4].

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confirm the diagnosis of any sort of chronic pancreatitis. In itself, however, FE-1 is not specific, neither for chronic nor autoimmune pancreatitis.

Conclusion

The only clinically relevant possibilities to diagnose AIP with blood-based assays are serum IgG and IgG4 under consideration of clinical findings. The only commercially available autoantibody assays exist for autoantibodies against lactoferrin, carbonic anhydrase type II, and SPINK1, the latter only in Japan and not in Europe. These three autoantibodies have been shown to be of relevance in several studies. Especially the newer autoantibodies against URB2 and trypsinogens warrant confirmation and the availability of commercial ELISA tests as well as results of the promising studies on next-generation sequencing. So far, attempts to find novel markers have been unsuccessful.

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What is the Evidence Measuring Immune Markers

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Introduction

Autoimmune pancreatitis (AIP) is a distinct type of chronic pancreatitis that is presumably caused by autoimmune mechanisms. Although several immune markers have been identified for AIP diagnosis, immunoglobulin (Ig) G4 has been established as the most reliable in differentiating AIP from such mimicking conditions as pancreatic cancer as well as in the prediction of relapse during follow-up [1,2]. This chapter will discuss the evidence on measuring immune markers in AIP, with special reference to their usefulness in diagnosis, differentiation from mimickers, and prediction of relapse. AIP has been restricted to type 1 in this chapter since the detailed clinical features of type 2 AIP remain unclear.

Evidence on the Utility of Markers in AIP Diagnosis

In earlier paper electrophoresis assays, most patients with AIP were observed to display a polyclonal band in the rapidly migrating fraction representative of the now characteristic phenomenon of β-γ globulin bridging (Fig. 74.1). Immunoprecipitation trials revealed this finding to be due to high serum concentrations of IgG4 [2]. Moreover, approximately 90% of AIP patients exhibited increased serum IgG4 values, whereas few patients with other diseases, including pancreatic cancer, chronic pancreatitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis, and Sjögren syndrome, showed such elevations (Fig. 74.2) [2]. In contrast, high levels of total IgG and IgE were detected in 70% and 33% of AIP patients, respectively, both of which were also positive in a variety of other conditions. The immune markers antinuclear antibody and rheumatoid factor showed low respective detection sensitivities for AIP of 40% and 30%. Disease-specific autoantibodies, such as anti-Sjögren syndrome A (SSA)/Ro, anti-Sjögren syndrome B (SSB)/La, and anti-mitochondrial antibodies, which have been useful in the diagnosis of Sjögren syndrome and PBC, were also rarely observed in AIP [1,3]. The above results strongly indicated IgG4 as a particularly sensitive and specific biomarker for AIP diagnosis. The efficacy of IgG4 in identifying AIP has since become well recognized worldwide. One meta-analysis of seven representative studies showed an overall sensitivity of 82%, specificity of 95%, diagnostic odds ratio (DOR) of 63.9, and favorable area under the receiver operating characteristic curve (AUROC) value of 0.920 ± 0.073 [4]. Another meta-analysis of 15 studies demonstrated similar overall results for IgG4, with a sensitivity of 74%, specificity of 94%, DOR of 62.91, and AUROC of 0.953 [5]. A recent meta-analysis of 13 studies reported comparable overall results of 72% sensitivity, 93% specificity, 51.37 DOR, and 0.72 AUROC [6], and a nationwide survey on AIP in Japan involving 1449 patients showed a sensitivity of 84.5% [7]. Consequently, serum IgG4 measurement has been adopted as a key item in numerous diagnostic criteria systems for AIP [8,9].

The infiltration of IgG4-bearing plasma cells in affected pancreatic tissue has been established as a histologic hallmark for the pathologic diagnosis of AIP [10]. Additionally, the discovery of extrapancreatic involvement with IgG4-bearing plasma cell infiltration in various tissues has helped identify the new disease concept of IgG4-related disease (IgG4-RD). AIP is now recognized as a pancreatic manifestation of this systemic

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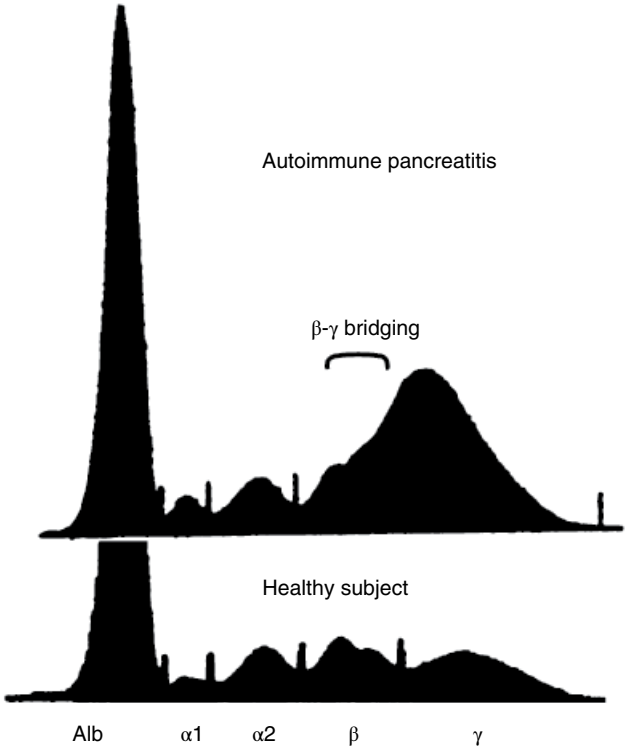


Figure 74.1 Paper electrophoresis of serum from a patient with AIP displaying characteristic β-γ globulin bridging and from a healthy subject. *Source:* Tan to Sui 2001. Reproduced with permission of Igakutosho-shuppan.

disease, for which IgG4 seems to exert a major pathogenic role and accordingly has been recognized as a useful diagnostic marker [1,11,12].

Apart from IgG4, the serum values of several other immunoglobulins also represent novel diagnostic markers of AIP. Taguchi et al. measured the serum levels of IgG, IgA, IgM, and IgG4 in individuals with AIP or other hepatopancreatic diseases and witnessed that IgM and IgA were markedly decreased in patients with untreated AIP, indicating a reciprocal correlation between IgM or IgA and IgG. Thereafter, the ratios of IgG to IgM and IgG to IgA were determined to be significantly higher in AIP than in other diseases, providing a diagnostic sensitivity and specificity for the differentiation of AIP from other hepatopancreatic conditions almost equivalent to those of IgG4 [13]. Those ratios show promise as useful, low-cost markers that require only simple calculations based on routine immunoglobulin examinations. Ikemune et al. have reported that patients with AIP display increased serum k and λ free light chain (FLC) concentrations, summated FLC, and κ/λ ratios, all of which may be useful in diagnosing AIP and monitoring disease activity [14]. Recent studies have also identified increased serum levels of interferon (IFN)-α and interleukin (IL)-33 [15], as well as several causative autoantigens in AIP and IgG4-RD including laminin 511 [16], annexin A11 [17], and galectin-3 [18]. Further research is needed to validate their utility as diagnostic immune markers.

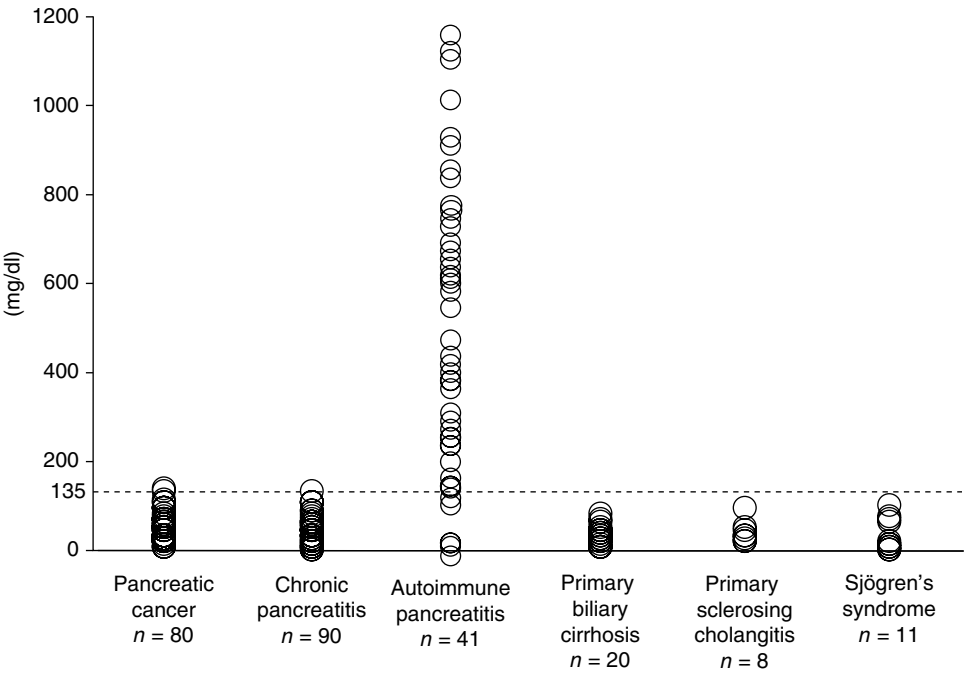


Figure 74.2 Scattergram of serum IgG4 values in AIP and various other conditions. *Source:* Adapted from [2].

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Evidence on the Utility of Markers in Differentiating AIP from Mimicking Conditions

AIP is reportedly characterized by elderly male preponderance, onset with obstructive jaundice, apparent pancreatic swelling in various imaging tests, irregular narrowing of the main pancreatic duct, and stenosis of the lower bile duct [1,3]. As these features mimic those of pancreatic cancer, extensive examination is needed for proper differentiation; in fact, 2–3% of individuals who underwent surgery based on a diagnosis of pancreatic cancer were later revealed to have had AIP [19,20]. At a cutoff value of 135 mg/dL, IgG4 level as a biomarker displayed a sensitivity of 90%, specificity of 98%, and accuracy of 95% in distinguishing between AIP and pancreatic cancer [2]. The efficacy of IgG4 in differentiating AIP from pancreatic cancer has since been supported worldwide. One meta-analysis of seven representative studies showed an overall sensitivity of 82%, specificity of 95%, DOR of 144.6, and favorable AUROC value of 0.914 ± 0.191 [4]. Another meta-analysis of 15 studies showed comparable overall results of 73% sensitivity, 93% specificity, 60.61 DOR, and 0.926 AUC [5], with a third such analysis of 13 studies yielding results of 72% sensitivity, 93% specificity, 51.37 DOR, and 0.72 AUROC [6]. However, mild (i.e., <twofold cutoff value) elevations in serum IgG4 have also been seen in pancreatic cancer [21,22]. It must therefore be emphasized that IgG4 elevation alone does not necessarily rule out the existence of malignancy since AIP complicated with pancreatic cancer has been reported as well [23–25]. Shih et al. revealed that AIP and pancreatic cancer patients have distinct IgG-glycosylation profiling. Using classification and regression tree analysis of IgG galactosylation and sialylation ratios to discriminate AIP from pancreatic cancer, the diagnostic accuracy of the glycan markers was 93.8%, with 94.6% sensitivity and 92.9% specificity [26].

AIP is histologically defined as lymphoplasmacytic sclerosing pancreatitis (LPSP) with abundant lymphoplasmacytic infiltration, storiform fibrosis, and obstructive phlebitis [27]. However, another type of AIP histologically identified as idiopathic duct-centric chronic pancreatitis (IDCP) [28] or AIP with granulocytic epithelial lesion (GEL) [29], which is characterized by granulocytic infiltration in the ductal epithelium has been identified mainly in Europe and America. Although both types of AIP share certain imaging finding similarities, IDCP/AIP with GEL has no known correlation with IgG4 [28,30]. AIP is now classified as type 1 or type 2 based on the pathologic subtypes of LPSP and IDCP/AIP with GEL, respectively [31]. In an international survey, type 2 AIP was observed in 8% of cases, with the proportion of this subtype being remarkably lower in Asian countries (3.7%) than in European (12.9%) and North American (13.7%) populations [32].

Evidence on the Utility of Markers in Predicting Relapse

Although individuals with AIP usually respond well to corticosteroid treatment, relapse is a characteristic feature of AIP that occurs in an estimated 23–31% of patients based on several long-term follow-up studies [7,33,34]. Relapse may be a predisposition factor for pancreatic calcification, which in turn possibly triggers the transition to a chronic pancreatitis state with exocrine and endocrine dysfunction [35,36]. Accordingly, useful biomarkers that predict AIP relapse are needed for the establishment of effective prophylactic measures.

IgG4 seropositivity at diagnosis was found to be a significant independent factor of relapse prediction in AIP patients [37–39]. Other investigations also reported significantly higher AIP relapse rates of approximately sixfold in AIP groups with elevated serum IgG4 levels than in those with normal IgG4 values [40,41].

In the clinical course of a 69-year-old woman with AIP who experienced two relapses, serum elevations of IgG4 and immune complex (IC) preceded the overt appearance of each clinical relapse by several months (Fig. 74.3) [42], indicating that IgG4 and IC could predict relapse and represent disease activity with high sensitivity. Elsewhere, persistently elevated serum IgG4 values were associated with AIP relapse and steroid therapy failure of disease control [33,43,44], and Matsubayashi et al. reported that high serum IgG4 levels were related to severe clinical profiles that included jaundice, large pancreatic lesions, a high frequency of extrapancreatic lesions, and relapse [45].

While steroid therapy is generally effective for AIP, the incidence of relapse within 3 years after the start of treatment is relatively high [46]. Maintenance therapy (MT) for 3 years may decrease the frequency of relapse as compared with simple discontinuation of symptomatic treatment at 26 weeks [47]. Thus, it will be crucial to identify accurate predictors of relapse related to the eventual tapering or discontinuation of steroids. Nakamura et al. found that at least four other organ involvements at diagnosis and IgG of 1400 mg/dL or greater at 3 years of MT were predictive factors of relapse after MT for 3 years [48]. Shimizu et al. revealed that the rate of serum IgG4 decrease after the start of treatment was significantly higher in a nonrelapse group than in a relapse one, suggesting that AIP patients responding to initial steroid therapy with a rapid drop in serum IgG4 were less likely

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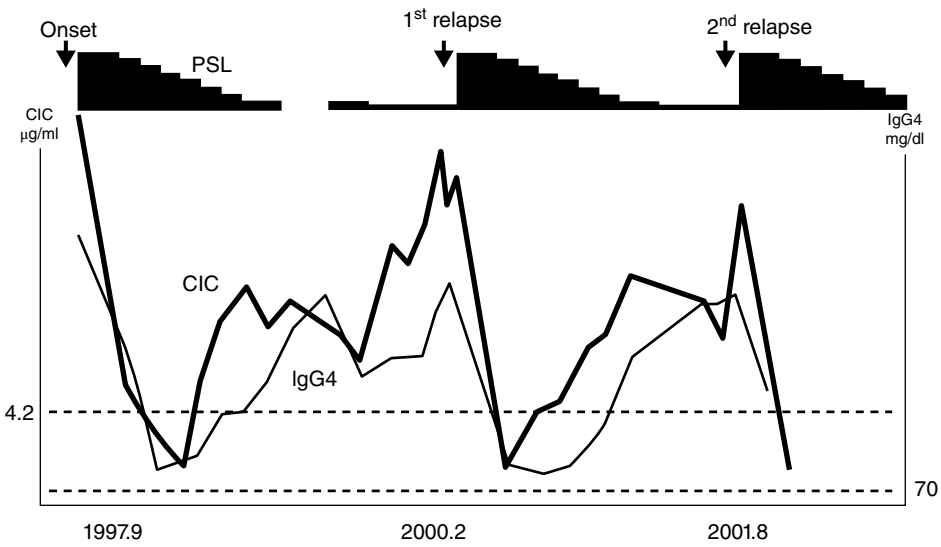


Figure 74.3 Clinical course of a 69-year-old female patient with AIP demonstrating a correlation between two recurrences and preceding IgG4 and IC increases. CIC: circulating immune complex; PSL: prednisolone. *Source:* [42]. With permission of Springer Nature.

to experience a relapse and implicating the rate of IgG4 decrease as a predictor AIP recurrence [49]. In agreement with those findings, the relative rise of serum IgG4 levels after steroid therapy was significantly higher in relapse than in nonrelapse cases [43].

Regarding other immune markers, IC values at treatment onset were significantly higher in a relapse than in a nonrelapse group, indicating possible use as a predictive marker [50]. Additional activity immune markers of AIP include total IgG, complement C3 and C4, soluble interleukin-2 receptor, and β2-microglobulin, all of which may have use in the prediction of AIP relapse [1,3]. Especially since IgG and complement C3 and C4 are low-cost and routinely measured, these parameters represent readily available means of predicting relapse in regular clinical practice and warrant further study.

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Autoimmune Pancreatitis and IgG4-Related Disease

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Concepts of IgG4-Related Disease

IgG4 related-disease (IgG4-RD) is a fibroinflammatory disorder recognized as a novel clinical entity with multi-organ involvement and unknown origin, associated with abundant infiltration of IgG4-positive cells and fibrosis [1–4] (Fig. 75.1). Involvement of the central nervous system, thyroid, lacrimal glands, salivary glands, breast, lung, liver, bile duct, pancreas, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, and skin have been reported [1–3]. Infiltration of IgG4-positive cells, increased serum levels of IgG4, storiform fibrosis, and obliterative phlebitis are characteristic findings of IgG4-RD. The patients with IgG4-RD, either synchronously or metachronously, have diffuse or focal organ enlargement and mass-forming or nodular/thickened lesions in systemic organs [1–4]. IgG4-RD mainly affects middle-aged to elderly men except for IgG4-related dacryoadenitis/sialadenitis, so-called Mikulicz disease. Clinical symptoms vary depending on individual organs and are dramatically relieved by steroid therapy in many cases [1–4]; however, the long-term prognosis still remains unclear. Some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic disease; hydronephrosis due to retroperitoneal fibrosis; or respiratory symptoms due to pulmonary disease.

At the 1st International Symposium on IgG4-RD, the nomenclature of individual organ manifestations was proposed (Table 75.1) using "IgG4-related" as a modifier, except for the pancreatic manifestation [3] termed "type 1 autoimmune pancreatitis (IgG4-related pancreatitis)," because it is widely accepted among gastroenterologists and pancreatic surgeons, and helps to discriminate between type 1 and type 2 AIP, which is not a part of the IgG4-RD spectrum. When the pathogenesis of type 2 AIP is clarified, the term "type 1 AIP" might be replaced by "IgG4-related pancreatitis" [3].

Diagnosis of IgG4-RD

The lesions of IgG4-RD are usually detected by imaging (computed tomography [CT], magnetic resonance imaging [MRI], gallium scintigraphy, fluorodeoxyglucose positron emission tomography [FDG-PET]) and blood tests (IgG4 concentration); however, these should be confirmed by histologic findings as much as possible. Organ lesions in IgG4-RD are sometimes misdiagnosed as other mimic disorders in the corresponding organs: lachrymal and salivary gland lesions for Sjögren syndrome, respiratory lesions for sarcoidosis, and sclerosing cholangitis for primary sclerosing cholangitis (PSC) [1–3]. Therefore, it is necessary to differentiate between IgG4-related diseases and mimickers. The patients can be diagnosed by using the Japanese revised comprehensive diagnostic criteria for IgG4-RD (Table 75.2) [5] in 2020 (CDC 2020) or 2019 ACR/EULAR classification criteria (Table 75.3) [6]. The patients who cannot be diagnosed by CDC 2020 may be diagnosed in combination with the CDC 2020 and individual organ-specific diagnostic criteria such as AIP [7], IgG4-related sclerosing cholangitis [8], IgG4-related kidney diseases [9], IgG4-related ophthalmic disease [10], IgG4-related pulmonary disease [11], and IgG4-related periaortitis/periarteritis and retroperitoneal fibrosis [12].

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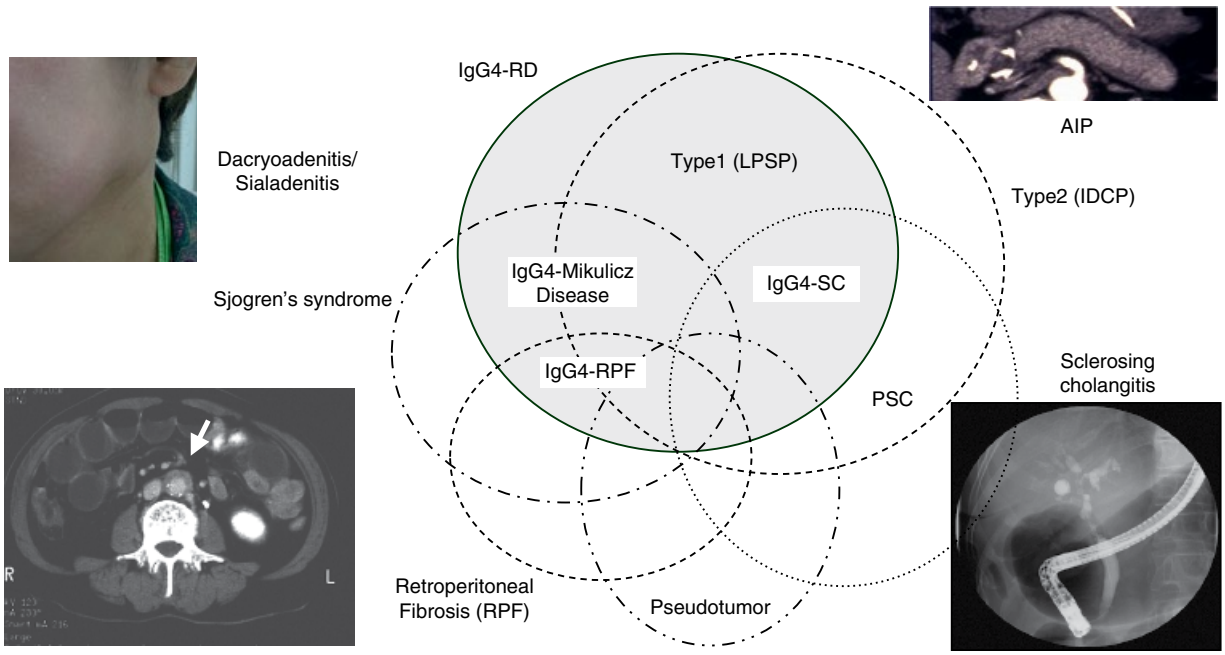


Figure 75.1 Current concept of IgG4-related disease. IgG4-RD contains multiorgan involvement simultaneously or metachronously. *Source:* Okazaki, K et al. [2015] / Reproduced with permission from Wolters Kluwer Health, Inc.

Table 75.1 Preferred nomenclature for individual organ manifestations of IgG4-related disease.

Organ System/Tissue	Preferred Name
Pancreas	Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
Eye	IgG4-related ophthalmic disease is the general term for the peri-ocular manifestations of this disease. There are several subsets, outlined below.
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue (orbital inflammatory pseudotumor)	IgG4-related orbital inflammation
Extra-ocular muscle disease	IgG4-related orbital myositis
Orbit with involvement of multiple anatomic structures	IgG4-related pan-orbital inflammation (includes lacrimal gland disease, extra-ocular muscle involvement, and other potential intra-orbital complications)
Salivary glands (parotid and submandibular glands)	IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
Pachymeninges	IgG4-related pachymeningitis
Hypophysis	IgG4-related hypophysitis
Thyroid (Riedel's thyroiditis)	IgG4-related thyroid disease
Aorta	IgG4-related aortitis/peri-aortitis
Arteries	IgG4-related periarteritis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis

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Table 75.1 (Continued)

Organ System/Tissue	Preferred Name
Liver	IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
Lung	IgG4-related lung disease
Pleura	IgG4-related pleuritis
Pericardium	IgG4-related pericarditis
Kidney	IgG4-related kidney disease. The specific renal pattern should be termed IgG4-related tubulointerstitial nephritis and membranous glomerulonephritis secondary to IgG4-RD. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis.
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis

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Table 75.2 The revised 2020 comprehensive diagnostic criteria for IgG4-related disease.

1) clinical and radiological features
   One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted.
2) serological diagnosis
   Serum IgG4 levels greater than 135 mg/dl.
3) pathological diagnosis
   Positivity for two of the following three criteria:
   ① Dense lymphocyte and plasma cell infiltration with fibrosis.
   ② Ratio of IgG4-positive plasma cells /IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high powered field.
   ③ Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis.

Diagnosis:
Definite: 1) + 2) + 3)
Probable: 1) + 3)
Possible: 1) + 2)

Source: [5]. With permission of Elsevier.
Explanatory note 1: Combination of organ-specific diagnostic criteria*.
Patients with a possible or probable diagnosis by comprehensive diagnostic criteria who fulfill the organ-specific criteria for IgG4-RD are regarded as being definite for IgG4-RD.
* Diagnostic criteria according to the IgG4-related organ: ① International consensus diagnostic criteria for autoimmune pancreatitis [7], ② IgG4-related lacrimal gland, saliva adenitis diagnostic criteria [8], ③ Diagnostic criteria for IgG4-related kidney disease [9], ④ Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012 [10], ⑤Diagnostic criteria for IgG4-related ophthalmic disease [11], ⑥Diagnostic criteria for IgG4-related respiratory disease [12], ⑦ Diagnostic criteria for IgG4-related large periarteritis/periarteritis and retroperitoneal fibrosis [13].
Explanatory note 2: exclusion diagnosis.
1) It is important to acquire tissue samples from each involved organ to distinguish malignant tumors (e.g., cancer, malignant lymphoma) and similar benign conditions (e.g., Sjögren syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, secondary retroperitoneal fibrosis, granulomatosis with polyangiitis, sarcoidosis, eosinophilic granulomatosis with polyangiitis).
2) It is important to exclude an infectious- or inflammation-related disease in patients with high fever, highly elevated CRP and neutrophilia.
Explanatory note 3: pathologic diagnosis.
1) The numbers of IgG4-positive cells are usually more abundant in resected organs and partially enucleated tissue than in tissue samples obtained by needle biopsy or endoscopic biopsy. Thus, it is important to not be too particular about cell number and to provide a precise judgment.
2) Storiform fibrosis is defined as spindle-shaped cells, inflammatory cells and fine collagen fibers forming a flowing arrangement. Obliterative phlebitis is defined as fibrous venous obliteration with inflammatory cells. Both are helpful for a diagnosis of IgG4-RD. ① and ③ without ② can only be applied in a case with poor IgG4 and/or IgG staining.
Explanatory note 4: steroid reactivity.
Steroid trial is not recommended. However, if patients do not respond to initial steroid therapy, the diagnosis should be reconsidered.

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Table 75.3 The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD.

Step	Categorical assessment or numerical weight
Step 1. Entry criteria	
Characteristic* clinical or radiological involvement of a typical organ (eg, pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges or thyroid gland (Riedel's thyroiditis)) OR pathological evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain aetiology in one of these same organs	**Yes**† or No
Step 2. Exclusion criteria: domains and items‡	Yes or **No**§
Clinical	
Fever	
No objective response to glucocorticoids	
Serological	
Leucopenia and thrombocytopenia with no explanation	
Peripheral eosinophilia	
Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase)	
Positive SSA/Ro or SSB/La antibody	
Positive double-stranded DNA, RNP or Sm antibody	
Other disease-specific autoantibody	
Cryoglobulinemia	
Radiological	
Known radiological findings suspicious for malignancy or infection that have not been sufficiently investigated	
Rapid radiological progression	
Long bone abnormalities consistent with Erdheim-Chester disease	
Splenomegaly	
Pathological	
Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
Markers consistent with inflammatory myofibroblastic tumour	
Prominent neutrophilic inflammation	
Necrotizing vasculitis	
Prominent necrosis	
Primarily granulomatous inflammation	
Pathologic features of macrophage/histiocytic disorder	
Known diagnosis of the following:	
Multicentric Castleman's disease	
Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present)	
Hashimoto thyroiditis (if only the thyroid is affected)	
If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.	
Step 3. Inclusion criteria: domains and items¶	
Histopathology	
• Uninformative biopsy	0
• Dense lymphocytic infiltrate	+4

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Table 75.3 (Continued)

Step	Categorical assessment or numerical weight
• Dense lymphocytic infiltrate and obliterative phlebitis	+6
• Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
• Immunostaining**	0–16, as follows: Assigned weight is 0 if the IgG4+:IgG+ ratio is 0%–40% or indeterminate and the number of IgG4+ cells/hpf is 0–9.‡‡Assigned weight is 7 if: (1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+cells/hpf is 0–9 or indeterminate or (2) the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is ≥10 or indeterminate.Assigned weight is 14 if: (1) the IgG4+:IgG+ ratio is 41%–70% and the number of IgG4+ cells/hpf is ≥10 or (2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50.Assigned weight is 16 if the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is ≥51.
Serum IgG_4 concentration	
• Normal or not checked	0
• >Normal but <2× upper limit of normal	+4
• 2–5× upper limit of normal	+6
• ≥>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual and submandibular glands	
• No set of glands involved	0
• One set of glands involved	+6
• Two or more sets of glands involved	+14
Chest	
• Not checked or neither of the items listed is present	0
• Peribronchovascular and septal thickening	+4
• Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
• Not checked or none of the items listed is present	0
• Diffuse pancreas enlargement (loss of lobulations)	+8
• Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
• Pancreas (either of above) and biliary tree involvement	+19
Kidney	
• Not checked or none of the items listed is present	0
• Hypocomplementemia	+6
• Renal pelvis thickening/soft tissue	+8
• Bilateral renal cortex low-density areas	+10
Retroperitoneum	
• Not checked or neither of the items listed is present	0
• Diffuse thickening of the abdominal aortic wall	+4
• Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8
Step 4: Total inclusion points	
A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20	

(*Continued*)

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Table 75.3 (Continued)

* Refers to enlargement or tumor-like mass in an affected organ except in (1) the bile ducts, where narrowing tends to occur, (2) the aorta, where wall thickening or aneurysmal dilatation is typical and (3) the lungs, where thickening of the bronchovascular bundles is common.
† If entry criteria are not fulfilled, the patient cannot be further considered for classification as having IgG4-RD.
‡ Assessment for the presence of exclusion criteria should be individualised depending on a patient's clinical scenario.
§ If exclusion criteria are met, the patient cannot be further considered for classification as having IgG4-RD.
¶ Only the highest weighted item in each domain is scored.
** Biopsies from lymph nodes, mucosal surfaces of the gastrointestinal tract and skin are not acceptable for use in weighting the immunostaining domain.
†† 'Indeterminate' refers to a situation in which the pathologist is unable to clearly quantify the number of positively staining cells within an infiltrate, yet can still ascertain that the number of cells is at least 10/hpf. For a number of reasons, most often pertaining to the quality of the immunostain, pathologists are sometimes unable to count the number of IgG4+ plasma cells with precision yet even so, can be confident in grouping cases into the appropriate immunostaining result category.
hpf, high-power field; IgG4-RD, IgG4-related disease.
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Concepts of AIP

AIP is a distinct form of pancreatitis clinically characterized by frequent presentation with obstructive jaundice with or without a pancreatic mass. Recent studies have suggested that AIP is classified as two distinct subtypes, types 1 (IgG4-related pancreatitis) and type 2 with granulocytic epithelial lesion (GEL) [13,14], and the International Consensus Diagnostic Criteria (ICDC) for AIP [7], which enabled the differentiation of type 1 from type 2 AIP and is the most accepted major diagnostic criteria.

Type 1 AIP (IgG4-Related Pancreatitis)

Type 1 AIP accounts for the great majority of cases in Asia, and is frequently associated with obstructive jaundice in elderly males and extrapancreatic manifestations that respond to steroid therapy [1–7]. Clinically, type 1 AIP seems to be the pancreatic manifestation of IgG4-RD, characterized by: (i) mild abdominal symptoms, usually without acute attacks of pancreatitis; (ii) occasional occurrence of obstructive jaundice; (iii) increased serum gammaglobulin, IgG, and/or IgG4 concentrations; (iv) presence of autoantibodies; (v) diffuse, segmental or focal enlargement of the pancreas with a capsule-like low-density rim on dynamic CT/MRI images; (vi) irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP) images; (vii) histopathologically, lymphoplasmacytic sclerosing pancreatitis (LPSP): abundant infiltration of lymphocytes and IgG4-positive plasmacytes and fibrosis, and obliterative phlebitis; (viii) occasional association with other organ involvements (Figs. 75.2 and 75.3).

Type 2 AIP

Although type 1 AIP often occurs in older men and is accompanied by a variety of extrapancreatic lesions, type 2 AIP has no gender difference, younger age at onset (often <40 years). The most characteristic feature of type 2 AIP is the GEL [13,14], often with destruction and obliteration of the pancreatic duct (Figs 75.4 and 75.5). Type 2 AIP has swelling of the pancreas, but no or very few IgG4-positive plasma cells. Clinical features show a distinctly different profile, without serum IgG4, IgG elevation, presence of autoantibodies, or other organ involvement, except for inflammatory bowel disease.

Diagnosis of AIP

The patients with type 1 or type 2 AIP often have obstructive jaundice with similar pancreas imaging, but differentiation between these two subtypes and their associated diagnostic criteria has been achieved in the ICDC for AIP [7], which enabled an independent clinical diagnosis for each type. The diagnosis of type 1 AIP by ICDC requires a combination of five primary cardinal features (Tables 75.4 and 75.5): (i) imaging features of (a) pancreatic parenchyma (CT or MRI) and (b) pancreatic duct (ERCP or magnetic resonance cholangiopancreatography [MRCP]); (ii) serology (IgG4); (iii) other organ involvement; (iv) histopathology of the pancreas; and (v) response to steroid therapy. Conversely, the diagnosis of type 2 AIP is made in a combination of four of the primary cardinal features from type 1, excluding serology (Tables 75.6 and 75.7): (i) imaging features of (a) pancreatic parenchyma (CT/MRI) and (b) pancreatic duct (ERCP or MRCP); (ii) ulcerative colitis as other organ involvement; (iii) histopathology of the pancreas; and (iv) response to steroid therapy. Each criterion, except

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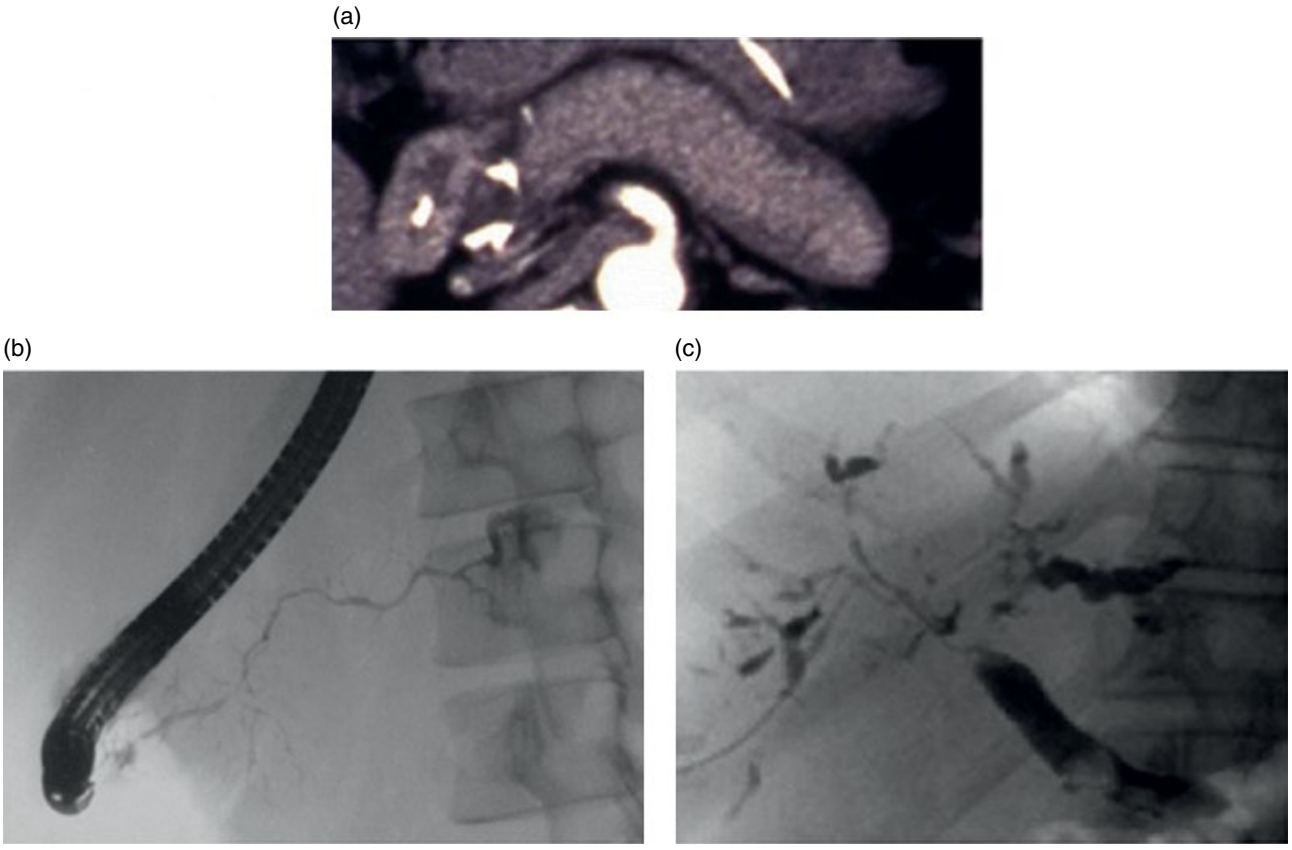


Figure 75.2 Pancreatic images of type 1 AIP. (a) Dynamic CT shows diffuse swelling of the pancreas with late phase enhancement and low-density rim. (b) Endoscopic pancreatography shows diffusely irregular narrowing of the main pancreatic duct. (c) Endoscopic cholangiography shows beaded like and long stenotic biliary duct similar to primary sclerosing cholangitis. *Source:* Okazaki, K et al. (2014) / Reproduced with permission from Elsevier.

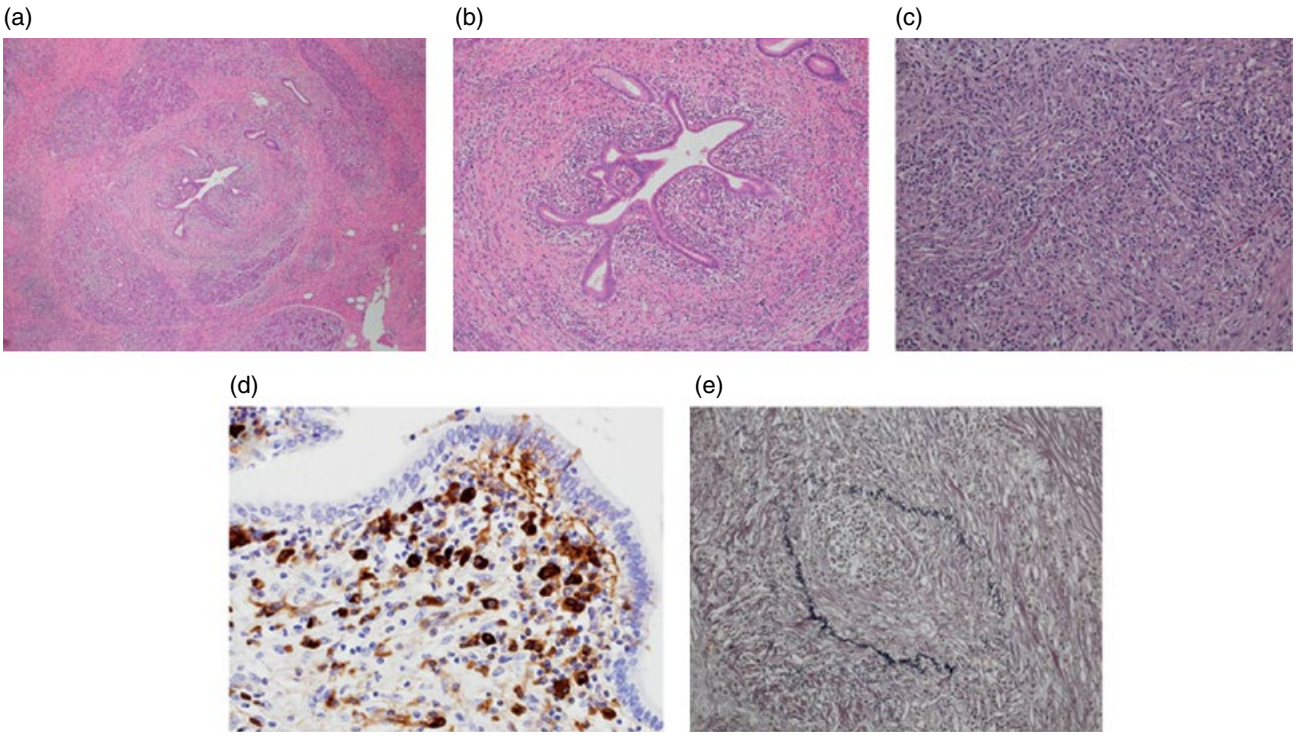


Figure 75.3 Lymphoplasmacytic sclerosing pancreatitis (LPSP). (a) Abundant infiltration of plasma cells and lymphocytes around the pancreatic duct with fibrosis (H&E, ×40). (b) Abundant infiltration of plasma cells and lymphocytes around the pancreatic duct with fibrosis (H&E, ×200). (c) Storiform fibrosis (H&E, ×400). (d) Abundant infiltration of IgG4-positive plasma cells (anti-IgG4 antibody staining, ×400). (e) Obliterative phlebitis (Evans staining, ×400). *Source:* Okazaki, K et al. (2014) / Reproduced with permission from Elsevier.

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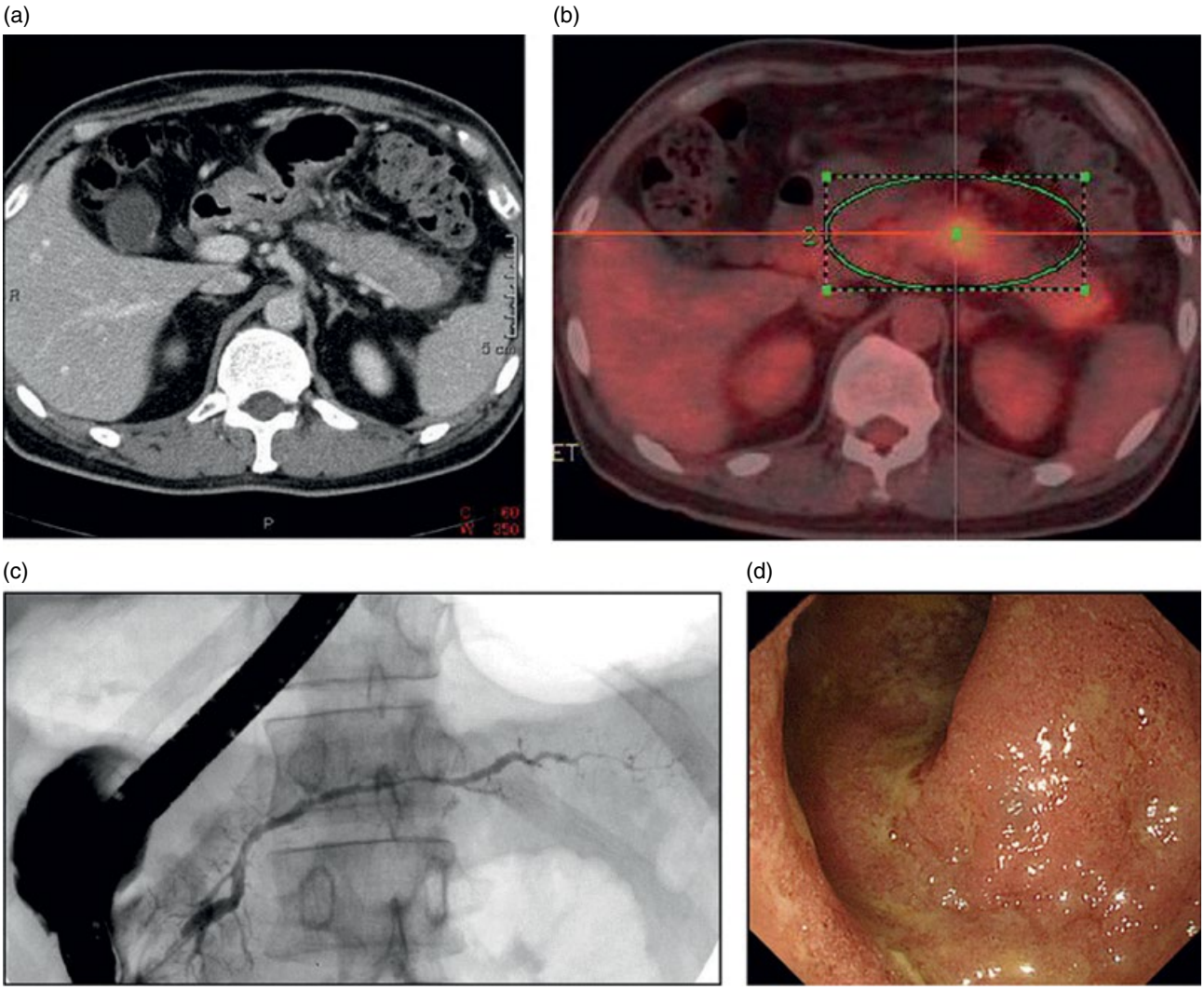


Figure 75.4 Pancreatic images of type 2 AIP. (a) Dynamic CT shows diffuse swelling of the pancreas with late phase enhancement and low-density rim (arrow) similar to type 1 AIP. (b) PET-CT shows diffusely abnormal accumulation of FDG. (c) Endoscopic pancreatography shows irregular narrowing of the main pancreatic duct. (d) Colonoscopy shows proctitis type of ulcerative colitis. *Source:* Okazaki, K et al. (2014) / Reproduced with permission from Elsevier.

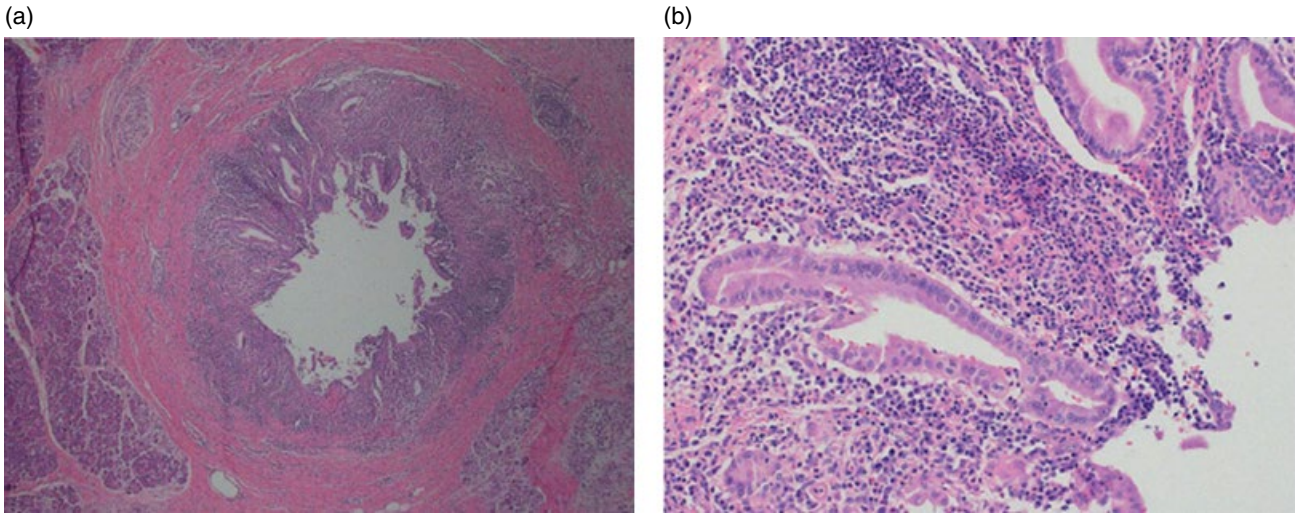


Figure 75.5 Granulocytic epithelial lesion. (a) Abundant infiltration of granulocytes into and around medium-sized pancreatic duct with destruction of epithelia (H&E, ×40). (b) Abundant infiltration of granulocytes into and around medium-sized pancreatic duct with destruction of epithelia (H&E, ×200). *Source:* Okazaki, K et al. (2014) / Reproduced with permission from Elsevier.

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Table 75.4 Diagnosis of definitive and probable type 1 AIP using ICDC.

Diagnosis	Primary Basis for Diagnosis	Imaging Evidence	Collateral Evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical Indeterminate	Any non-D level 1/level 2 Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

* Level 2 D is counted as level 1 in this setting. *Source:* [7]. With permission of Wolters Kluwer Health, Inc.

Table 75.5 Level 1 and level 2 criteria for type 1 AIP.

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2 × upper limit of normal value	IgG4, 1–2 × upper limit of normal value
OOI	Other organ involvement	a or b a) Histology of extrapancreatic organs Any three of the following: 1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration 2) Storiform fibrosis 3) Obliterative phlebitis 4) Abundant (>10 cells HPF) IgG4-positivc cells b) Typical radiological evidence At least one of the following: 1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture 2) Retroperitoneal fibrosis	a or b a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct‡: Both of the following: 1) Marked lymphoplasmacytic infiltration without granulocytic infiltration 2) Abundant (>10 cells/HPF) IgG4-positivc cells b) Physical or radiological evidence At least one of the following: 1) Symmetrically enlarged salivary/lachrymal glands 2) Radiological evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection) At least 3 of the following: 1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2) Obliterative phlebitis 3) Storiform fibrosis 4) Abundant (>10 cells/HPF) IgG4-positive cells	LPSP (core biopsy) Any 2 of the following: 1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2) Obliterative phlebitis 3) Storiform fibrosis 4) Abundant (>10 cells/HPF) IgG4-positive cells
Response to steroid (Rt)*		Diagnostic steroid trial Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

* Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.
† Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative (see algorithm).
‡ Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla often is involved pathologically in AIP.
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Table 75.6 Level 1 and level 2 criteria for type 2 AIP.

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
OOI	Other organ involvement		Clinically diagnosed inflammatory bowel disease
H	Histology of the pancreas (core biopsy/resection)	IDCP: Both of the following: 1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation 2) Absent or scant (0–10 cells/HPF) IgG4-positive cells	Both of the following: 1) Granulocytic and lymphoplasmacytic acinar infiltrate 2) Absent or scant (0–10 cells/HPF) IgG4-positive cells
Response to steroid (Rt)*		Diagnostic steroid trial Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in manifestations	

* Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.
† Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative (see algorithm).
Source: [7]. With permission of Wolters Kluwer Health, Inc.

Table 75.7 Diagnosis of definitive, probable type 2 AIP, and AIP-not otherwise specified using ICDC.

Diagnosis	Imaging Evidence	Collateral Evidence
Definitive type 2 AIP	Typical/ indeterminate	Histologically confirmed IDCP (level 1 H) or clinical inflammatory bowel disease + level 2 H + Rt
Probable type 2 AIP	Typical/ indeterminate	Level 2 H/clinical inflammatory bowel disease + Rt
AIP-not otherwise specified	Typical/ indeterminate	D 1/2 + Rt

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for steroid responsiveness, is classified as either level 1 or level 2 collateral criteria.

Patients with obstructive jaundice and a diffusely enlarged pancreas (especially with a capsule-like rim) without pancreatic ductal dilatation/cutoff or low density pancreatic masses on CT/MRI are highly likely to have AIP. However, subjects with typical findings of pancreatic cancer (e.g., low-density mass on contrast-enhanced CT, pancreatic ductal dilatation/cutoff with or without pancreatic atrophy) should be considered as having pancreatic cancer. Subjects without features typical of AIP or pancreatic cancer should first be investigated for pancreatic cancer. AIP should be considered only after negative workup of malignancy. Response to steroids can confirm a strong suspicion of AIP; however, steroid trial as a means to diagnose AIP is to be used sparingly and should not be used as a substitute for a thorough search for an etiology.

Treatment

Although some studies of the treatment for IgG4-RD have been reported [15,16], a comprehensive management of IgG4-RD has not yet been established. As clinical features of the patients with IgG4-RD depend on characteristics of involved organs, the current consensus for treatment of type 1 AIP [17] as a representative lesion of IgG4-RD is described (Fig. 75.6).

Induction for Remission

Steroid treatment can successfully induce remission in most of the patients with type 1 AIP (~90%) [16–24]. The Japanese guidelines [19] and international consensus [17] have recommended steroids as the first-line agent in all active and symptomatic patients with untreated AIP, who have obstructive jaundice or abdominal and/or back pain due to pancreatic or other organ involvements, unless patients have any contraindications or high risk for steroid use. They have also recommended steroid

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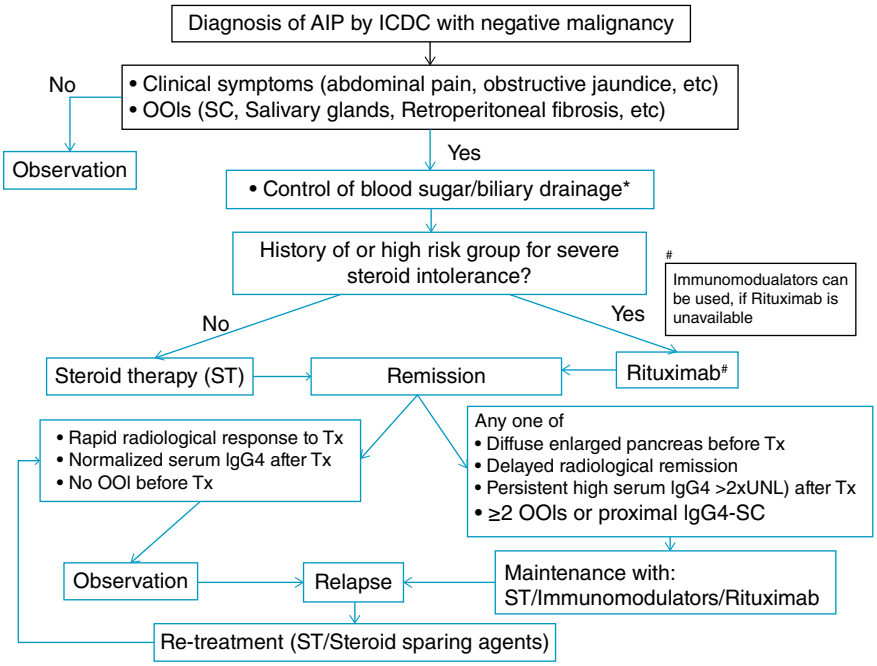


Figure 75.6 Therapeutic algorithm for type 1. This algorithm is based on Eastern and Western experts' opinions to recommend standard treatment of AIP worldwide. ICDC: International consensus of diagnostic criteria for autoimmune pancreatitis; OOI: other organ involvement; ST: steroid treatment. *Source:* [17]. With permission of Elsevier.

treatment even in asymptomatic patients with persistent pancreatic mass on imaging, or those with associated IgG4-related sclerosing cholangitis (IgG4-SC) who have persistent liver test abnormalities [17]. In those with contraindications to steroid treatment, rituximab can induce remission as a single agent [17,21]. Except for rituximab, however, other steroid-sparing agents such as thiopurines are poorly effective as a single agent for induction of remission [21]. Before an initial steroid therapy, management of blood glucose in diabetic patients or biliary drainage in patients with obstructive jaundice are recommended [23], because biliary drainage can prevent biliary infection, and brushing or bile juice cytology can differentiate IgG4-SC from biliary malignancy. In some cases of mild jaundice without signs of infection, however, steroid treatment alone can be performed safely without biliary stenting [22].

Relapse and Second-Line Treatment

According to the international or Japanese multicenter study [23], 30–50% of the subjects with type 1 AIP experienced relapse. Most of the risk factors for relapse remain poorly understood and require further study. A history of relapse seems to be a strong risk factor for future relapse. Although an international study [18] could not confirm, the Japanese national retrospective [23,24] studies have suggested that diffuse pancreatic enlargement type, and persistently high, low decreased rate or re-elevation of serum IgG4 levels after steroid therapy, may be predictors of AIP relapse. Association with IgG4-related SC, especially the proximal type of IgG4-SC seems to be a risk factor for relapse. In addition to serum IgG4 levels, circulating immune complexes have been reported as useful early predictors of relapse [19].

Although the usefulness of steroid as an initial treatment is agreed upon, there is no "gold standard" for treatment in relapse cases. The international consensus recommend readministration or dose-up of steroid or steroid-sparing agents such as immune-suppressive agents or rituximab [17].

Maintenance Treatment

Although there is no high-level evidence regarding maintenance therapy, certain patients benefit from maintenance therapy following a successful course of induction therapy [17,19]. Whereas some patients do not relapse following withdrawal of steroids after remission is achieved, some patients relapse during steroid taper or require relatively high-dose maintenance therapy. Therefore, to determine the indications for maintenance therapy, it is important to evaluate disease activity during induction therapy.

Maintenance therapy may consist of low-dose glucocorticoids or any of the steroid-sparing agents.

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Retrospective studies from Asian countries, mainly Japan [19], have suggested that steroid maintenance monotherapy may prevent relapse after remission. In addition to retrospective studies, a recent prospective Japanese multicenter study has shown that steroid maintenance therapy provides beneficial outcomes after remission [25].

In cases of low disease activity such as involvement in the pancreas alone with segmental/focal lesion without any OOI and complete radiologic remission with normalized IgG/IgG4 in rapid response to steroid treatment, steroids can be tapered off within 3 months followed by no steroid maintenance [17]. Conversely, maintenance therapy using a low dose of steroid, immune-modulators, or rituximab is recommended in patients with type 1 AIP showing diffuse enlargement of the pancreas, delayed radiologic remission or persistently high serum IgG4 (>2 × UNL) after treatment, or more than two OOI (≥2) or association with proximal IgG4-SC before treatment [17].

Recent Advances in the Pathogenic Mechanisms of IgG4-RD

Although it is unclear whether the pathogenic mechanism is the same among individual organs or not, recent studies have suggested possible multipathogenic factors in the development of AIP similar to other immunogenic diseases. Based on genetic factors, disease-specific or related antigens, abnormal innate and adaptive immunity may be involved [26] (Fig. 75.7).

Immunogenic Backgrounds

Although immunogenic backgrounds are unknown in IgG4-RD, the susceptibility to AIP in Japanese patients, most of whom exhibit IgG4-RD, may be associated with the class II antigen haplotype of the major histocompatibility complex (HLA-DRB1*0405-DQB1*0401) [27,28], polymorphism of nuclear factor-κB, *Fc-receptor-like* (*FCRL*) *3* genes expressed on B cells [29], and *FCGR2B* gene encoding Fc-gamma receptor [28,30]. An inhibitory molecule, *cytotoxic T lymphocyte antigen-4* (*CTLA-4*; *CD152*), expressed on the activated memory T cells or CD4+CD25+ regulatory T cells (Treg), was independently reported as a susceptibility factor [31].

Innate Immunity

Recently, abnormal innate immunity has been demonstrated in some patients with IgG4-RD [32–34]. Activation of NOD-2 and Toll-like receptor (TLR) ligands on monocytes or basophils from patients with IgG4-related AIP enhances IgG4 responses via B-cell activating factor (BAFF) and IL-13, although the specific pathogens still remain unclear [32,33]. Moreover, abundant infiltration of TLR-7 positive M2-macrophages was observed in the pancreatic tissues from type 1 AIP cases [34]. In animal models, activation of TLR3 (polyinosinic:polycytidylic acid) or TLR4 (LPS) can induce immune-mediated cholangitis, pancreatitis, and sialadenitis similar to human IgG4-RD [35,36]. Recently, possible roles of basophils, which are activated via TLR signaling, may be involved in the development of type 1 AIP [37].

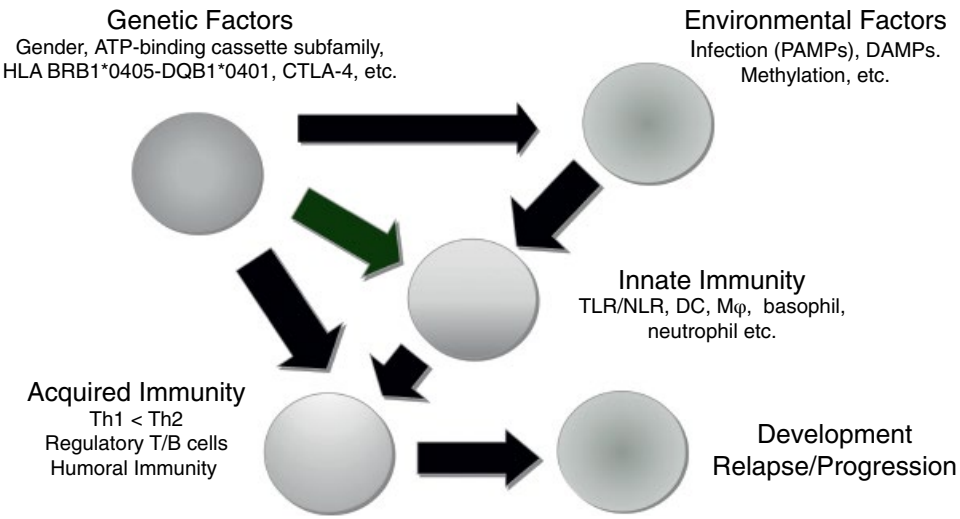


Figure 75.7 Multiple pathogenic factors in the development of type 1 AIP. Based on genetic factors, disease-specific or related antigens, abnormal innate and adaptive immunity may be involved. *Source:* [26]. With permission of Elsevier.

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Possible Roles of IgG4 in IgG4-RD

Although the association of IgE-mediated allergy and IgG4 antibodies is well known, IgG4 characteristics are still poorly understood. IgG4 is involved in an immune process referred to as "Fab-arm exchange," which is a swapping of a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule. This usually results in asymmetric antibodies with two different antigen-combining sites [38]. While these modified antibodies are hetero-bivalent, they behave as monovalent antibodies. Another aspect of IgG4 is that it mimics IgG rheumatoid factor (RF) activity by interacting with IgG, namely through Fc-mediated aggregation [39]. IgG4 seems to be associated with a pathogenic effect in a few situations. In pemphigus, recognition of skin autoantigens (desmogleins) by IgG4 is at the origin of the disease process [40]. The most recent study of structural determinants of human IgG4-Fc using crystallization suggested that Fc–Fc interactions are compatible with intact IgG4 molecules and may provide a model for the formation of aggregates of IgG4 that can cause disease pathology in the absence of antigen [41].

Another recent study of the regulation of IgG4 showed that IgG4-related diseases may reflect an excessive production of anti-inflammatory cytokines such as IL-10, which triggers an overwhelming expansion of IgG4-producing plasma cells [26]. Increased peripheral inducible-memory Treg are positively correlated with serum levels of IgG4 [26]. In addition, prominent infiltration of Treg upregulated IL-10 in livers of patients with IgG4-SC. These findings suggest that IgG4 does not act as a pathogenic factor, nor is it an anti-inflammatory factor in IgG4-RD. Further studies are necessary to clarify the precise role of IgG4 in IgG4-RD.

The Complement System

Patients in active stages of AIP occasionally show decreased complement (C3, C4) with elevated circulating immune complex, as well as elevated serum levels of IgG4 and the IgG4 subclass of immune complexes [42]. However, a previous study showed that the classical pathway of complement activation through IgG1 may be involved in the development of AIP, as opposed to mannose-binding lectin or alternative pathways through IgG4 [42].

Autoantibodies and Candidates of Target Antigens

Although some patients with IgG4-RD have nonspecific antibodies such as an anti-nuclear antibody (ANA), this is rare. From the view of IgG4 function, it remains unclear whether IgG4-RD is an autoimmune or an allergic disease. Although disease-specific targets are unknown, the occasional coexistence of OOI leads us to consider that there may be common target antigens in the involved organs, especially in the pancreas, which exhibit a high coincidence. Among candidate antigens previously reported, lactoferrin (LF), carbonic anhydrase (CA)-II, CA-IV, pancreatic secretory trypsin inhibitor (PSTI) are distributed in the pancreas, salivary glands, biliary duct, lungs, and renal tubules, among others. Immunization with CA-II or LF-induced systemic lesions such as pancreatitis, sialadenitis, cholangitis, or interstitial nephritis in mice models is similar to human IgG4-RD [26]. Amylase alpha-2A, heat shock 10kDa protein 1 (HSP10) and *Helicobacter pylori* are also disease-associated antigen candidates [26].

Recently, four novel candidates of target antigens related with connective tissues in some of the patients with type 1 AIP have been reported; prohibitin [43], annexin A11 [44], laminin 511-E8 [45], and galectin-3 [46,47]. However, autoantibodies against these four antigens are found in only a small portion of the patients with IgG4-RD.

Role of B Cells

In addition to steroid and immune-modulators, the B-cell depletion by rituximab, which reduces only IgG4, but not IgG1, IgG2, or IgG3, is useful in the therapeutic strategy in IgG4-RD [26]. A recent study showed expansion of IgG4+ B-cell receptor (BCR) clones in blood and tissue from patients with active IgG4-cholangiopathy, and disappearance of the clones with corticosteroid treatment. A recent study showed that increased $CD19^{+}CD24^{high}CD38^{high}$ Breg may suppress the disease activity of type 1 AIP, whereas the decreased $CD19^{+}CD24^{high}CD27^{+}$ Breg might be involved in the development of type 1 AIP [26].

Th1 and Th2 Immune Balance

CD4+ T-cells differentiate from naïve T-cells (Th0) into Th1, Th2, Th17, and regulatory T (Treg) cells. In the livers of IgG4-SC patients, a Th2-type immune reaction is predominant over the Th1 responses [26]. Recent studies suggested that IL-33 [48], IL-35 [49], and miRNA-21 [50], promote Th2 immune responses, which may be involved in the progression of the disease process, especially through the maturation and proliferation of local B cells and plasmacytes. Moreover, IL-33

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and TNFα may be an additional biomarker monitoring disease activity of type 1 AIP other than serum levels of IgG4 [26].

Regulatory T Cells

Forkhead box P3 (FOXP3) plays as the master regulator in the development of CD4+CD25+ regulatory T cells (Treg). Treg are classified as a naturally occurring CD4+CD25+ Treg (nTreg) that originates in the thymus, while adaptive Treg (aTreg) are induced in the periphery by different antigens [26]. In type 1 AIP, circulatory naïve (CD45RA+) Treg are significantly decreased in the peripheral blood, whereas memory (CD45RA-)-Treg are significantly increased [26]. In addition, prominent infiltration of Treg with upregulation of IL-10 is observed in the liver of type 1 AIP and IgG4-SC patients. These findings suggest that increased memory-Treg in the periphery and local tissues may be an inhibitory immune response against inflammation, although decreased naïve Treg may be pathogenic.

Conclusion

Recent advances support the concept of IgG4-RD, a unique clinical entity, as a systemic disease, and the classification of two distinctive subtypes of AIP. Type 1 AIP is proposed as a pancreatic manifestation of IgG4-RD and type 2 AIP is associated with GEL and inflammatory bowel disease. In the pathogenesis of AIP, multipathogenic factors include genetic backgrounds and disease-specific antigens. The role of IgG4 must be clarified in the near future.

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Imaging Diagnosis of Autoimmune Pancreatitis

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Introduction

The disease concept of autoimmune pancreatitis (AIP) was proposed in 1995 by Yoshida et al.[1], and subsequently this condition has been recognized as the pancreatic manifestation of IgG4-related disease (IgG4-RD) [2]. After several revisions of the concept, AIP is currently recognized as being classified into two distinct types [3,4]. AIP is subclassified according to the International Consensus of Diagnostic Criteria (ICDC) for autoimmune pancreatitis as either type 1 (IgG4-related) or type 2 (granulocytic epithelial lesions; GEL). Both types of AIP present with pancreatic swelling or mass formation often leading to obstructive jaundice. These features are similar to pancreatic cancer on the basis of the clinical and radiologic findings alone.

Histopathologic feature of type 1 (IgG4-related) AIP, termed lymphoplasmacytic sclerosing pancreatitis, is characterized by abundant infiltration of lymphocytic and IgG4-positive plasma cells, obliterative phlebitis, and fibrosis [3,5,6]. Type 2 AIP is characterized by GEL [5,8], histopathologically termed as idiopathic duct-centric chronic pancreatitis (IDCP) [7] and appears to be more common in Western countries than in Asian countries, whereas type 1 AIP accounts for the majority of cases in the world.

This chapter outlines pancreatic imaging based on current diagnostic criteria because of a particularly important role of these techniques in the diagnosis of AIP. Abdominal ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging are useful in the morphologic diagnosis of the pancreatic parenchyma. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde pancreatography (ERP) are useful in the morphologic diagnosis of the pancreatic duct. In addition, positron emission tomography (PET) may be useful in evaluating the response to steroid therapy as well as extrapancreatic involvements. ERP has long been considered essential in Japan for potential AIP cases marked by localized pancreatic swelling [1]. However, in the ICDC and Japanese diagnostic criteria of 2011 it is stated that a possible diagnosis of AIP can be made without ERP if a fine-needle aspiration under endoscopic ultrasonography (EUS) excludes malignancy, and the patient responds to steroid treatment.

Pancreatic Parenchyma Imaging

Diffuse swelling of the pancreas corresponding to a sausage-like appearance is highly characteristic for AIP. This feature can be demonstrated by US, CT, or MRI. However, localized (segmental or focal) swelling in AIP requires differentiation from pancreatic cancer. Concerning the definition of pancreatic swelling many investigators use the Haaga criteria (pancreatic head: ≥1 vertebral body, pancreatic body and tail ≥2/3 of a vertebral body define a pancreatic swelling and correspond roughly to a head of ≥3 cm and a body and tail of ≥2 cm) [12]. As the pancreas may be atrophic in the elderly a strict definition is difficult to achieve, but these criteria make it possible to recognize pancreatic swelling also in cases with shrinkage of the pancreas due to steroid treatment. Although "diffuse" and "localized" are not strictly defined, the ERP findings in the majority of cases with chronic pancreatitis are consistent with the Cambridge classification (2/3<diffuse, 1/3<segmental<2/3, focal<1/3) [13].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Abdominal Ultrasonography (US) [5,11]

The typical US appearance of the pancreas in AIP shows a diffusely swollen organ that resembles a sausage. The swollen portion is hypoechoic with scattered hyperechoic spots. In cases with localized swelling, the differential diagnosis between pancreatic cancer and mass-forming pancreatitis is problematic. Dilatation of the main pancreatic duct is frequently not detected by US, but delineation of the main pancreatic duct within the mass—known as the "duct penetration sign"—is helpful in differentiating AIP from pancreatic cancer [14]. However, the findings of only mild ductal dilatation or multiple hypoechoic masses within the pancreatic parenchyma make a differentiation between AIP and metastatic pancreatic tumors or lymphoma difficult.

Endoscopic Ultrasonography [5,11]

In AIP, typical pancreas EUS findings show a relatively diffuse homogeneous hypoechoic pattern and linear or reticular (tortoiseshell pattern) hyperechoic inclusions in the parenchyma along with a hypoechoic band in the periphery. Compared with chronic pancreatitis, EUS in AIP typically reveals a homogeneous hypoechoic pattern in the pancreatic parenchyma, rarely showing the characteristics of chronic pancreatitis (e.g., heterogeneous texture, lobule-shaped margin, and hyperechoic ductal margin). EUS of localized masses in AIP also display hypoechoic patterns that mimic those of pancreatic cancer. Linear or reticular (tortoiseshell pattern) hyperechoic inclusions and duct penetration are useful signs for distinguishing AIP from pancreatic cancer. Contrast-enhanced EUS sometimes provides useful findings for the differentiation of AIP from pancreatic cancer. EUS with fine-needle aspiration (EUS-FNA) has diagnostic utility not only for discounting pancreatic cancer, but also for diagnosing AIP.

Abdominal CT Imaging [5,11]

The CT features are pancreatic swelling with a straightened margin of the pancreas, a pattern of delayed contrast enhancement on dynamic CT, and a capsule-like rim surrounding the pancreas (Fig. 76.1) [15–17]. Most AIP patients are elderly and therefore tend to have some atrophy of the pancreas before the onset of AIP. This can obscure the presence of pancreatic swelling in the early stages of the disease. Conversely, there are also cases in which pancreatic swelling can be judged to have been present at onset based on a decrease in the size of the pancreas following steroid therapy. Other cases are characterized by atypical findings of mild diffuse swelling of the pancreas alone, and/or partial dilatation of the MPD, cystic lesions, or, in rare cases, calcification of the pancreatic parenchyma.

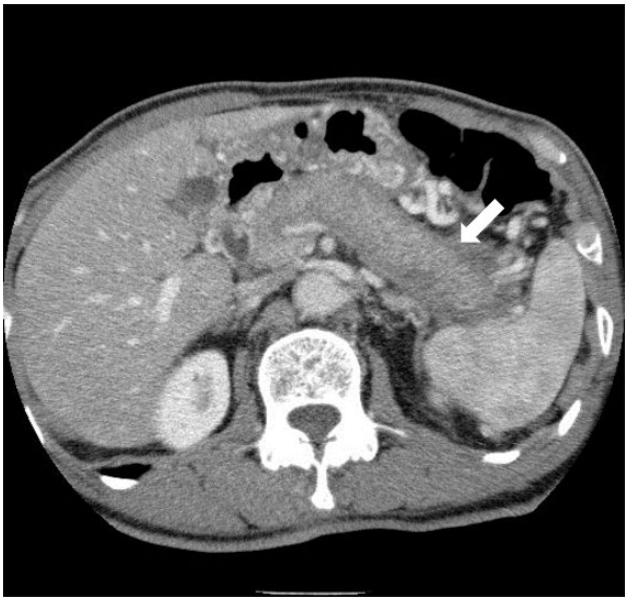


Figure 76.1 Abdominal CT images of autoimmune pancreatitis (diffuse swelling). It shows pancreatic swelling with delayed enhancement (sausage-like) and capsule-like low density rim (arrow).

Pancreatic Swelling and Delayed Enhancement

Delayed enhancement is characteristic on the portal phase of dynamic CT, but the specific findings vary according to disease stage and activity. The enhancement effect can be altered by the degree of fibrosis. If the extent of fibrosis is only mild, the amount of enhancement may be difficult to distinguish from normal pancreas. Thus, the absence of delayed enhancement does not exclude AIP in the early stages of the condition, when extensive fibrosis is unlikely. Speckled/dotted enhancement on the pancreatic phase of dynamic contrast-enhanced CT (DCE-CT) and homogeneous delayed enhancement on the delayed phase of DCE-CT are characteristic features of AIP and are useful for differentiation from pancreatic cancer.

Capsule-Like Low-Density Rim

The finding of a low-density, capsule-like rim around the pancreas is less common than delayed enhancement, but such a finding has a high specificity for AIP [15]. The capsule-like rim is thought to reflect fibrosis at the edge of the lesion, corresponding to the delayed pattern of enhancement observed on dynamic CT. A capsule-like rim is extremely helpful in differentiating AIP from pancreatic cancer. The absence of such a rim, however, by no

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means excludes AIP. Pancreas imaging alone cannot distinguish type 1 from type 2 AIP due to the similarity of their morphologic appearance.

Abdominal MR Imaging [5,11]

Pancreatic Swelling and T1/T2-Weighted Pancreatic Parenchyma Findings

Hypointensity on T1-weighted MR images and delayed enhancement on the portal phase of dynamic MRI are characteristic of AIP in addition to diffuse swelling. Because the normal pancreas is hyperintense relative to the liver on T1-weighted images, any relative hypointensity detected must be considered abnormal. However, hypointensity on MR is also found in both pancreatic cancer and chronic pancreatitis from other causes, and therefore does not distinguish AIP among these entities. In AIP patients, a duct-penetrating sign is occasionally seen on T2-weighted imaging or MRCP, which is almost never observed in pancreatic cancer. Similar to CT, differentiation of the normal pancreas from cases of only mildly fibrotic AIP is challenging. Conversely, severe fibrosis can be associated with only slight hypointensity on T2-weighted images, because of the limited inflammation present at that point. Similar to DCE-CT images, speckled/dotted enhancement on the pancreatic phase of dynamic contrast-enhanced MRI and homogeneous delayed enhancement on the delayed phase of MRI are characteristic features of AIP and are useful for differentiation from pancreatic cancer.

Capsule-Like Rim

Both a capsule-like rim and a delayed enhancement pattern can be detected by MRI. Both of these findings reflect fibrosis and are highly characteristic for AIP. The capsule-like rim is visualized as a hypointense region on T2-weighted images. Dynamic MRI is the most effective means of demonstrating delayed enhancement.

Nuclear Medicine Examinations

Gallium citrate (Ga-67) scintigraphy and fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) [5,11].

Patients with AIP display an accumulation of gallium citrate (Ga-67) and FDG in pancreatic and extrapancreatic lesions, which disappear shortly after steroid treatment. The characteristic accumulation patterns and kinetics of Ga-67 and FDG following steroids can be used for AIP diagnosis. Ga-67 and FDG accumulate in pancreatic lesions, making the differentiation from lymphoma difficult. Ga-67 and FDG accumulation is not limited to pancreatic lesions alone, but is also found at sites of extrapancreatic involvement, notably in the hilar lymph nodes of the chest, the lacrimal glands, and the salivary glands, which is useful for differentiation from pancreatic cancer. Such lesions frequently disappear rapidly after glucocorticoid administration [18–20]. However, the expense of these examinations further limits their clinical utility and has so far prevented them from entering routine practice.

Pancreatic Duct Imaging

ERCP Findings [5,11]

A characteristic irregular narrowing of the main pancreatic duct (MPD) constitutes strong evidence in favor of the diagnosis of AIP (Fig. 76.2a) [11]. Irregular narrowing of the MPD refers to a situation in which the pancreatic duct diameter is thinner than usual and irregular. These lesions tend to affect greater lengths of the duct than do occlusive or stenotic lesions. In typical cases, irregular narrowing accounts for more than one-third of the entire pancreatic duct length (~5 cm). Even in localized lesions marked dilatation of the main pancreatic duct upstream to the stenotic portion is frequently not observed. In cases with a short irregular narrowing pancreatic duct (roughly <3 cm), the differentiation from pancreatic cancer is difficult. Side branches arising from the narrow area of the MPD and skip lesions are useful signs in the differentiation from pancreatic cancer [5,15]. In the earlier diagnostic criteria for AIP put forth in Japan the finding of characteristic irregular narrowing within the MPD was considered to be an essential piece of diagnostic evidence [5,11]. In cases with focal irregular narrowing, the need to differentiate AIP from pancreatic cancer must be kept in mind. In AIP bile duct stenosis is found in about 80% of cases. Bile duct stenosis is most common in the inferior bile duct (Fig. 76.2b, c), but may also develop in the extrahepatic and intrahepatic bile ducts. Although a locally enlarged AIP lesion is sometimes difficult to differentiate from pancreatic cancer, AIP enlargement is improved by corticosteroid therapy.

MRCP Findings [5,11]

When evaluating patients with possible AIP and other disorders that mimic it, delineation of the morphologic features of the MPD by ERP or another direct visualization method is essential. At present, MRCP does not delineate the pancreatic duct with sufficient accuracy for reliable diagnosis of AIP or the precise evaluation of irregular narrowing in the MPD. Its ability to demonstrate noncontinuity of the duct is helpful in making the diagnosis of AIP (Fig. 76.3), although the specificity of this finding, in itself, is imperfect. However, 3-dimensional

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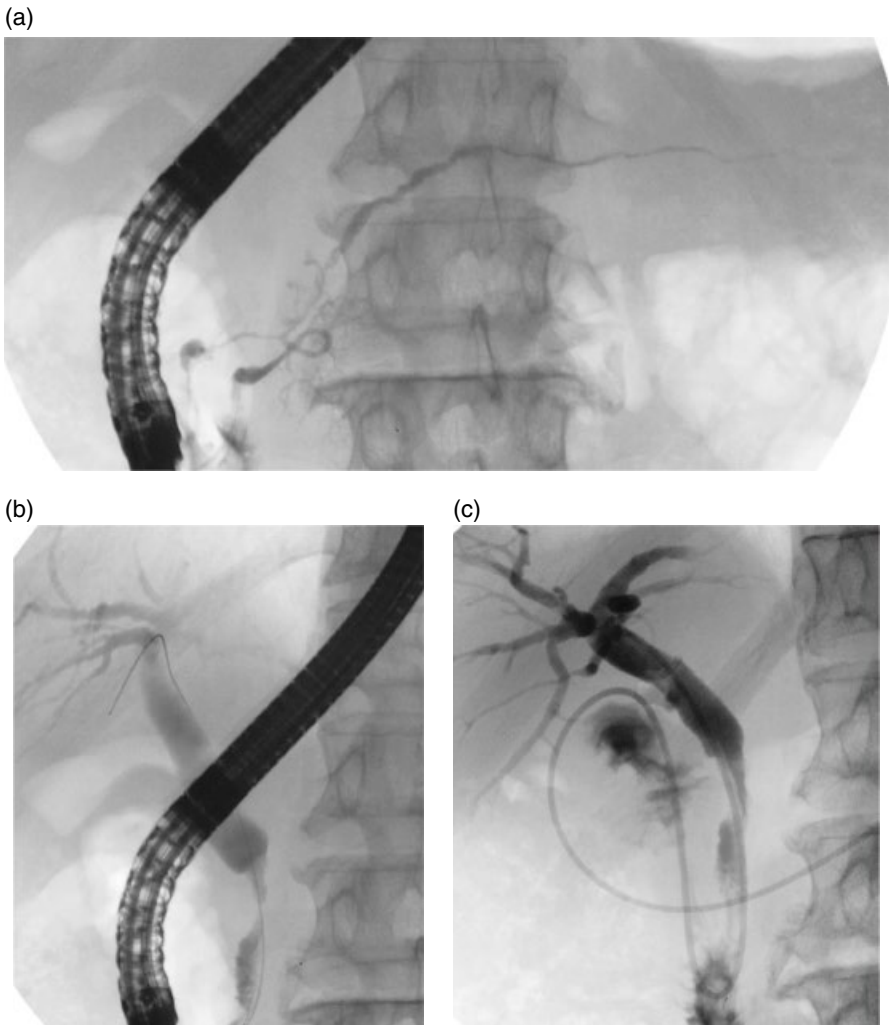


Figure 76.2 ERCP images of autoimmune pancreatitis. ERP (a) shows irregular narrowing in the pancreatic head and tail. Side branches arising from the stenotic portion of the main pancreatic duct (MPD) in the pancreas head can be observed. Before steroid treatment, ERC (b) shows stenosis of the terminal common bile duct and improvement of stenotic change after steroids (c).

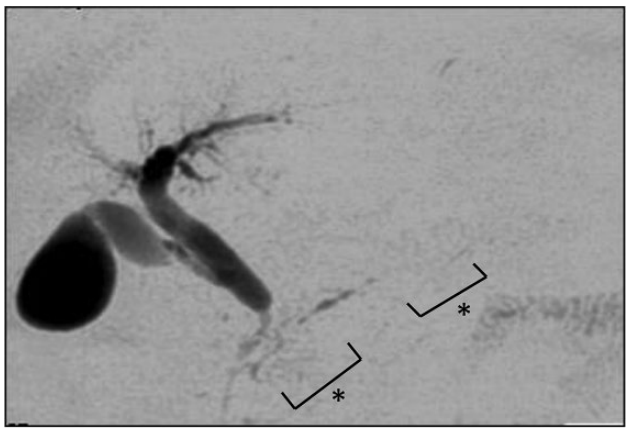


Figure 76.3 MRCP findings of autoimmune pancreatitis. MRCP usually fails to identify the correct presence of irregular narrowing of the MPD. In this case, MRCP shows the segmented MPD (skip lesions), suggesting the possibility of autoimmune pancreatitis (*).

MRCP can now detail the MPD within a normal pancreas and failure to identify the main duct suggests the presence of irregular narrowing. With the recently introduced 3.0 Tesla MR imagers, further enhancement of the image quality of MRCP is anticipated and MRCP may have a greater role to play in the assessment of the response of AIP to therapy and in follow-up observations.

Acknowledgement

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Medical Management of Autoimmune Pancreatitis

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Introduction

In 1995, Yoshida et al. coined the term autoimmune pancreatitis (AIP) to describe a condition reminiscent of autoimmune hepatitis because it was corticosteroid-responsive and associated with elevated levels of autoantibodies and gamma globulins [1]. Earlier, Kawaguchi had described its histopathologic features and called it lymphoplasmacytic sclerosing pancreatitis (LPSP) [2]. Subsequently, this entity was shown to be the pancreatic manifestation of a multiorgan disorder called IgG4-related disease (IgG4-RD).

A different disease entity was seen to share some histopathologic and clinical features with LPSP, and was termed idiopathic duct-centric chronic pancreatitis (IDCP) [3]. The term AIP eventually came to be used for both diseases with LPSP termed type 1 AIP and IDCP as type 2 AIP. Here the term AIP will be used to indicate LPSP and the term IDCP to describe this distinct entity.

Management of Autoimmune Pancreatitis: An Overview

AIP is managed medically; surgical intervention, usually pancreatic resection or biliary bypass for "unresectable" disease, occurs when the condition is mistaken for pancreaticobiliary cancer. Like other autoimmune disorders, treatment of AIP includes induction of remission, treatment of relapse, and maintenance of remission. The cornerstone of medical management of AIP is the use of corticosteroids to target the inflammatory response in the affected organ. This provides symptom relief, often dramatic, which in some instances can be helpful for confirming the diagnosis. Although the early use of corticosteroids may delay progression to fibrosis, pancreatic parenchymal fibroatrophic changes that accompany the initial presentation of the disease are usually permanent. Steroid-sparing agents are mostly used for long-term maintenance of remission or in steroid-intolerant patients.

Definitions

The consistent use of well-defined terms to describe treatment goals is an important component of the treatment algorithm of AIP. AIP is a fibroinflammatory disease and treatment targets the inflammatory component; the accompanying fibrosis may permanently alter organ structure and function. Currently, there are no therapies that specifically prevent or halt fibrosis.

"Remission" indicates the complete resolution of the inflammatory component of the disease with or without restitution of normal structure and function. The rapid and complete resolution of symptoms such as jaundice or abdominal pain after initiation of corticosteroids has diagnostic utility; persistent symptoms on high-dose steroids indicate an alternate diagnosis. Even with remission organs affected may never return to normal morphology and function due to fibrosis-related damage. Biochemical abnormalities in liver tests and pancreatic enzymes typically resolve completely with disease remission. Confirmation of histologic remission after treatment, although ideal, is not feasible and is almost never

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needed in clinical practice. Normalization of serum IgG4 levels is not a reliable treatment target and does not correlate with disease remission.

"Recrudescence" is the worsening of disease or "flare" during treatment when the disease is still not in remission. This may happen in the setting of corticosteroid dose reduction or premature withdrawal.

"Relapse" refers to disease recurrence after complete remission has been achieved. This could be in the form of recurrent clinical, radiologic, or biochemical features of disease that often mimic the initial presentation. AIP being part of a multiorgan disease (IgG4-RD), relapse may occur in the organ being treated or in another, previously unaffected, organ. Abdominal pain as a standalone symptom is rarely a manifestation of relapse. Similarly, isolated "serologic relapse," that is, elevation of IgG4 without biochemical or radiologic change, is not indicative of disease relapse and should not be treated.

Management of Initial Presentation

Induction of Remission

Corticosteroids are the mainstay of initial treatment. High-dose induction therapy with 30–40 mg/day of prednisone or equivalent-dose corticosteroid is typically administered for 4 weeks. Clinical and radiologic response is assessed at the end of 4 weeks of high-dose therapy and in patients demonstrating remission or significant interval improvement in target organ inflammation, this is followed by a gradual corticosteroid taper using a decremental dose of 5 mg per week. Subsequent need for therapy is determined by treatment response. For patients with no previous history of AIP who have limited disease burden that rapidly resolves, steroid therapy is typically tapered to discontinuation at this stage.

Maintenance of Remission

In patients who achieve complete remission with induction therapy, there is considerable debate regarding the continued use of low-dose corticosteroid treatment for maintenance of remission. In a meta-analysis that included 36 studies, the relapse rate in AIP patients treated successfully with corticosteroid induction was noted to be 20% at 1 year and 53% at 4 years [4]. Several Asian centers favor the long-term continuation of low-dose corticosteroid therapy for several years and even indefinitely, whereas most centers in Europe and North America recommend weaning to discontinuation over 8–10 weeks after the initial 4 weeks of high-dose treatment. However, in a large study of 459 subjects with AIP from Japan who received maintenance corticosteroid treatment nearly one fourth relapsed (23%, 63/273) [5]. Though this was lower compared to patients in whom corticosteroids were discontinued after achieving remission (34%, 35/104; $P = 0.048$), the authors do not provide treatment alternatives for those who did relapse on steroids [5]. In a more recent randomized controlled trial, after induction of remission with corticosteroids, patients were randomized to either maintenance therapy with prednisolone at 5–7.5 mg/day for 3 years or steroid withdrawal at 26 weeks. The 3-year relapse rate was significantly lower in the maintenance therapy group than that in the cessation group (23% vs. 58%) [6].

An alternative approach to steroid maintenance therapy is the use of immunomodulators as a steroid-sparing agent. The choice of immunomodulator does not impact treatment outcomes with 6-mercaptopurine, mycophenolate mofetil, and azathioprine all having similar efficacy. Intolerance to one agent can be managed by substituting one of the other agents. The optimal dose and duration of treatment is not well defined. However, for azathioprine, higher doses similar to those used in the management of inflammatory bowel disease (2.0–2.5 mg/kg), have a greater likelihood of preventing subsequent relapses compared to lower doses (1 mg/kg) [7]. Although azathioprine may be effective in maintaining remission in patients with AIP it is important to recognize that up to 20% patients will relapse while on treatment with azathioprine [8].

Follow-Up and Management of Disease-Related Sequelae

Exocrine Insufficiency

Steatorrhea is uncommon in patients with AIP. A study using a diagnostic cutoff of FE-1 < 200 µgm/gm reported an abnormal test result in more than 80% of patients with AIP [9]. A recently published meta-analysis estimated the pooled prevalence of exocrine insufficiency to be 45% at diagnosis; however, there appears to be wide variability of estimates among studies. This remains discordant with our clinical observations that clinically overt exocrine insufficiency is uncommon. It is unlikely that FE-1 values at a cutoff <200 µgm/gm accurately reflect the true prevalence of exocrine pancreatic insufficiency in patients with AIP. Significant pancreatic parenchymal atrophy is seen in up to 25% patients after corticosteroid therapy and may contribute to the development of exocrine dysfunction over time [10]. The use of pancreatic enzyme replacement therapy should be

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limited to patients with clinical evidence of fat malabsorption.

Endocrine Insufficiency

Risk factors for the development of new-onset diabetes in patients with AIP include extensive pancreatic parenchymal atrophy, long duration of disease, advanced age, smoking, and alcohol consumption. Periodic monitoring of glycemic status should be considered for early detection and timely intervention, especially in patients with the aforementioned risk factors and in those with frequent high-dose or long-term corticosteroid exposure.

Risk of Pancreatic Malignancy

There is conflicting evidence regarding the risk of pancreatic cancer in patients with AIP. Although some studies have shown increased risk, others have failed to establish an association. The risk of cancer appears to be highest in the first year after diagnosis of AIP [11]. In a study of 107 AIP patients with a median follow-up of 74 months, none of the study subjects developed pancreatic cancer [12]. Interestingly, eight patients developed a nonpancreatic malignancy and the cancer risk in this study cohort was comparable to an age- and gender-matched reference population. The concomitant diagnosis of AIP and pancreatic cancer has also been reported [13]. Although this phenomenon is exceedingly rare, it highlights the importance of a detailed diagnostic workup to exclude pancreaticobiliary malignancy before embarking on an AIP treatment protocol. Also, malignancy should be considered in the differential diagnosis of patients who do not respond to corticosteroid induction since primary nonresponse to steroid therapy is extremely unusual. Both synchronous and metachronous pancreatic cancer has been reported in AIP, the latter appears to be more common and typically arises from the part of the gland affected by AIP.

Management of Medication Side-Effects

Corticosteroids

Hyperglycemia, sleep disturbance, and altered mood are the most frequent and clinically relevant treatment-related complications linked to high-dose corticosteroid therapy. For those with a preexisting mood disorder, careful assessment of mental health status, and if necessary, medication dose adjustment should be considered prior to initiation of treatment. A baseline fasting plasma glucose should be obtained in all patients and those with a preexisting diagnosis of diabetes mellitus closely monitored to modify steroid and insulin dosing. Less commonly encountered serious side-effects of high-dose steroids include avascular necrosis, osteoporosis, hypertension, and worsening heart failure.

Immunomodulators

Unfortunately, in most reported series up to a quarter of patients treated with immunomodulators have experienced treatment-limiting side-effects [7]. The commonly encountered adverse effects that result in drug discontinuation include nausea, liver enzyme elevation, drug rash, myelosuppression, and bacteremia. A switch to a different immunomodulator is tolerated in about half of these patients.

Management of Idiopathic Duct-Centric Pancreatitis (Type 2 AIP)

IDCP is exquisitely steroid-responsive. The dose and duration of induction treatment with corticosteroids is similar to AIP. Clinical response is often dramatic and relapses are infrequent. A Mayo Clinic study of 31 subjects with a definitive diagnosis of IDCP reported a relapse rate of 10.6% at 12 months [14]. Initial presentation with acute pancreatitis predicted a lower relapse-free survival. Relapses almost always respond to retreatment with corticosteroids. In view of the relatively low relapse rate, maintenance therapy with steroids or immunomodulators is currently not recommended. Long-term disease-related sequelae such as pancreatic duct stones, pancreatobiliary malignancy also appear to be less common compared to type 1 AIP.

Conclusion

In patients with a confirmed diagnosis of AIP the initial medical management is straightforward. Treatment of relapses and disease that does not respond or incompletely responds to high-dose corticosteroids requires a thoughtful approach with the judicious use of immunomodulators and B-cell depletion therapy (Fig. 77.1). Although, RTX appears to be the agent of choice for the treatment of patients with refractory disease, the optimum dosing regimen and duration of treatment continues to evolve and needs further study. Novel biomarkers that allow disease activity surveillance and predict relapse may facilitate more accurately tailored treatment regimens in the future.

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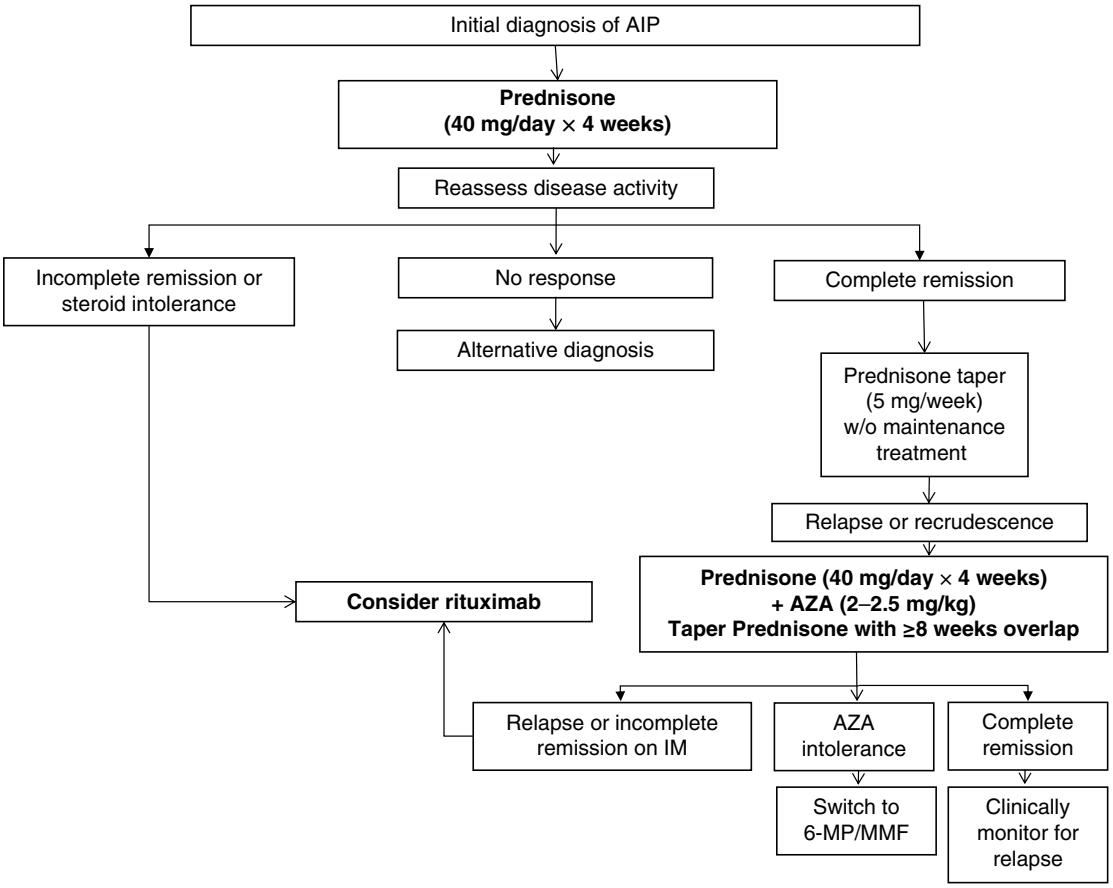


Figure 77.1 Mayo Clinic treatment algorithm for management of initial presentation and subsequent disease relapses for patients with established autoimmune pancreatitis. *Source*: Adapted from [4].

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Management of Intractable Autoimmune Pancreatitis

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Introduction

Autoimmune pancreatitis (type 1) is exquisitely steroid sensitive, both initially and in relapse. However, in a small subset of patients it may be hard to induce remission or maintain remission. This group has been termed "intractable or refractory," though it does not necessarily mean complete lack of responsiveness to steroids, which is rare.

Definition of Intractable or Refractory Disease

Intractable or refractory AIP can be defined as disease that is hard-to-treat due to inability or inefficacy of first-line treatments for induction and/or maintenance of disease remission.

Subsets of Refractory AIP

These have not been systematically characterized or studied. Based on our experience there are five possible scenarios (A–E): (A) steroid intolerance; (B) prompt relapse after or during withdrawal of steroid induction treatment or relapse on low-dose steroid maintenance; (C) immunomodulator intolerance or inefficacy; (D) prompt relapse following withdrawal of maintenance treatment; or (E) relapse on rituximab (RTX) maintenance or RTX intolerant. Such scenarios are reported [1–9], but systematic studies of individual scenarios are limited.

Management of Refractory Disease (Fig. 78.1)

A) **Steroid intolerance**

While steroid intolerance is not very common, therapeutic options are fairly limited in these patients (scenario A). RTX, a chimeric monoclonal antibody against CD20 antigen on B cells, is the only currently known agent other than corticosteroids that can induce remission on its own. Generally reserved for treatment of relapsing disease, it can be used as a first-line agent in select clinical scenarios when steroids are contraindicated or poorly tolerated. The most used induction regimen for RTX is two doses (1 gm each) 2 weeks apart. There is limited data and no consensus on the use of RTX as first-line treatment for AIP. In a Mayo Clinic series, complete remission was achieved in three out of three patients who were corticosteroid-naïve and were treated with RTX as the first-line agent [4]. However, experience from treatment of other manifestations of IgG4-RD and more recent published experience from our center suggests that RTX can be used as first-line and sole agent for induction and maintenance of remission, if necessary [2,6]. The safety and efficacy of RTX in IgG4-related disease has recently been reported [5].

B) **Prompt recurrence on or during withdrawal of standard steroid induction treatment or disease requires high doses of steroids to induce remission**

Some patients will relapse soon after steroid taper despite successful and complete improvement while on steroids, while others may be unable to be weaned off high-dose

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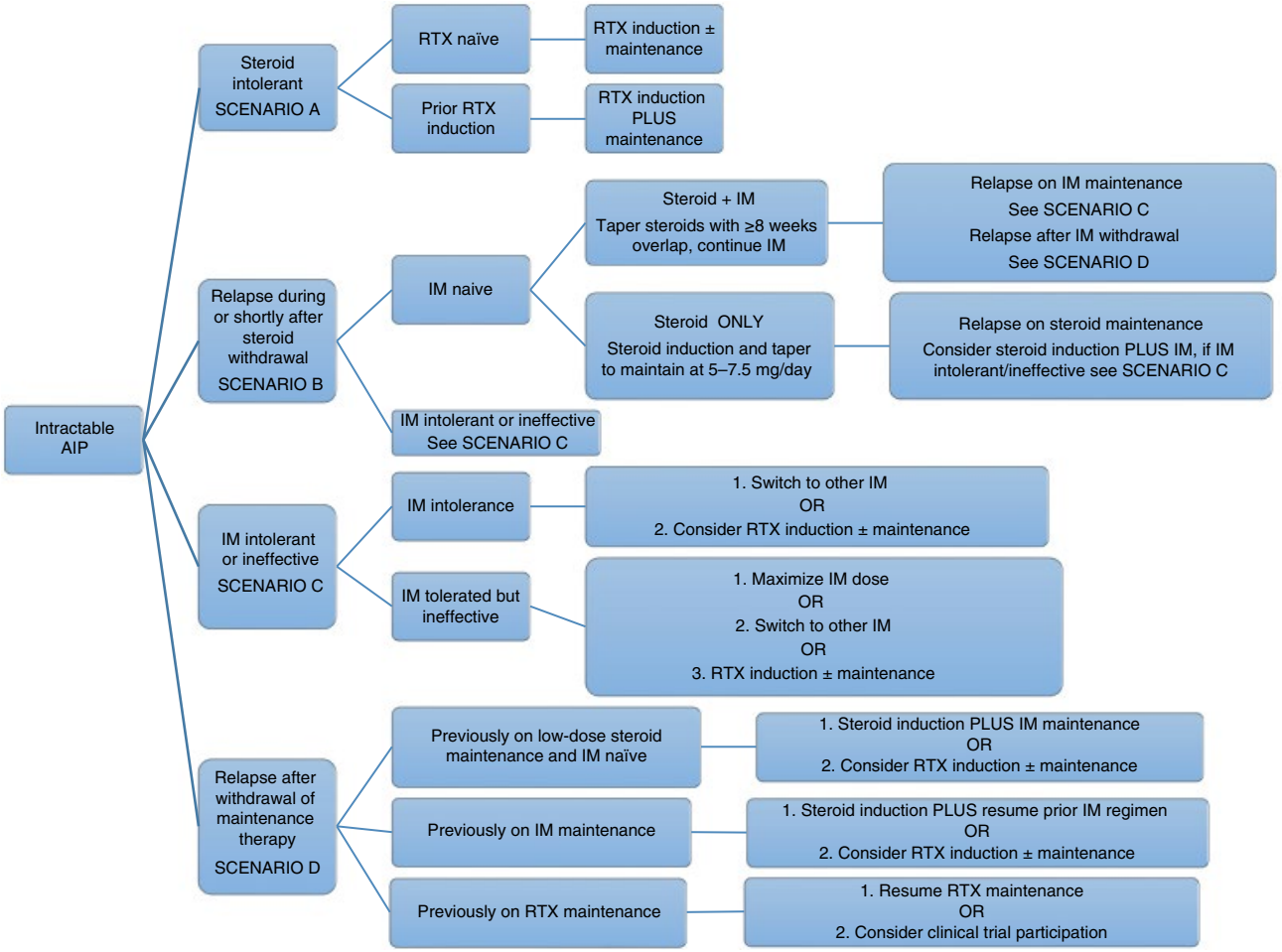


Figure 78.1 Management of refractory AIP. IM: immunomodulator; RTX: rituximab.

corticosteroids following induction therapy due to disease recrudescence. Options for such patients include reintroducing high-dose steroids and adding immunomodulators like azathioprine or mycophenolate, overlapping the two for 4–6 weeks before tapering steroids again. The other option is to consider RTX as noted in scenario A. These two approaches of using maintenance therapy at index presentation of disease may be considered for patients at the highest risk of early relapse. This includes patients with proximal biliary tract disease, diffuse enlargement of the pancreas, elevated baseline IgG4, IgE, peripheral eosinophilia, and possibly those with persistent elevation of IgG4 at the end of induction therapy [9]. It is to be noted that immunomodulators do not induce remission; hence, if the disease is still active when steroids are withdrawn or there is early relapse, there is a high likelihood of disease recrudescence, despite use of immunomodulators (see scenario C below).

C) **Inability to use or inefficacy of immunomodulators**

A subset of patients started on immunomodulators may be intolerant to the drug [4]. There are others who do not go into remission when transitioned from steroids to immunomodulators. Some may achieve and stay in remission on immunomodulators, but relapse months later while still on treatment. Relapse may occur in the same organ for which treatment was initiated or in another previously unaffected organ. While all such scenarios have been reported in AIP [4], there is no systematic study of management of such patients.

In those with drug intolerance, one could potentially switch to another class of agents (e.g., mycophenolate for azathioprine or 6-MP or vice versa). If not intolerant to drug, one strategy is to reintroduce steroids, and increase immunomodulator dose (up to 2 mg/kg for azathioprine or 1 gm b.i.d. for mycophenolate). After reinduction of

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remission, steroids may be tapered while continuing the immunomodulator. In both these strategies it can take months to know if a successful and sustained remission has been achieved, all the while being on double immunosuppression (steroid + immunomodulator) and attendant risks.

As we have noted above managing immunomodulators in the difficult-to-treat patient can be cumbersome and time-consuming. Due to this, we have not used this strategy. We have instead elected to use RTX as the sole immune-suppressive agent [4] as described in scenario A. This strategy has worked consistently and successfully [4,6].

D) **Prompt recurrence of disease after withdrawal of maintenance treatment**

While we have chosen, in general, to stop immunesuppression after 2 years, a small subset of patients seem to require indefinite immunosuppression to keep disease in remission. This can happen with all approaches to maintenance therapy (low-dose steroids, steroid-sparing immunomodulators or biologic agents [RTX]). The management in these patients is similar to that in scenario B: using steroids for reinduction while reintroducing the immunosuppression used previously for maintenance vs. using RTX alone with a short course of steroids if patient has an urgent indication, like obstructive jaundice. If using RTX, such patient will require reinduction with two doses of 1000 mg 2 weeks apart.

E) **Relapse on rituximab maintenance or rituximab intolerance**

In our experience relapse on RTX maintenance is a very rare event. However, some patients may develop RTX intolerance due to allergic reactions and recurrent infections or may not be an ideal candidate for RTX maintenance therapy due to concomitant medical comorbidities. Possible treatment options for these patients include low-dose prednisone if able to tolerate it or immunomodulators, if not previously tried. This further highlights the need for clinical trials to identify novel treatment options for refractory AIP while recognizing the challenges associated with drug development in a small subset of an uncommon disease.

Frequency and Dose of RTX for Maintenance Therapy

For maintenance therapy a single dose of 1000 mg of RTX has been used [6]. Lower doses have not been systematically studied. We tend to use it every 4–6 months for a total duration of 2 years of maintenance therapy. Although relapses may occur after discontinuation of RTX maintenance, it is relatively infrequent (approximately 10% in our limited experience) and currently it remains unclear if the risks of long-term immunosuppression outweigh the benefits of maintaining remission. In patients with refractory AIP and a high disease burden associated with prior relapses such as hospitalization, sepsis, need for urgent endoscopic biliary decompression, or significant end-organ dysfunction, maintenance therapy beyond 2 years may be considered as an individualized approach. The Mayo experience suggests that median time to relapse is 14 months [6]. Based on these data, it is possible that longer intervals (9 months or 12 months) may suffice. However, the number of patients treated with various intervals is too small to draw firm conclusions.

Use of Biosimilars as a Substitute for RTX

A biosimilar is a biologic product that is highly similar to a licensed biologic ("originator"). Biosimilar and originator have no clinically meaningful differences in safety, purity, or potency. A number of RTX biosimilars are being tested in Europe and the United States and some have been approved for clinical use. In a recent study an RTX biosimilar Truxima was shown to be a safe and effective alternative to RTX in IgG4-related disease [10].

Side-Effects of RTX

Rituximab treatment is fairly well tolerated, and infections are the most common side-effect. All patients should be screened for hepatitis B virus prior to initiation of therapy since reactivation hepatitis B can potentially result in fulminant liver failure [11]. Common infusion-related adverse reactions include flu-like symptoms, pruritus, transient hypotension, and bronchospasm. Serious infusion reactions are rare, but near-fatal infusion reactions have been reported [12]. Other rare serious reactions that would necessitate discontinuation of therapy include toxic epidermal necrolysis and progressive multifocal leukoencephalopathy.

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79

Long-Term Outcome After Treatment of Autoimmune Pancreatitis

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Introduction

Autoimmune pancreatitis (AIP) is a clinical entity that is well described in clinical and imaging findings at the onset of the disease [1]. The early phase is well defined, particularly the outcome after first steroid treatment, which represents a diagnostic criterion. However, the long-term outcome of patients suffering from AIP is still largely unknown. Many aspects are not yet fully clarified, particularly the need for and efficacy of treatment with nonsteroidal immunosuppressants (azathioprine) or biologics (rituximab [RTX]) in preventing disease relapse and progression toward chronic pancreatitis in terms of loss of pancreatic function (exocrine and endocrine insufficiency), onset of pancreatic calcifications, and the risk for pancreatic cancer.

Since the term "autoimmune pancreatitis" was introduced in 1995 [2] and the disease was recognized later as a clinical entity, when a steroid treatment has become the norm, the long-term outcome of the disease has been modified by the use of steroids, nonsteroidal immunosuppressant drugs, and/or RTX. Therefore, while the natural history of the disease remains obscure, what can be observed nowadays is the long-term outcome of AIP after therapy. An unanswered question is the fate of patients suffering from AIP before 1995 and more appropriate maintenance treatment. We know that some of them underwent surgery because of the suspicion of pancreatic cancer. To answer this question may lead to a better understanding of the natural history of AIP.

Disease Relapse After Steroids and Treatment

Relapse of AIP may be symptomatic, evident on imaging, serologic, and/or histologic [3]. However, an AIP relapse may be clinically asymptomatic and detectable only on imaging [4]. The site of the relapse is mainly in the pancreas, but may involve extrapancreatic organs (kidney, salivary glands, biliary tree, and retroperitoneum) [4–7]. Positron emission tomography/computed tomography has been proposed as a useful imaging modality both for staging and for evaluation of treatment response in IgG4-related diseases, which include type 1 AIP [8–10]. Relapse rates reported in the literature include symptomatic and asymptomatic patients with both pancreatic and extrapancreatic involvement without distinction.

After a first course of steroids, disease relapse has been reported in between 13% and 64% of cases (Table 79.1) [6,11–25]. Disease relapse does not differ between patients who underwent surgery compared to those treated conservatively (Table 79.2) [6,12–16,18,26]. Furthermore, relapse rates are significantly higher and more frequently observed in AIP type 1 compared to type 2 [6,21,27]. De Pretis et al. [28] reported a 15% relapse rate of AIP-NOS (not otherwise specified), lower than in type 1 (34%) and similar to that of type 2 AIP (6%) [21]. Furthermore, the authors observed a 25% probability to switch from a diagnosis of type NOS to type 2 AIP at 5 years, and never to AIP type 1.

High levels of serum IgG4 [6,7,12,15,27,29–31], intrahepatic biliary involvement [6,29,32], and other organ involvement [7], have all been identified as risk factors for relapse. These factors were all strictly correlated with type 1 AIP, which may therefore be considered as a more aggressive disease.

The treatment of choice for disease relapse is a new course of steroids (prednisolone) to induce remission [33]. This therapeutic approach is widely accepted, even if it is based only on cohort studies. The dosage of prednisolone is the same as that proposed after the diagnosis of AIP (prednisolone, 30–40 mg/day or a weight-adjusted dose range from 0.5 to 1 mg/kg of body weight

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Table 79.1 Frequency of relapse in patients suffering from autoimmune pancreatitis.

Author	Year	Country	Patients *N*	Relapse rate
Ryu et al. [11]	2008	Korea	67	15%
Frulloni et al. [12]	2009	Italy	87	25%
Raina et al. [13]	2009	USA	26	57%
Maire et al. [14]	2010	France	44	27%
Kubota et al. [15]	2011	Japan	70	34%
Kamisawa et al. [16]	2011	Asia	327	13%
Kamisawa et al. [17]	2011	Asia, Europe, USA	731	from 15% to 64%
Song et al. [18]	2012	Korea	52	24%
Hart et al. [6]	2013	Asia, Europe, USA	1064	29%
van Heerde et al. [19]	2014	Netherlands	111	37%
Wu et al. [20]	2014	China	43	15%
Rush et al. [21]	2016	Germany	53	28%
Buechter et al. [22]	2017	Germany	36	36%
Vujasinovic et al. [23]	2018	Svezia	71	27%
Lee et al. [24]	2018	Korea	138	48%
Barresi et al. [25]	2020	Italy	173	21%

Table 79.2 Frequency of relapse in patients suffering from autoimmune pancreatitis divided into those treated with steroids and those who underwent surgery.

Author	Year	Country	Steroids	Relapse rate	Surgery	Relapse rate
Frulloni et al. [12]	2009	Italy	67	34%	20	30%
Raina et al. [13]	2009	USA	15	60%	4	0%
Maire et al. [14]	2010	France	26	31%	12	33%
Kubota et al. [15]	2011	Japan	42	9%	20	17%
Kamisawa et al. [16]	2011	Asia	231	21%	42	13%
Song et al. [18]	2012	Korea	27	40%	11	10%
Hart et al. [6]	2013	Asia, Europe, USA	736	33%	141	25%
Yurci et al. [25]	2013	USA	11	27%	21	19%

per day), which can be varied according to disease activity. After the induction of remission in relapsing AIP a maintenance regimen has been suggested. Long-term maintenance therapy with low-dose steroids (prednisolone, 5–10 mg/day) is used in Asian countries but is still debated elsewhere. Steroid-sparing agents, in particular azathioprine (2–2.5 mg/kg/day), have been proposed for long-term treatment of relapsing AIP [34–36], even in the absence of controlled trials, but again their use is still under debate. However, experts recommend an add-on therapy with steroid-sparing agents for IgG4-related disease [37], to which AIP type 1 belongs.

Rituximab (RTX), an anti-CD20 antibody inducing B-cell depletion, seems to be effective in inducing specific serum IgG4 reductions and for better disease control in IgG4-RD, even in steroid refractory cases [38]. RTX probably interferes with the immunologic processes underlying IgG4-RD, but the exact mechanism is still unknown. Since AIP type 1 is considered a manifestation of IgG4-RD, the use of RTX has been suggested for this subtype of AIP [37,39]. Some preliminary cohort studies seem to confirm the efficacy of RTX in AIP type 1 [40–42]. There is still no consensus regarding the dosage and the RTX schedule. A rheumatologic (intravenous infusions at a dosage of 375 mg/m^2 body surface area at time points 0 and 15 days, repeated after 6 months) rather than a hematologic schedule (intravenous 375 mg/m^2 body surface area four times at weekly

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intervals, then repeated infusions every 2–3 months up to 24 months) can be suggested, but randomized trials are needed to better understand the most appropriate protocol for AIP patients.

Loss of Pancreatic Function and Evolution Toward Chronic Pancreatitis

The long-term outcome of AIP patients is described in only few studies and limited to the first 10 years after clinical onset. The key points about the natural history of AIP are the deterioration of exocrine and endocrine function, the onset of pancreatic calcifications, and, more generally, the evolution toward "ordinary" chronic pancreatitis.

Exocrine pancreatic function is already reduced at clinical onset of the disease (Table 79.3) [5,12,14,23–25,43–45] and its improvement has been observed in a significant proportion, but not all, patients after steroids [43,46]. The exocrine pancreatic function evaluated by secretin-cerulein test is reduced at clinical onset of the disease in nearly all AIP patients, involving particularly enzyme production more than bicarbonate secretion [47]. After steroids, studies have shown that exocrine pancreatic insufficiency evaluated by PABA test [43] or fecal elastase-1 [46] improved, but severe pancreatic insufficiency remained in 33–50% of cases. However, pancreatic exocrine insufficiency remains present in a large portion of AIP patients (80%) in the long-term follow-up after steroids [45]. Therefore, evaluation of pancreatic function in AIP is recommended to identify patients who may benefit from pancreatic enzyme replacement therapy.

Similar data have been published for endocrine pancreatic function (Table 79.3) [5,12,14,43–46], and diabetes is quite common in AIP. Steroid-induced diabetes is frequently observed at clinical onset of the disease, particularly in older patients [46,48].

The results of long-term follow-up suggest that some patients with AIP could develop pancreatic calcifications, generally after several disease relapses [30,31,49]. Steroid treatment seems to prevent progression toward chronic pancreatitis [50].

Loss of pancreatic exocrine and endocrine function, onset of calcifications, and atrophy of the pancreatic gland seem to suggest that AIP can transform into "ordinary" chronic pancreatitis. This hypothesis, even if not completely supported by clinical data and imaging findings, could explain why AIP was not identified in the past and may have been confused with chronic calcifying pancreatitis in its advanced stage.

This hypothesis also implies that imaging is only typical for AIP in the early phase of the disease and the diagnosis can be more easily achieved. In the more advanced stage, the radiologic features are less suggestive for AIP, and it is highly probable that the diagnosis of AIP will be missed.

Figure 79.1 shows a diagram of the postulated natural history of AIP.

Risk for Pancreatic and Extrapancreatic Cancer

A risk for pancreatic cancer in AIP has been reported [30,44,51–59], as for other chronic inflammatory gastrointestinal diseases, but studies are limited to case reports or small series. The risk for pancreatic adenocarcinoma is highest in the early phase of the

Table 79.3 Frequency of pancreatic exocrine and endocrine insufficiency in patients suffering from autoimmune pancreatitis.

Author	Year	Country	Patients *N*	Follow-up months	PEI	Diabetes
Kamisawa et al. [43]	2003	Japan	12	41	67%	83%
Frulloni et al. [12]	2009	Italy	87	89	28%	26%
Uchida et al. [44]	2009	Japan	21	41	48%	46%
Maire et al. [14]	2010	France	44	41	34%	37%
Bujis et al. [45]	2015	Netherlands	68	41	82%	57%
Lopez-Serrano et al. [5]	2016	Spain	47	50	36%	36%
Vujasinovic et al. [23]	2018	Sweden	71	46	48%	21%
Lee et al. [24]	2018	Korea	138	60	3%[a]	46%
Barresi et al. [25]	2020	Italy	173	42	69%[b]	20%

[a] Clinically overt steatorrhea.
[b] Only 54 patients tested for fecal elastase-1.
PEI: pancreatic exocrine insufficiency.

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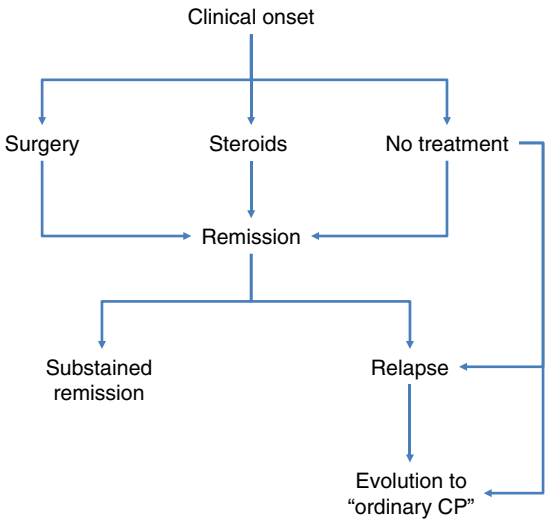


Figure 79.1 Natural history of autoimmune pancreatitis based on evidence in the literature.

disease, probably because the imaging features of AIP and pancreatic cancer can overlap, and lower in a more advanced phase.

The clinical implication is therefore to exclude cancer at the clinical onset of the disease, and to monitor AIP patients by imaging techniques during follow-up, not only to diagnose the disease relapse, often asymptomatic, but also for an early diagnosis of cancer.

The incidence of extrapancreatic cancer within 5 years from diagnosis of AIP is high, ranging from 6.6% to 13.9% [6,60–62]. The increased risk for extrapancreatic malignancy has been reported for AIP type 1, but not for AIP type 2, which may be related to the patient's age more than the AIP subtype. It is still debated whether this incidence is increased compared to the general population. In any case, physicians should be aware that 10% of patients could develop a cancer after diagnosis of AIP and, therefore, the use of immunosuppressant drugs and biologics should be carefully evaluated.

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Section 6

Neoplastic Tumors of the Exocrine Tissue: Benign Cystic Neoplasms of the Pancreas

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Epidemiology of Cystic Neoplasms of the Pancreas

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Introduction

Pancreatic cystic lesions (PCL) can be histopathologically classified as nonneoplastic or neoplastic. Nonneoplastic cysts do not have any malignant potential and include pseudocyst, lymphoepithelial cyst, retention cyst, hydatid cyst, and enteric duplication cyst. Neoplastic cysts, termed pancreatic cystic neoplasms (PCN) have potential to develop malignancy or are malignant at diagnosis. PCN are further classified as serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) (including branch-duct and main-duct IPMN), solid-pseudopapillary neoplasm (SPN), and cystic change in an otherwise solid tumor (e.g., ductal adenocarcinoma or neuroendocrine tumor). The risk of malignancy in these cysts varies from <1% in SCN to >60% in main-duct IPMN [1–3].

PCL are increasingly being identified in asymptomatic patients on routine imaging studies [4]. While a neoplastic nature of PCL <5 mm in size is not always certain, larger, surgically resected cysts are mostly neoplastic, with IPMN being the most common PCN [5]. However, the vast majority of PCL are not resected [6] and therefore, PCL >10 mm in size are presumed to be PCN and are managed accordingly. Studies based purely on imaging diagnosis of pancreatic cysts can provide information on incidence and prevalence of PCL in the general population [7,8]. However, these studies lack confirmatory histopathologic diagnosis and are based on referral populations in the healthcare setting. In contrast, although surgical series cannot be used to determine the true incidence and prevalence in the general population, they have the advantage of providing histopathologic confirmation [5,6]. We use the term PCL in reference to data from imaging studies and PCN for data from surgical series. Although, some studies on PCL do make presumptive histopathologic diagnoses based on imaging and, when available, cyst fluid characteristics; however, preoperative diagnosis may be incorrect in nearly one-third of PCL when correlated with surgical histopathology [9].

Pancreatic Cyst Lesions

Incidence

There is limited information on the incidence of PCL in the general population. A study from Olmsted County, MN showed the prevalence of PCL suspected to be IPMN was 4.35 per 100,000 persons in 2005 [8] (Fig. 80.1). The age- and sex-adjusted incidence had risen 14-fold compared to 1985, when it was 0.31 per 100,000 (Fig. 80.1). This growing incidence was felt to be secondary to diagnostic scrutiny rather than a true increase in incidence over time. In this study, other non-IPMN pancreatic cysts such as SCN were excluded.

Prevalence

In hospital-based studies, the prevalence of PCL has been reported to range between 0.2% and 41.6% [4,10–17]. In a meta-analysis of 17 studies including 48,860 patients, the pooled prevalence of PCL was 8% (95% CI: 4–14%) [18]. Various factors influence the reported prevalence of PCL, including study-related factors and patient-related factors. Study-related factors include study design, imaging modality, and year of study. A recent study showed that incidental PCL were

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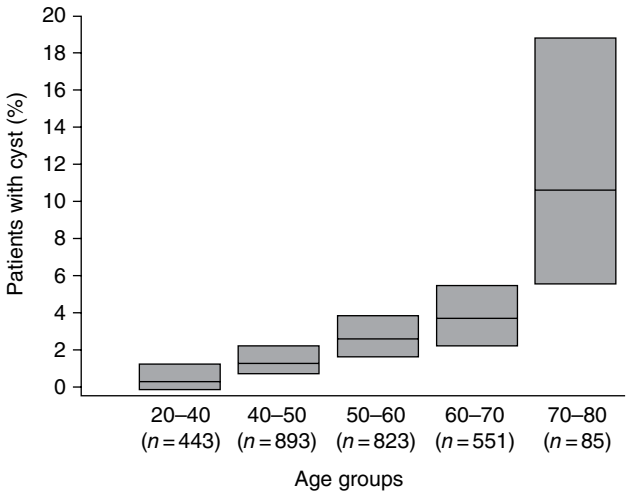


Figure 80.1 Prevalence of pancreatic cysts per age group. The *black line* shows the prevalence and the *gray boxes* represent the CI. For patients older than age 80, see the text for more details. *Source:* Reproduced from [8], Fig.1/With permission of Elsevier.

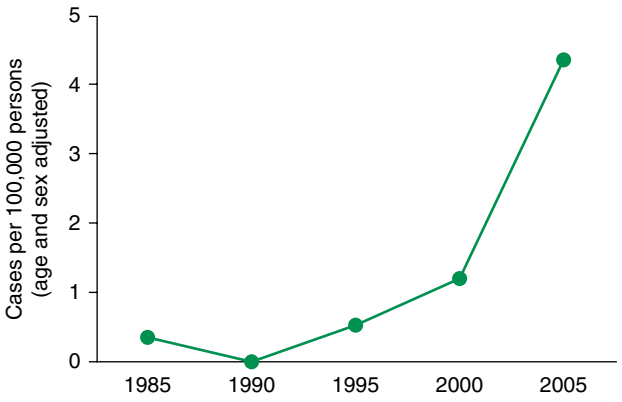


Figure 80.2 Incidence of total IPMN per 100,000 person-years as reflected by the Rochester Epidemiology Project. *Source:* Reproduced from [8], Fig.1/With permission of Elsevier.

documented in only 31% of radiology reports [11]. Thus, retrospective studies based on review of radiology reports rather than review of images underestimate the prevalence rates of PCL. Type of imaging modality also affects the prevalence rate, with increasing prevalence rates reported in studies using US, CT, MRI, and EUS, respectively [17,19]. Older studies report lower prevalence rates compared to newer studies. For instance, PCL were identified in 1.4% of abdominal scans in a study from 1980 [20], compared to 9.3% in a recent study from 2015 [7]. Higher prevalence in the newer studies is likely to be due to better quality of cross-sectional imaging hardware and software. In an interesting study by Moris et al., newer versions of MRI hardware and software were independently associated with higher PCL detection rates [4].

Risk Factors

Age

The likelihood of a PCL being present increases with age (Fig. 80.2). In general, when study populations consist primarily of older individuals the reported prevalence is high. For example, an autopsy series reported PCL prevalence of 24.3% in a population with a mean age of 79.3 years [16]. A study based on MRI in asymptomatic individuals with a mean age of 51.1 years, the prevalence was 2.4% [14]. PCL are infrequent under the age of 40 years; the prevalence in this age group varies from 0–1.2%, depending on the imaging modality used to identify PCL [12,13]. However, in one study using single-shot fast spin-echo MRI sequence, the overall prevalence of PCL was 9.1% in this age group [21]. The risk rises gradually over age 40 years. In a large study the odds of a PCL being present increased by 1.06 for each additional year after age 40 [12]. In individuals over 70 years, up to 40% patients appear to have a PCL [11]. In older patients, not only does PCL prevalence increase, but also the size and number of cysts increases [11,21]. In addition, compared to younger patients, older patients have a greater likelihood of finding malignant pathology and a greater probability of undergoing pancreatic surgery for PCL [22].

Gender

Although one study showed greater prevalence of PCL in women [23], most studies have not shown any difference in prevalence of PCL between the two sexes [11,12,14,15]. Most studies have not shown a difference in size of PCL between men and women [11,14,22], except one study, which showed larger cyst size in men compared to women [12]. There is no difference between rates of malignancy and number of PCL between the sexes [11,22].

Race and Geography

There are limited data on prevalence of PCL based on racial background. Only one study showed that the cysts are 3.5 times more prevalent in Asians compared to non-Asians after controlling for age as a risk factor [12]. Although the prevalence was higher in Asians, cyst size, location, or number was not different compared to non-Asians. In an autopsy study from Japan the prevalence was 24.3% [16]. By contrast, in an ultrasound-based study from Japan the prevalence was 0.21%. In a study from the Netherlands, MRI done in asymptomatic individuals showed a prevalence of 2.4% [14]. In a recent study based on CT scans from San Marino, prevalence in asymptomatic individuals was 5.4% [7]. The estimated standardized population prevalence for the state of San

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Marino was 2.2% [7]. An MRI study from Brazil reported a prevalence of 9.3% [13]. Studies from the United States have shown a prevalence rate of 1.2–19.6% [11,12,21]. The estimated pooled prevalence of PCL appears to be higher in US studies compared to Europe and Asia [18]. It is unclear if this difference in prevalence is due to geographical factors, since various other factors that could impact prevalence, such as age and modality of imaging, were not adjusted.

Family History of Pancreatic Cancer

Based on a case-control study, PCL were reported to be nearly three times more common in individuals with a first-degree relative who had pancreas cancer [15]. A multicenter US screening study in high-risk individuals for pancreatic cancer, such as individuals from familial pancreatic cancer families, hereditary pancreatitis, familial atypical multiple mole melanoma, familial breast–ovarian cancer with breast-related cancer mutation, and hereditary nonpolyposis colorectal cancer, and Peutz–Jeghers syndrome have shown a prevalence of 42% with multiple modalities—CT, EUS, and MRI [19]. The prevalence increased with age, as nearly 65% high-risk individuals over 70 years of age were noted to have a PCL. Another similar study from Sweden showed a prevalence of 40% in such high-risk individuals undergoing MRI screening for pancreatic cancer [24]. In the authors' experience, 5–10% of patients with PCL have a family history of pancreatic cancer in first-degree relatives. In patients with PCL, family history of pancreatic cancer in one first-degree relative is not associated with increased 5-year risk of pancreas cancer when compared to those without family history of pancreatic cancer [25]. Whether risk for pancreatic cancer is higher when there is more extensive family history of pancreas cancer is not known.

History of Pancreatitis

PCN such as IPMN can cause acute pancreatitis. IPMN have also been reported in patients with chronic calcifying pancreatitis [26]. Conversely, individuals with a history of pancreatitis can develop pseudocysts, which are often indistinguishable from PCN [27–29]. Given such issues, studies on the prevalence of PCL have typically excluded patients with a history of pancreatitis. Studies including patients with a history of pancreatitis have reported a prevalence of 16.6–42% [21,22]. However, whether these cysts represented pseudocysts or PCN was not known.

Miscellaneous

Recent studies have shown diabetes mellitus and insulin use as independent risk factors for PCL [15]. Presence of extrapancreatic cysts has also been strongly associated with PCL [4,14,21]. In a study, 70% patients with PCL had an extrapancreatic cyst [4]. The most frequent organs involved were kidneys (50%) and liver (50%). The presence of liver cysts is independently associated with PCL [14]. PCL are seen in 11% of solid organ transplant recipients [30]. Fortunately, pancreatic cancer is rarely seen in this group of patients. Lifestyle factors such as cigarette smoking and alcohol consumption are not associated with development of PCL [11–14,21,22].

PCL are seen in association with autosomal dominant polycystic kidney disease (ADPKD). About 5% to 10% of individuals with ADPKD have PCL, based on ultrasound [31]. However, ADPKD is rarely seen in patients with pancreatic cysts (~1%) [21]. In contrast, pancreas involvement is frequently seen in patients with von Hippel–Lindau disease (VHL). In a large French multicenter study, 77.2% of patients with VHL had pancreatic involvement, mostly PCL and typically serous cystic neoplasms and neuroendocrine tumors [32]. In 7.6% of these patients, the pancreas was the only organ involved. In this series, VHL patients with PCL had fewer pheochromocytomas than those without.

Cyst Size and Morphology

The majority of incidentally identified PCL are subcentimeter in size, the average cyst size being 8–10 mm [11–14,21]. However, cyst size increases gradually with age. For instance, in a study by Lee et al., the median cyst size in patients >90 years was 14 mm compared to 3 mm for those <39 years [11]. Large cysts (>3 cm) are infrequent, seen in <5% cases.

Among patients with incidentally identified cysts, almost half have more than one cyst [13,21]. Multifocal (>5) cysts have been reported in 10% to 40% of cases [13,14,21]. Cyst distribution is generally equal throughout the gland, with half the cysts located in the proximal part of the gland (head, neck, or uncinate) and the other half in the distal part of the gland (body or tail) [11,14].

Morphologically, the majority of PCL (80–90%) identified incidentally are simple in nature without any wall thickening, septations, or mural nodules [11,14]. Communication with the main pancreatic duct, which often implies a diagnosis of IPMN, is seen in 8% to 35% of cases [11,21].

Pancreatic Cystic Neoplasms

As discussed in the preceding section, although PCL are commonly identified, especially in older patients, most of these patients do not undergo surgery and therefore, their histologic diagnosis remains unknown. In one of

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the largest surgical series of 851 patients at Massachusetts General Hospital undergoing surgery for PCL, IPMN were the most common PCN, seen in 38% of cases [5] (Fig. 80.3). MCN were the next most common (23%), followed by SCN (16%), cystic neuroendocrine tumors (7%), and SPN (3%).

IPMN are mucinous neoplasms arising from the pancreatic ducts. When they arise from the side branches, they are referred to as branch-duct IPMN (BD-IPMN) and are called main-duct IPMN (MD-IPMN) if they involve the main pancreatic duct. Mixed-IPMN involve both branch and main ducts, but for practical purposes they are considered together with MD-IPMN.

The median age of surgery for BD-IPMN is about 65 years with an almost equal distribution between males and females [33]. However, studies from Asia have reported male sex predilection with a 3 : 1 ratio [34]. The median size of resected BD-IPMN varies between 2 to 3 cms [33,35]. BD-IPMN appear as a solitary cyst, multifocal cysts, or a cluster of cysts. They arise from the side branches of the pancreatic duct, although the communication with the main pancreatic duct may not always be discernable on imaging. Almost 60% are in the head of the pancreas and 40% in the body/tail region; 15–40% are multifocal [33,35]. Malignancy is present in less than 20% of surgically resected cases [33,35]. About 12% have a history of pancreatitis and 35% have a history of smoking [33,35].

Similar to BD-IPMN, the median age for MD-IPMN is between 65 and 70 years [5]. They appear as dilation of the main pancreatic duct without any obstructing mass or stricture. The majority (64%) are in one location, most commonly in the head of the pancreas [3,5]. Among the 36% involving multiple locations, almost half have diffuse involvement of the entire pancreatic duct [3]. Malignancy can be seen in up to 60% of MD-IPMN, and is associated with older age, jaundice, and new-onset diabetes mellitus [3]. The malignancy risk in mixed-IPMN is like MD-IPMN.

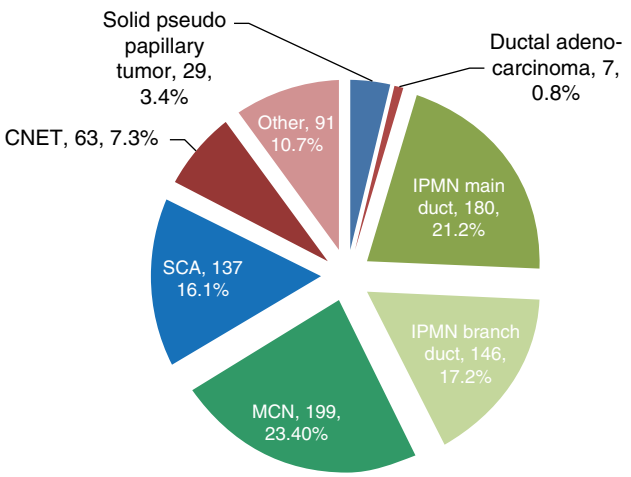


Figure 80.3 Distribution of pathologic diagnoses in 851 resected cystic neoplasms of the pancreas. Lesions classified as "other" included pseudocysts, 25; benign epithelial cysts, 11; acinar cell cystadenomas and cystadenocarcinomas, 3; lymphoepithelial cysts, 5; choledochal cysts, 4; lymphangiomata, 4; hemangiomata, 2; and other unclassified epithelial cysts. *Source:* Reproduced from [5], Fig.1/with permission of Elsevier.

MCN are almost exclusively seen in females (>95%) [36–39]. The median age is 40–50 years, and most patients are <60 years [36–39]. The median size of MCN typically varies between 5 cms to 10 cms [36,39]. MCN with an associated invasive carcinoma are generally larger than benign MCN and an associated invasive carcinoma is rarely seen in MCN <4 cms [36,39]. These PCN are solitary and often have septations and a thick wall. Wall calcification can be seen in about 25% of cases [37,38]. They are almost always (>90%) located in the body/tail region of the pancreas [36–39]. Less than 5% have communication with the main pancreatic duct [38]. An associated invasive carcinoma at the time of surgical resection is found in 10–20% [37–39]. Older age, larger cyst size, presence of mural nodules, and elevated CA-19-9 are associated with malignant transformation [36–39].

SCN are seen more commonly in females (75%) and the median age is 58 years [1]. Their median size at diagnosis is about 3 cms [40]. They are solitary, and generally appear as a cluster of multiple cysts separated by thin fibrous septae with a characteristic central scar seen in 30% of cases [41]. The pattern of cysts is microcystic in 45%, macrocystic in 32%, both microcystic and macrocystic in 18%, and solid in 5% of cases [1]. Cyst calcification is seen in about 15% of cases [1]. They are equally distributed in the pancreas with 40% in the head, 34% in the body, and 26% in the tail [1]. Malignancy is very rare (0.1%) [1].

SPN are predominantly seen in females (>85%) [42,43] and the median age of diagnosis is 35 years [43]. They are typically large at the time of diagnosis with an average size of 8.5 cms [42]. They are solitary, well encapsulated, round-oval, and have a variable amount of solid and cystic component, hemorrhage, and necrosis [43,44]. Cyst calcification can be seen in nearly half the cases [44]. They are equally distributed between the head, body, and tail of the pancreas [43]. Metastases can be seen in 15–20% of cases at surgery [43,44].

Cystic pancreatic neuroendocrine tumors present at a median age of 55–60 years and are equally distributed between the sexes [45,46]. The mean size varies between 2 to 5 cms [45,46]. These are typically solitary cystic lesions with a varying degree of solid/cystic component. Most have arterial hyperenhancement of solid component, as is seen with other solid neuroendocrine

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tumors of the pancreas [45,46]. Nearly half of these have a characteristic hypervascular rim noted as an enhancing cyst wall on imaging [45]. Calcification is infrequent [46]. They can be seen in association with von Hippel–Lindau and multiple endocrine neoplasia (MEN) syndromes [45,46].

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Histologic Classification and Staging of Cystic Neoplasms

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Introduction

With the increased use of cross-sectional imaging in the workup of numerous abdominal complaints, cystic lesions of the pancreas have been increasingly identified. The prevalence of incidental pancreatic cystic lesions in the adult population is high, and ranges from 2.6% to 19.6% [1]. Autopsy series report an increase in pancreatic cystic neoplasms prevalence with age: 8% in patients <70 years of age, up to 35% >90 years of age [2]. In the clinical practice, only 5% to 15% of pancreatic cysts have been reported as neoplastic (Table 81.1) [3]. Recently, most pancreatic cysts are considered to be small intraductal papillary mucinous neoplasms (IPMN) or retention cysts. Cystic neoplasms, including serous cystic neoplasms (SCN), mucinous cystic neoplasms (MCN), IPMN, intraductal oncocytic papillary neoplasms (IOPN), solid pseudopapillary neoplasms (SPN), and some types of acinar cell neoplasms can be classified according to their malignant potential into benign, precursor, and malignant [4]. It is important to recognize pancreatic cystic neoplasms before an invasive carcinoma develops, especially in MCN and IPMN. MCN and IPMN show ductal differentiation of the neoplastic epithelium; however, the differentiation of epithelial cells in SCN and SPN has not been fully recognized. The histopathologic classification and staging of major cystic neoplasms are discussed in this chapter.

Serous Cystic Neoplasms

Serous cystic neoplasms (SCN) are almost always benign, and indolent pancreatic neoplasms composed of innumerable small cysts lined by epithelial cells showing a clear cytoplasm and round, uniform nuclei. Patients are usually women (female/male ratio: 7:3) with a mean age at diagnosis of 60 years [5–7]. Approximately 40% of SCN are incidentally detected by imaging studies at routine physical examinations or for other diseases. Other patients complain of symptoms related to local mass effects, such as abdominal pain, palpable mass, nausea, and vomiting. Patients with von Hippel–Lindau (VHL) syndrome are at an increased risk for development of serous cystic neoplasms. SCN are observed in 12% of patients with this syndrome [8]. Sporadic SCN have been found to feature somatic mutations in the *VHL* gene in 50% of cases [9].

Macroscopically, SCN are multilocular, large cystic neoplasms and their cut surface typically shows a well-circumscribed, sponge-like appearance (called "microcystic type") with a central scar (Fig. 81.1a). The size of the cysts is variable, and there are several variants described below. The cysts contain serous watery fluid. They usually do not communicate with the pancreatic larger ductal system.

Histologically, the cysts are separated from one another by thin fibrous septa and the internal surface of the cysts is covered by a monolayer epithelium (Fig. 81.1b). The lining epithelial cells have a clear cytoplasm and round, uniform, centrally located nuclei. Although a moderate nuclear pleomorphism is not unusual, necrosis and mitoses are not identified.

Because the cells contain large amounts of glycogen, they stain strongly with the periodic acid–Schiff (PAS) reaction, but only without diastase digestion. Immunohistochemically, the epithelial cells lining the cysts express cytokeratins (CK), such as CK7 and CK19, and epithelial membrane antigen (EMA), MUC6, inhibin alpha, and Glut1, but not CEA, trypsin, or chromogranin A [3,4].

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Table 81.1 Classification of cystic lesions of the pancreas.

Cystic neoplasms – Epithelial
Serous cystic neoplasm
Mucinous cystic neoplasm
Intraductal papillary mucinous neoplasm
Intraductal oncocytic papillary neoplasm
Solid pseudopapillary neoplasm
Acinar cystic transformation
Acinar cell carcinoma (intraductal papillary variant)
Mature cystic teratoma
Cystic neoplasms – Nonepithelial
Lymphangioma
Cystic degeneration of the nonepithelial neoplasms
Nonneoplastic cystic lesions
Pseudocyst
Retention cyst
Lymphoepithelial cyst
Mucinous nonneoplastic cyst
Congenital cysts
Enterogenerous cyst
Endometrial cyst

According to the current World Health Organization (WHO) classification, serous cystadenomas are classified into microcystic serous cystadenoma, macrocystic (oligocystic) serous adenoma, solid serous adenomas, VHL-associated serous cystic neoplasms, and mixed serous-neuroendocrine neoplasms [4]. The lining epithelium of these subtypes of SCN is the same as that of the common type (microcystic type) of SCN. Serous cystadenocarcinoma (malignant neoplasm) is defined by the presence of distant metastases because SCN with locally aggressive features, such as direct invasion into adjacent tissues, can rarely recur or even metastasize [4–6].

The most important differential diagnoses, especially in the macrocystic type of SCN, are with the two mucinous neoplasms, MCN and IPMN.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasm (MCN) occurs almost exclusively in women (male/female ratio: 1:10–20), arises in more than 90% of cases in the body-tail of the pancreas, and has no, or very infrequent, communication with the pancreatic ductal system [4,10]. The mean age at diagnosis is approximately 45 years. Like the other cystic neoplasms of the pancreas, growing numbers of MCN are being detected in asymptomatic patients through imaging studies.

Macroscopically, MCN present as a round mass with a smooth, intracystic surface and a fibrous pseudocapsule with variable thickness and frequent calcifications. The tumor size ranges from 2 cm to 35 cm in greatest dimension. The cut surface shows unilocular or multilocular tumor cysts (so-called "cyst-in-cyst appearance") that contain mucus, watery fluid, or hemorrhagic-necrotic material (Fig. 81.2a). The internal surface can be smooth or may present with papillary projections and/or solid nodules. The presence of larger dimension papillary projections and/or mural nodules correlates significantly with malignancy.

Histologically, MCN is composed of the following two distinct components: a mucinous epithelium and a densely cellular ovarian-type stroma (OS) that represents the entity-defining feature (Fig. 81.2b). The epithelium frequently displays areas with pseudopyloric,

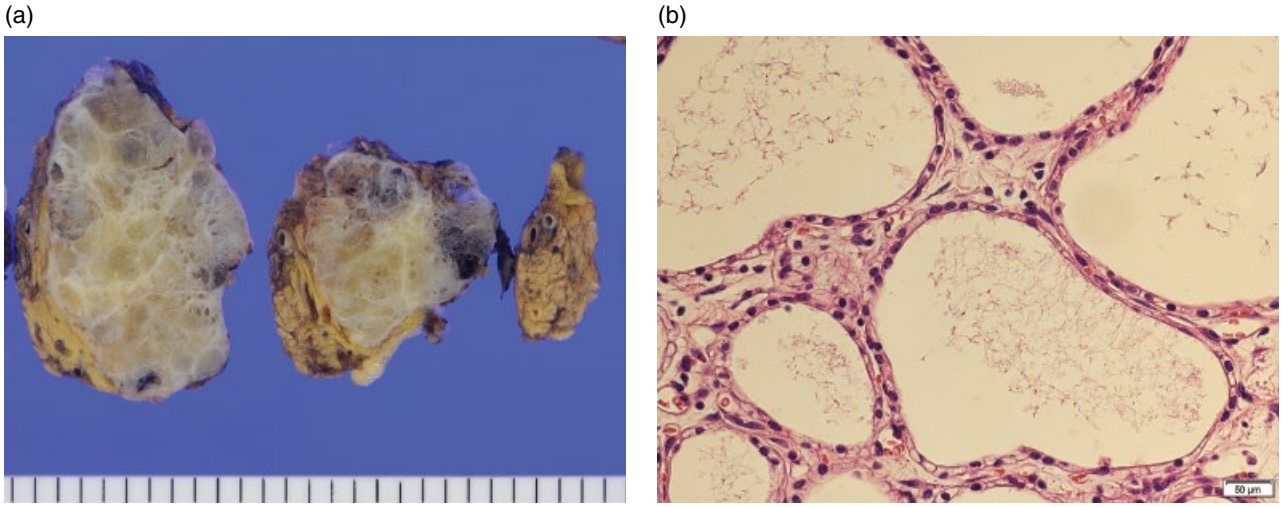


Figure 81.1 (a) Macroscopic feature of serous cystadenoma (microcystic type). The cut surface shows the well-circumscribed sponge-like appearance with a central scar. (b) Histology of serous cystadenoma (microcystic type). The internal surface of the cyst is covered by a monolayer epithelium. The lining cells show clear cytoplasm and small, round nuclei.

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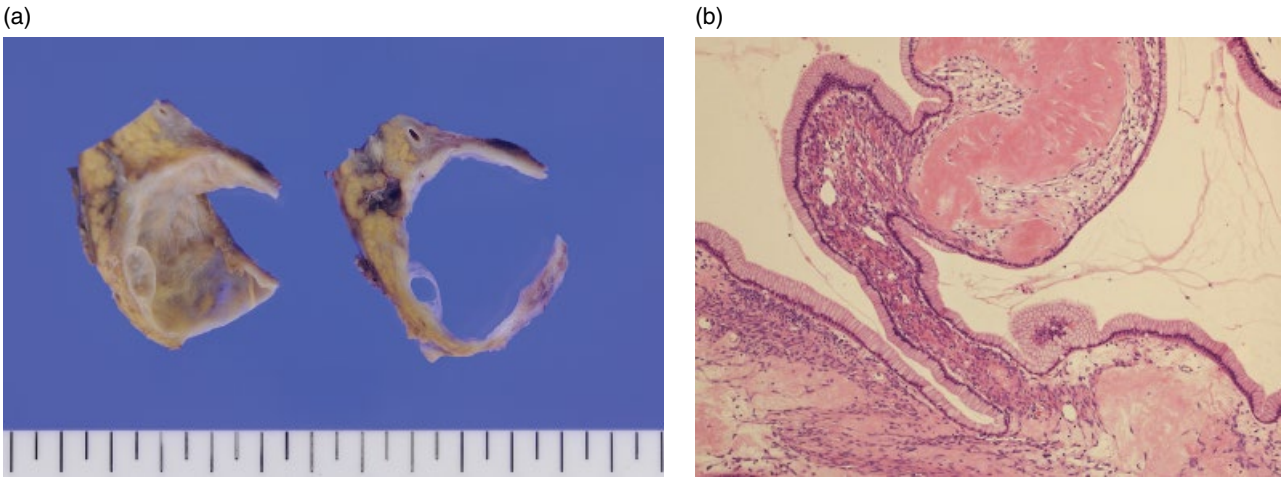


Figure 81.2 (a) Macroscopic feature of mucinous cystic neoplasm. The cut surface shows a "cyst-in-cyst appearance." (b) Histology of mucinous cystic neoplasm. MCN is composed of a mucinous neoplastic epithelium and a subepithelial densely cellular ovarian-type stroma.

gastric foveolar, and small and colonic intestinal differentiation. Noninvasive MCN are subcategorized into low- and high grades [4]. Low-grade MCN are characterized by a minimally dysplastic epithelium, whereas the high-grade MCN (the equivalent of carcinoma *in situ*) show papillae with irregular branching, budding, severe nuclear atypia, and frequent mitosis. The epithelial cells frequently show immunoreactivity for gastric foveolar type mucin marker MUC5AC, whereas MUC2 is only present in the goblet cells and MUC1 is usually expressed in high-grade MCN and invasive carcinomas.

The OS is a compact layer of cellular stroma that underlines the mucinous epithelium. It is constituted by spindle cells that show immunoreactivity for vimentin, smooth-muscle actin, progesterone receptors (PR), and estrogen receptors (ER). Occasional plump, eosinophilic cells, resembling luteinized cells and expressing alpha-inhibin, may be present. The presence of OS, currently requested for the diagnosis of MCN, in some cases can be hard to identify, because the OS can be replaced by a hyalinized stroma, secondary to a long history and high pressure-related atrophy.

Up to one third of MCN are associated with an invasive carcinoma, which usually resembles the common ductal adenocarcinoma, and colloid carcinomas are extremely rare [11,12].

The staging of the MCN with invasive carcinoma should be determined following the recent scheme proposed by Tanaka et al. [13]. The term "minimally invasive," that has been variably defined by different authors, should be avoided and replaced by the conventional staging protocols, including the AJCC/TNM [14]. The overall size of the invasive carcinoma should be recorded and categorized as early (≤2 cm, pT1) and advanced (>2 cm, pT2 and beyond). pT1 tumors should be subcategorized into pT1a (<0.5 cm), pT1b (0.5–1 cm), and pT1c (>1 cm) [13,14].

MCN have a potential to evolve into malignant tumors through low-grade to high-grade neoplasms [15]. The survival of invasive MCN may vary from excellent to 63% at 5 years [10,11]. Jang et al. [12], using the UICC/TNM staging, reported an aggressive clinical course with 3- and 5-year survival rates of 44% and 26%, respectively. Recent large-scale studies showed small (less than 4 or 5 cm in size) MCN with no symptoms or features of concern may safely be observed as a low risk of malignant transformation [15,16], though the neoplasms without radiologic features of malignancy tend to be resected.

Intraductal Neoplasm

Intraductal neoplasms of the pancreas are a heterogeneous category of radiographically and grossly detectable lesions defined as cystic or mass-forming epithelial neoplasms with ductal differentiation that grow primarily within the ductal system, and that can progress to invasive carcinoma.

According to the current WHO classification, intraductal neoplasms were classified into IPMN, IOPN, and intraductal tubulopapillary neoplasms (ITPN) [4]. Of these, ITPN is an important entity in the differential diagnosis of IPMN; however, this is usually not recognized as a cystic lesion [17]. The neoplastic epithelium shows nonmucinous and high-grade morphology. IOPN is a grossly cystic epithelial neoplasm composed of exophytic nodular projections lined by oncocytic glandular epithelium, which grows within dilated pancreatic ducts [4]. IOPN was previously classified as a subtype of

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IPMN; however, this neoplasm is now considered a distinct entity from IPMN according to the genomic abnormalities such as fusions in PRKACA and PRKACB genes [18,19].

IPMN are more common in men than in women. The mean age is approximately 65 years. Most IPMN are solitary and located in the pancreatic head, although 20–40% are multifocal. IPMN can be classified by several viewpoints, such as localizations (main duct or branch duct), histologic grading (low to high grade), histologic differentiation (gastric, intestinal, or pancreatobiliary), and mucin hypersecreting or not.

Macroscopically, IPMN is an intraductal neoplasm usually showing flat to papillary epithelial proliferation within the dilated pancreatic ducts (>1 cm) by abundant mucus (Fig. 81.3a). IPMN can be classified into main-duct type IPMN (MD-IPMN), branch-duct IPMN (BD-IPMN), and combined type IPMN according to the ductal portion of tumor involvement [4,13]. MD-IPMN typically show diffuse dilatation of the main pancreatic duct with abundant mucus and villous neoplastic components. BD-IPMN show multiple cystic dilatations of pancreatic ducts called "grape-like appearance." They arise more often in the head and neck and frequently involve the uncinate process. IOPN typically form relatively large, tan collar, friable papillary projections or solid nodules within cystically dilated pancreatic duct.

Histologically, the direction of differentiation of the neoplastic epithelial cells varies among IPMN, including gastric, intestinal, and pancreatobiliary types of differentiation. IPMN have varying degrees of cytologic and architectural atypia, and noninvasive IPMN can be categorized into low- and high grades with the same grading system as MCN. These various differentiations and grades of neoplasm are frequently mixed up within one neoplasm. Many intestinal-type IPMN arise in the larger pancreatic ducts, such as the main pancreatic duct (MD-IPMN), and usually show villous or high papillary projections of neoplastic epithelium with abundant extracellular mucus (Fig. 81.3b). If they invade outside the pancreatic duct, invasive components often form a colloid (mucinous) carcinoma. Intestinal-type IPMN show MUC2, MUC5AC, and CDX2 on immunohistochemistry. Gastric-type IPMN frequently occur in branch ducts (BD-IPMN).Their inner surface is covered by low papillary or flat neoplastic epithelium with low-grade dysplasia. Many of these gastric-type IPMN have an indolent course. Gastric-type IPMN are immunoreactive with MUC5AC and MUC6 in some cases. Pancreatobiliary-type IPMN characteristically grow with arborized pattern, and this type of neoplasm is immunoreactive with MUC1, MUC5AC, and MUC6 in some cases. These different phenotypes can be observed together, with the IPMN classified according to the predominant type. Despite similarities to IPMN, histology of IOPN is notable for complex, thick, arborizing papillae lined by multiple layers of cuboidal and columnar oncocytic (eosinophilic) mitochondria-rich epithelial cells. Based on both the architectural complexity and the degree of nuclear atypia, essentially all IOPN have high-grade dysplasia [4].

The 5-year survival rate for patients with a surgically resected IPMN without invasion is 90–95%. There are significant differences in the prevalence of invasive cancer between the MD-IPMN and the BD-IPMN. Carcinomatous transformation is reported in 30–50% of

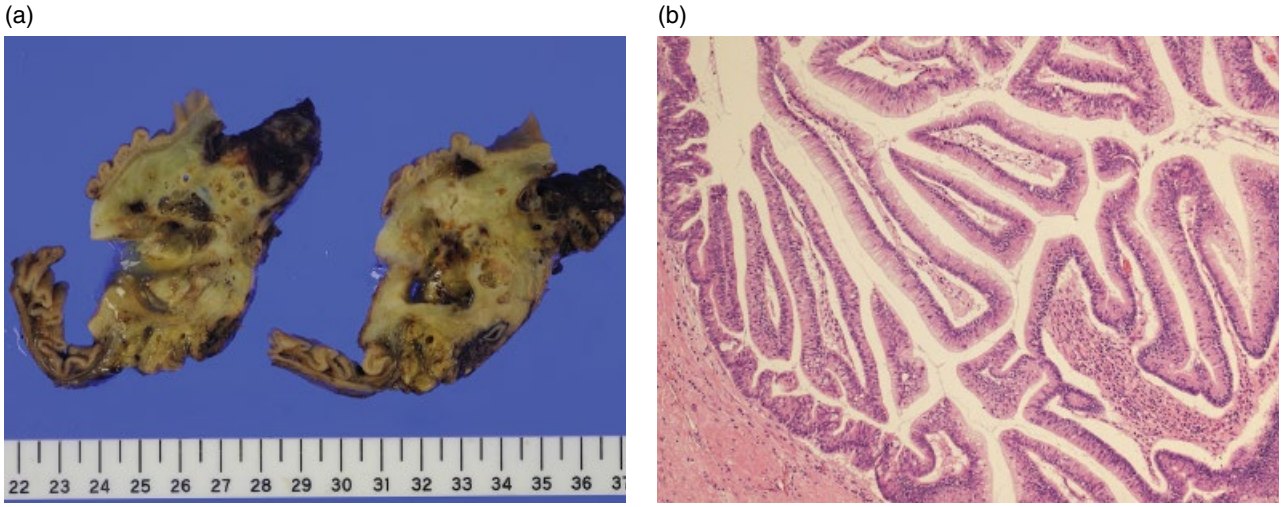


Figure 81.3 (a) Macroscopic feature of intraductal papillary mucinous neoplasm (main-duct type). The cut surface shows intraductal papillary lesions within the dilated main pancreatic duct. (b) Histology of intraductal papillary mucinous neoplasm (intestinal type). Intestinal type IPMN shows villous projections of neoplastic epithelium.

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MD-IPMN or mixed-IPMN, whereas the BD-IPMN have a lower risk of carcinomatous transformation, with 24% of surgically resected BD-IPMN found to have high-grade dysplasia or invasive adenocarcinoma [13]. Most of the invasive carcinomas that arise in MD-IPMN are colloid carcinomas, whereas tubular-type adenocarcinomas, characterized by the presence of malignant glands similar to conventional pancreatic ductal adenocarcinoma (PDAC), are associated with both pancreatobiliary-type IPMN and, in a small percentage, with gastric-type BD-IPMN. The type of invasive carcinoma has major prognostic implication: colloid carcinoma has a better prognosis than tubular adenocarcinomas, with the latter behaving like a conventional PDAC.

In contrast, approximately 10% of IPMN are concomitant with the conventional PDAC (histologically separated from the IPMN) [20]. Although the identification of the concomitant carcinomas has biologic (GNAS mutations) and prognostic (worse prognosis) relevance, at times their correct identification can be hard to achieve. The most frequent molecular anomalies of IPMN are either a *GNAS* or a *KRAS* mutation, and more than half IPMN have both mutations. The targeted genes found in PDAC, including *KRAS2*, *p16/CDKN2A*, *SMAD4*, and *TP53* genes, are found much less [21,22].

The stage of the invasive carcinoma, similarly to invasive MCN, is one of the most important prognostic parameters, and should be determined following the criteria suggested by Tanaka et al. [13] and the recommendations of the Consensus at the Verona meeting on IPMN [23]. The UICC/AJCC staging protocol is suggested, with their subcategorization of pT1 into pT1a (<0.5 cm), pT1b (0.5–1 cm), and pT1c (>1 cm).

Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade epithelial neoplasm primarily occurring in girls and young women (20–40 years) and shows solid and cystic areas at macroscopy and pseudopapillary and poorly cohesive features at histology [4,24].

Macroscopically, SPN are frequently large, round, well-circumscribed masses and show variable proportions of solid and cystic areas filled with hemorrhagic fluid and necrotic debris (Fig. 81.4a). At the extreme ends of the spectrum of macroscopic appearances, some cases can be exclusively solid (usually the smaller lesions), whereas others (usually the larger tumors) may be entirely cystic.

Histologically, the tumors are composed of a mixture of solid and cystic areas, usually surrounded by a fibrous capsule. The tumor cells, collected in solid areas or lining pseudopapillae, are monomorphous with round to oval nuclei and eosinophilic, granular cytoplasms (Fig. 81.4b). PAS-positive globules, stromal myxoid degeneration, necrotic changes with foam cells, and hemorrhage are distinctive features of SPN. Mitotic figures are virtually absent. Despite the well-demarcated gross appearance, infiltrative edges entrapping acinar cells and islets are common findings in SPN [24].

The histogenesis of SPN remains unknown. The neoplastic cells show positivity for the endocrine markers CD56, NSE, and occasionally for synaptophysin, but the staining for chromogranin is always negative. Similarly, staining for acinar and ductal markers is consistently negative. Consistent positivity is present for vimentin, CD10, CD117, and progesterone receptors. Paranuclear dot-like immunostaining for

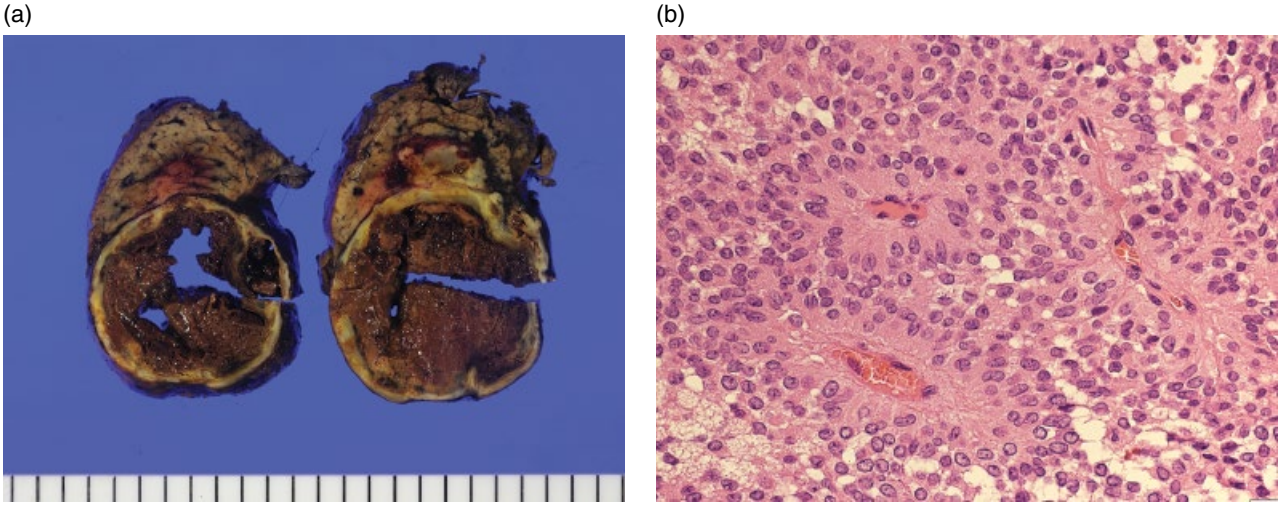


Figure 81.4 (a) Macroscopic feature of solid pseudopapillary neoplasm. The cut surface shows round, well-circumscribed masses with hemorrhagic and degenerative material. (b) Histology of solid pseudopapillary neoplasm. Solid area of the tumor shows pseudopapillary structures composed of monomorphous cells with round to oval nuclei and eosinophilic, granular cytoplasm.

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CD99 is characteristic [25]. The most constant and diagnostically useful finding is the abnormal nuclear immunoexpression for β-catenin, which reflects the somatic point mutations in exon 3 of the β-catenin gene [26].

SPN are considered to be potentially malignant neoplasms, but most of the cases do not recur after complete resection of the tumor. Only 10–15% of cases progress aggressively, almost always involving the liver or the peritoneum. Even in such cases, the patients survive for many years. Only a few patients have died of a metastasizing tumor [23,24].

Acinar Cystic Transformation

Acinar cystic transformation, previously called acinar cyst adenoma, is a recently recognized cystic lesion lined by cells with acinar differentiation, and is believed to behave in a benign fashion [4]. Many of these lesions, particularly those that diffusely involve the gland, are considered not neoplastic [29]. The lining cells of the cystic inner surface lack atypia, and transitions between the cysts and preexisting acinar structures are often observed. Acinar cell carcinomas may rarely form intraductal papillary tumors.

Mature Cystic Teratoma

Mature cystic teratomas, also known as dermoid cysts, are rare, benign cystic neoplasms commonly composed of multiple cell types derived from one or more of the three germ layers (ectoderm, mesoderm, and endoderm). These cystic neoplasms are filled with thick, yellow, sebaceous material. Histologically, the cysts are lined by a simple ciliated or stratified squamous epithelium and skin appendages and other tissues, such as cartilage, bone, and brain, can be seen.

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Molecular Mechanisms of Cystic Neoplasia-

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Introduction

Cystic neoplasms of the pancreas can pose significant clinical challenges. Some cystic neoplasms are precursors to invasive pancreatic cancer and they therefore offer unique opportunities to save lives through early detection and early treatment [1]. However, other cystic neoplasms are entirely benign, and will never progress to invasive cancer. These harmless cystic neoplasms, because they can be hard to distinguish clinically from high-risk cystic lesions, present a real risk for over-treating patients [2–4].

While enhancements in imaging and years of clinical experience have improved the preoperative clinical classification of cystic neoplasms, currently available imaging technologies still have relatively poor sensitivity and specificity in diagnosing high-grade dysplasia, and there is still enormous room for improvement [5,6]. Simply put, too many pancreatic cysts are clinically misclassified, and when they are, patients can be harmed [2,3]. Preoperative misclassification of pancreatic cysts is the result of a lack of accurate classifiers compounded by the fact that sometimes a cyst of one type can radiographically mimic a different cyst type (Table 82.1). A common consequence of misclassification of a cyst is unnecessary surgery. The surgical resection of a benign pancreatic cystic lesion for the reason that it clinically mimics a potentially malignant tumor is a significant clinical problem, because pancreas surgery, even at high-volume centers, is associated with significant morbidity and even a 1–2% risk of operative mortality [2].

A great deal of effort has therefore gone into defining the molecular alterations underlying the development of the different pancreatic cyst types, with the hope that knowledge of these alterations may be translatable into clinical tests to determine cyst type and the need for surgery preoperatively.

All of the major cystic neoplasms of the pancreas have recently been well characterized at the molecular level, providing insights into the fundamental processes driving these tumors (Table 82.2) [7–9]. Importantly, studies in which both the cyst fluid and the tissue from the same neoplasm were available showed excellent concordance between the genetic changes present in the cyst fluid and in the tissue. Cyst fluid can be sampled at the time of endoscopy. Therefore, analysis of cyst fluid can be used preoperatively to identify genetic and epigenetic changes present in the neoplastic cells lining cysts, to aid in the classification of the cyst, and guide therapy [10–12A].

In this chapter we will review the molecular mechanisms driving each of the major types of cystic neoplasms of the pancreas, with emphasis placed on translating this new knowledge into patient care.

Serous Cystic Neoplasm

Serous cystic neoplasms (SCN) are cyst-forming neoplasms composed of uniform cuboidal neoplastic cells containing abundant glycogen [13]. Although SCN are benign and most can simply be observed clinically, many SCN are surgically resected because they cannot be distinguished clinically from potentially malignant cystic neoplasms. For example, the oligocystic variant of SCN forms large cysts, and these large cysts can clinically mimic other cystic neoplasms of the pancreas, particularly mucinous cystic neoplasms [2,13]. Similarly, the solid variants of SCN can mimic pancreatic neuroendocrine tumors.

The exomes of a series of well-characterized SCN have been sequenced [7,14]. SCN contain an average of 10 intragenic somatic mutations per tumor, and the *VHL* gene on chromosome 3p is mutated in ~50% of SCN [7]. These mutations are typically inactivating mutations.

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Table 82.1 Identification of cyst type can be problematic.

Cyst type	Clinical characteristic	Clinical management goal	Reason for misclassification
SCN	Benign	Surveillance	Cystic SCN mimics MCN; solid SCN mimics PanNET
IOPN	A fraction progresses to malignancy	Surgery for high-grade; low-grade are rare	Can mimic other intraductal lesions
IPMN	A fraction progresses to malignancy	Surgery for high-grade; surveillance for low-grade	Difficult to determine grade preoperatively
MCN	A fraction progresses to malignancy	Surgery for most	Sometimes radiographically mimic SCN
SPN	Malignant	Curative surgery	Cysts associated with SPN can radiographically mimic other types of pancreatic cysts

IOPN: intraductal oncocytic papillary neoplasm; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm; PanNET: pancreatic neuroendocrine tumor; SCN: serous cystic neoplasm; SPN: solid pseudopapillary neoplasm.

Table 82.2 Types of cysts with their major genetic alterations.

	AVG # of intragenic mutations	CTNNB1	GNAS	KLF4	KRAS	PIK3CA	PRKACA/PRKACB fusions	RNF43	SMAD4	TP53	VHL
IOPN	–						X				
IPMN	27		X	X (LGD)	X	X		X	X (HGD)	X (HGD)	
MCN	16				X	X		X	X (HGD)	X (HGD)	
SCN	10										X
SPN	3	X									

HGD: high-grade dysplasia; IOPN: intraductal oncocytic papillary neoplasm; IPMN: intraductal papillary mucinous neoplasm; LGD: low-grade dysplasia; MCN: mucinous cystic neoplasm; SCN: serous cystic neoplasm; SPN: solid pseudopapillary neoplasm.

In addition, the neoplastic cells of SCN often have loss of heterozygosity (LOH) on chromosome 3p at the *VHL* locus, providing a "second hit" that inactivates gene function [7]. Germline mutations in the *VHL* gene can lead to the development of serous cystadenomas, as patients with the von Hippel–Lindau syndrome often develop serous cystadenomas of the pancreas [15]. As will be discussed later in the section on clinical implications, both *VHL* gene mutations and LOH on 3p are detectable in cyst fluid and cyst fluid analysis for these markers can therefore be used to characterize a cyst as an SCN [14].

The *VHL* gene codes for a protein, VHL, which functions in the hypoxia-induced factor (HIF) pathway [16]. The VHL protein forms a complex with other proteins, and this complex has E3 ubiquitin ligase activity, functioning in the ubiquitination and subsequent degradation of hypoxia-inducible factor alpha (HIFα) [16]. HIFα is a transcription factor that functions to control gene expression in response to cellular oxygen levels. HIFα stabilization created by the inactivating mutations in *VHL*, among other things, promotes the expression of a number of genes including vascular endothelial growth factor (VEGF), which in turn promotes angiogenesis and ultimately tumorigenesis [16].

The role of the VHL in the HIF1 pathway led Yip-Schneider and colleagues to hypothesize that vascular endothelial growth factor A (VEGF-A) levels may be elevated in SCN [17]. They therefore determined VEGF-A levels in cyst fluid samples obtained from surgically resected pancreatic cysts [17]. VEGF levels were determined by a simple enzyme-linked immunosorbent assay (ELISA) test. Although the number of cases they examined was relatively small, they found that VEGF-A levels are significantly increased in cyst fluid from SCN compared with cyst fluid from all other types of pancreatic cysts ($P < 0.0001$). They reported that VEGF-A has 100% sensitivity and 97% specificity as a biomarker for SCN [17]. Yip-Schneider and colleagues also found that the presence of a *VHL* mutation in the neoplastic cells of an SCN correlated with elevated cyst fluid VEGF levels. These studies nicely illustrate that both gene and protein markers can be useful clinically, and how genetic changes can be used to inform protein expression studies.

MicroRNA expression has not been well studied in SCN.

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Intraductal Papillary Mucinous Neoplasm

Intraductal papillary mucinous neoplasms (IPMNs) are distinct mucin-producing neoplasms that are usually papillary and which, by definition and name, involve the pancreatic duct system [13]. IPMNs are common in the general population, especially in the elderly [18,19]. Imaging studies suggest that ~3% of the population has an IPMN [18,19]. A small fraction of IPMNs progress to invasive carcinoma, and it can be difficult to determine clinically which IPMNs need to be resected, and which can be safely followed.

Intragenic somatic mutations have been reported in a number of genes in IPMNs. These genes include *KRAS*, *GNAS, p16/CDKN2A, PIK3CA, RNF43, SMAD4*, and *TP53* [7,9,20].

KRAS (v-Ki-ras2; Kirsten rat sarcoma viral oncogene homolog) gene mutations are present in ~80% of IPMNs [7,9]. These are activating point mutations in codons 12, 13, or 61 of the *KRAS* gene. *KRAS* gene mutations activate a number of very complicated downstream pathways including the RAF (rapidly accelerated fibrosarcoma)/MAPK (mitogen-activated protein kinase) and phosphoinositide 3′-kinase (PI3′K) pathways [21–23]. Activated KRAS also upregulates the GLUT1 glucose transporter and alters the expression of enzymes involved in glucose utilization producing the so-called "Warburg effect" in the neoplastic cells [21–24]. In addition, activated KRAS signaling leads to constitutively high levels of autophagy [22]. All of these changes conspire to promote tumorigenesis.

Activating point mutations in the *GNAS* (guanine nucleotide binding protein [G protein] alpha stimulating activity polypeptide 1) gene, usually at codon 201 (R201C and R201H), are present in ~75 % of IPMNs [7–9]. *GNAS* mutations appear to be more common in IPMNs with "intestinal" differentiation than they are in IPMNs with "pancreatobiliary" or "gastric-foveolar" differentiation [9,25]. A *GNAS* mutation and/or a *KRAS* gene mutation are seen in >90% of IPMNs [8,9]. The *GNAS* gene codes for a protein that forms a protein complex which activates adenylate cyclase.

Several studies integrating *GNAS* and *KRAS* mutational analyses with tissue pathology have provided insight into IPMNs biology and clinical behavior. For example, IPMNs have historically been defined pathologically as lesions >1 cm, while smaller precursor lesions (<0.5 cm) are categorized pathologically as pancreatic intraepithelial neoplasia (PanIN) [26]. This leaves a large unclassified grey zone for lesions between 0.5 cm and 1.0 cm. PanIN lesions have not been shown to harbor *GNAS* mutations, while IPMNs do. Matthaei and colleagues therefore examined 21 lesions in the grey zone (0.5–1.0 cm) for *KRAS* and *GNAS* mutations [27]. *GNAS* mutations were identified in seven (33%) of these lesions, helping to define them as small ("incipient") IPMNs rather than large PanIN lesions [27]. As a result the new pathologic classification system for precursor lesions in the pancreas now includes the new term "incipient IPMN" for lesions ≤1.0 cm with histologic or genetic features of a larger IPMN [28].

The *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene codes for a protein that forms the catalytic subunit of the phosphatidylinositol 3-kinase (PI3K) enzyme. This enzyme activates a number of downstream functions that in turn promote cell proliferation and migration, and ultimately cell survival and tumorigenesis. *PIK3CA* gene mutations have been reported in 10% of IPMNs [9]. These mutations are, as was true for *GNAS* mutations, more common in IPMNs with intestinal differentiation.

Inactivating mutations in the *RNF43* gene are present in 30–70% of IPMNs [7,9]. The *RNF43* gene codes for a ubiquitin ligase protein that functions in the Wnt/β-catenin signaling pathway [29,30]. As will be discussed later in this chapter, the presence of genetic alterations of the *RNF43* gene in some IPMNs suggests that Wnt/β-catenin signaling is a potential therapeutic target for invasive carcinomas that arise from *RNF43* mutant IPMN [29,31].

The *KLF4* gene on chromosome 9q encodes for the transcription factor Kruppel-like factor 4. Hotspot mutations (K409 and S411) in the *KLF4* gene have been reported in slightly more than half of the IPMNs examined [20]. What is interesting about these mutations is that they are more prevalent in low-grade IPMNs than they are in high-grade IPMNs. The implications of this finding are not clear, but suggest that these *KLF4* mutations, while they promote proliferation, may not be sufficient to promote neoplastic progression.

SMAD4, *p16/CDKN2A*, and *TP53* are all tumor suppressor genes that have been reported to be inactivated in IPMNs [7,9,32]. The *p16/CDKN2A* gene, which encodes CDKN2A, an important regulator of the cell cycle, is inactivated in ~30% of IPMNs. The gene can be inactivated by intragenic mutation, usually a deletion or an inactivating mutation of one allele, coupled with loss of the second allele, and in additional cases by hypermethylation of the gene's promoter [7,9,33]. Mutations in this gene can be seen in IPMNs with both low- and high-grade dysplasia [32]. By contrast, *SMAD4* and *TP53* inactivation appear to be late genetic events, and are found in IPMNs with high-grade dysplasia and in invasive carcinomas that rose in association with an IPMN [7,9,32].

Studies of the genetic alterations present in the noninvasive and invasive components of IPMNs have shown that the invasive and noninvasive components virtually always harbor identical mutations [7,9,32]. This finding

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helps establish that invasive carcinomas can arise from IPMNs (they are not chance coincidental lesions). Furthermore, low-grade IPMNs contain multiple genetic clones, and a dominant clone emerges as the neoplasm progresses to high-grade dysplasia [34,35].

Recent molecular analyses of a histologic variant of IPMN, the intraductal oncocytic papillary neoplasm (IOPN), have identified novel fusion genes that characterize this tumor type [36,37]. In particular, Singhi and colleagues found recurrent fusions of *ATP1B1-PRKACB*, *DNAJB1-PRKACA*, or *ATP1B1-PRKACA* in IOPN [36]. While virtually all IOPNs harbor one of these fusion genes, these rearrangements were absent from all of the IPMNs Singhi and colleagues examined [36].

The expression of a number of microRNA is dysregulated in IPMN. These microRNA may have important biologic functions in the neoplasms, and some may be useful clinical markers [38–42]. For example, Matthaei and colleagues compared the expression of 750 microRNA in a series of microdissected IPMNs to their expression in normal ductal epithelium and identified a panel of microRNA that have the potential of being used to distinguish IPMN with low-grade dysplasia from IPMN with high-grade dysplasia [38]. Similarly, Caponi and colleagues found that miR-21 and miR-155 are upregulated in IPMN with an associated invasive carcinoma, as compared with IPMN without an invasive carcinoma, and, conversely that miR-101 levels are higher in IPMN without an invasive component than in IPMN with an invasive component [42]. Going a step further, Matthaei and colleagues also identified a panel of microRNA that could help distinguish IPMNs from other types of cysts in the pancreas [38]. Of note, microRNA can be identified in cyst fluid samples, suggesting that quantifying microRNA levels in cyst fluid aspirated at the time of endoscopy could be used to improve the clinical classification of pancreatic cysts [38,40].

A number of alterations in protein and glycoprotein expression have also been reported in IPMNs [43–48]. As is true for microRNA, several proteins and glycoproteins are differentially expressed in IPMNs with low-grade as compared to IPMNs high-grade dysplasia, and most are detectable in cyst fluids [43–45]. Pandey and colleagues have established a useful online resource that summarizes many of the proteins whose expression is altered in invasive pancreatic cancer, and the expression of many of these proteins is also altered in IPMNs [46].

Mucinous Cystic Neoplasm

Mucinous cystic neoplasms are mucin-producing and cyst-forming neoplasms that contain a characteristic ovarian-type stroma [13]. In contrast to IPMNs, the cysts of MCNs almost never communicate with the main duct system of the pancreas [13]. As is true for IPMNs, only a fraction of MCNs progress to invasive carcinoma.

Many of the genes targeted in IPMNs are also targeted in MCN [7]. These genes include *KRAS*, *RNF43*, *PIK3CA*, *p16/CDKN2A*, *SMAD4*, and *TP53* [7]. The major difference is that, in contrast to IPMNs, the *GNAS* gene is rarely, if ever, targeted in MCNs. The function of these genes is described in detail above in the section on IPMNs.

Just as the genetic alterations found in IPMN have proven useful, so too have a number of groups attempted to use the genetic alterations in MCNs clinically. As noted earlier, oligocystic serous cystadenomas can mimic MCNs, and, as a result, some benign serous cystic neoplasms are surgically resected [13]. There is therefore a great clinical need to distinguish between these two entities. The initial clinical results using molecular approaches to distinguish between serous cystic neoplasms and MCNs are not as promising as they are with IPMNs [50]. For example, Singhi and colleagues tested 546 pancreatic cyst fluid samples obtained by fine-needle aspiration at the time of endoscopic ultrasound (EUS) for *KRAS* gene mutations and found that although *KRAS* mutations had a specificity of 100% and a sensitivity of 54% for mucinous differentiation (IPMN and MCN), the sensitivity was only 14% when limited to MCNs [50]. However, with improvements in methodology, addition of more genes, and new algorithms the sensitivity of detecting MCNs has increased significantly [7,11].

The patterns of microRNA expression in MCNs have been studied, and as is true for the genetic mutations, there is some overlap with IPMNs [40]. For example, mir-21 is elevated in MCNs [40].

Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasms (SPNs) are epithelial neoplasms composed of poorly cohesive, relatively uniform, neoplastic cells [13]. Although all SPNs are now classified as malignant, the vast majority (~90%) of patients with an SPN can be cured with surgical resection [13].

The exomes of a series of well-characterized SPNs have been sequenced, and, quite remarkably, virtually all SPNs harbor a *CTTNB1* (β-catenin) gene mutation, and practically no other genetic alterations [7,51,52]. The *CTTNB1* mutations observed prevent the degradation of the β-catenin protein, which is then translocated from the cytoplasm to the nucleus. In the nucleus β-catenin functions to activate the Wnt (int/Wingless) signaling pathway, which in turn mediates gene expression through the lymphoid enhancer-binding factor 1 (LEF1) /T-cell factor transcription complex [53]. Indeed, Singhi and colleagues have shown that *CTTNB1* gene mutations strongly correlate with LEF1 nuclear overexpression in

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SPNs [53]. The combination of immunolabeling for LEF1 (expressed in SPN) and INSM1 (expressed in pancreatic neuroendocrine tumors [PanNet]) has proven useful in distinguishing SPNs from PanNETs [54].

Of interest, SPNs are also characterized by alterations in E-cadherin expression, including loss of expression of the extracellular domain of the E-cadherin protein [55,56]. Recently Huels and colleagues have suggested that reduced E-cadherin expression has a synergistic effect with activating mutations in β-catenin in promoting tumorigenesis [57].

Little is known of the changes in microRNA and protein expression in SPNs [58–60]. In large part this is because the normal cell type that corresponds to the neoplastic cells of SPNs is not well defined. Therefore, expression studies are challenged by the absence of a good control tissue/normal cell type. Several immunohistochemical labeling studies using a candidate marker approach have shown that CD99 and CD10 are overexpressed in SPNs, that the β-catenin protein is abnormally localized to the nucleus, and that E-cadherin expression is lost (when antibodies to the extracellular domain are used) or abnormally localized to the nucleus (when antibodies to the intracellular domain are used) [61,62].

Other Cystic Neoplasms of the Pancreas

For completeness sake we should mention that some typically solid neoplasms of the pancreas can present as cystic masses. For example, pancreatic neuroendocrine tumors (PanNET) can be cystic, as can some ductal adenocarcinomas [13]. These cystic variants appear to have the same molecular alterations as do the solid variants of these same tumors.

Clinical Applications

Several clinical applications of our growing knowledge of the molecular events that drive the formation of cystic neoplasms of the pancreas have been mentioned above, and here we focus on what we believe to be the most promising clinical applications close on the horizon.

First, the genes mutated in IPMNs can be used clinically to distinguish IPMNs from other neoplasms, and in so doing prevent unnecessary surgeries [7,8]. For example, as noted earlier, serous cystic neoplasms virtually never harbor *KRAS* or *GNAS* mutations, while one or both of these mutations is seen in 90–95% of IPMN [14]. Since mutant DNA present in neoplastic cells is shed into the cyst fluid, EUS aspiration of cyst fluid coupled with sequencing of the fluid for *KRAS* or *GNAS* mutations can be used to distinguish serous cystadenomas from IPMNs [14,50]. Furthermore, the cysts of IPMNs communicate with the pancreatic duct system, suggesting that a similar approach can be taken with sequencing secretin-stimulated pancreatic secretions ("juice") obtained in the duodenum at the time of endoscopy [63,64]. It is hoped that additional markers, such as *SMAD4* and *TP53* gene mutations and patterns of LOH and aneuploidy, will be useful in distinguishing IPMNs with low-grade dysplasia from IPMNs with high-grade dysplasia [14].

Second, some of the molecular alterations present in cystic neoplasms that progress to invasive carcinoma are potentially therapeutically targetable. As mentioned previously, a significant fraction of IPMNs and MCNs harbor *RNF43* gene mutations that are predicted to activate the Wnt signaling pathway [7,29,65]. A number of new agents, including selective inhibitors of the porcupine protein in the Wnt pathway, are being developed that could be effective in treating invasive pancreatic cancers that have *RNF43* mutations because they arose from a precursor IPMN with an *RNF43* mutation [29].

The *PIK3CA* gene functions in the mTOR pathway and *PIK3CA* is targeted in ~10% of IPMNs [9]. A number of agents targeting PIK3CA have been developed, and again, these agents could be effective in treating invasive pancreatic cancers that have *PIK3CA* gene mutations because they arose from an IPMN precursor with a *PIK3CA* gene mutation.

Implications for Families

Several familial cancer syndromes are associated with an increased risk of developing a pancreatic cystic neoplasm. Roberts and colleagues reported that almost 3% of patients with an IPMN harbor a deleterious germline mutation in a cancer predisposition gene [66]. Perhaps the greatest risk is seen in patients with the Peutz-Jeghers syndrome (PJS) [67]. Patients with PJS have a 130-fold increased risk of developing invasive pancreatic cancer, and Su and colleagues have demonstrated that some of these invasive cancers arise from noninvasive IPMN precursor lesions [68]. This suggests that patients with PJS may benefit from screening for early curable pancreatic neoplasms (noninvasive IPMNs) [69–71].

Although not strictly a "familial genetic syndrome," the McCune-Albright syndrome is caused by *GNAS* mutations acquired very early during embryogenesis [72,73]. Affected individuals harbor mosaic *GNAS* mutations, and ~15% of individuals with the McCune-Albright syndrome, in addition to the characteristic skin and bone changes, develop an IPMN, some of which progress to invasive carcinoma [72,73]. Of note, Parvanescu and

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colleagues screened 272 patients operated on for an apparently sporadic IPMN and found a patient with polyostotic fibrous dysplasia and café-au-lait spots suggestive of McCune-Albright syndrome [72].

Finally, as noted earlier, germline *VHL* gene mutations cause the von Hippel–Lindau syndrome (VHL), and patients with VHL frequently develop serous cystadenomas of their pancreas [15]. Fortunately, these are virtually always benign.

Conclusions

It is clear that there is a clinical need to better classify cysts preoperatively. Current guidelines do not appear to be adequate [74]. Molecular analyses of cystic neoplasms of the pancreas have helped validate the existing histologic classification of these cysts, and have provided new opportunities to improve the clinical management of patients with a cystic tumor of the pancreas.

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Clinical Presentation of Pancreatic Cystic Neoplasms

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Introduction

A variety of pancreatic neoplasms show a cystic form. Some of them are originally grow in a cystic form (Group A), including intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasm (SCN), and solid pseudopapillary neoplasm (SPN). Some others are cystic degeneration of solid neoplasms (Group B), consisting of cystically degenerated neuroendocrine neoplasm, acinar cell carcinoma, pleomorphic carcinoma, adenosquamous carcinoma, leiomyosarcoma, Schwannoma, and malignant fibrous histiocytoma. There are some rare types of pancreatic cystic tumors which may be misidentified as cystic neoplasms but are not really neoplastic (Group C), including epidermoid cyst arising in the intrapancreatic accessory spleen and lymphoepithelial cyst. Like this, many entities arising in the pancreas may form a cystic pattern, but those in Group A are within the scope of this chapter.

Most cystic neoplasms are asymptomatic and diagnosed by chance when a patient undergoes imaging diagnostic studies such as ultrasonography, computed tomography, and magnetic resonance imaging performed for a health check or investigation of some other diseases. Some cystic neoplasms of the pancreas, however, may present with vague abdominal symptoms such as epigastric discomfort and fullness of the stomach when the neoplasm grows very large. Rather rare events of cystic neoplasms of the pancreas are acute pancreatitis when the neoplasm *per se* or its product causes obstruction of the main pancreatic duct. This may happen when a branch duct IPMN expels mucin into the nondilated main pancreatic duct, resulting in obstruction of the main duct.

Intraductal Papillary Mucinous Neoplasm

IPMN is a precancerous lesion that is most frequent in all cystic neoplasms of the pancreas [1]. IPMN are classified into three morphologic types: (i) branch-duct type (BD-IPMN), which only involves the pancreatic duct branches; (ii) main-duct IPMN (MD-IPMN), which involves the main pancreatic duct; and (iii) mixed-type IPMN, which is mixture of BD-IPMN and MD-IPMN [2]. The morphologic classification is important to predict the probability and potential of malignant transformation of IPMN. BD-IPMN have a low risk for progression to cancer, whereas MD- and mixed-type IPMN are more liable to cancerous changes [1].

When a pure BD-IPMN produces a lot of mucin, a mucin plug expelled from the IPMN into the main pancreatic duct may block the duct especially at its outlet. The blockade may cause acute pancreatitis that is usually mild to moderate, transient, and self-limiting but sometimes severe (Fig. 83.1). When this phenomenon occurs frequently, the patient may be advised to undergo pancreatic resection to remove the IPMN. If there is no risk of malignant changes (no high-risk stigmata or worrisome features), resection may be limited to the cyst and connecting ductal branch [3]. However, most centers perform partial or segmental pancreatectomy to avoid pancreatic leak as a complication of nonanatomical limited pancreatic resection as much as possible. Resection of the IPMN is also acceptable as symptomatic BD-IPMNs are more prone to malignant transformation [4].

Likewise, epigastric pain or discomfort due to chronic pancreatitis or its acute exacerbation may occur due to mucin plugs produced in the main pancreatic duct by MD- or mixed-type IPMN. Less frequently, obstruction of the

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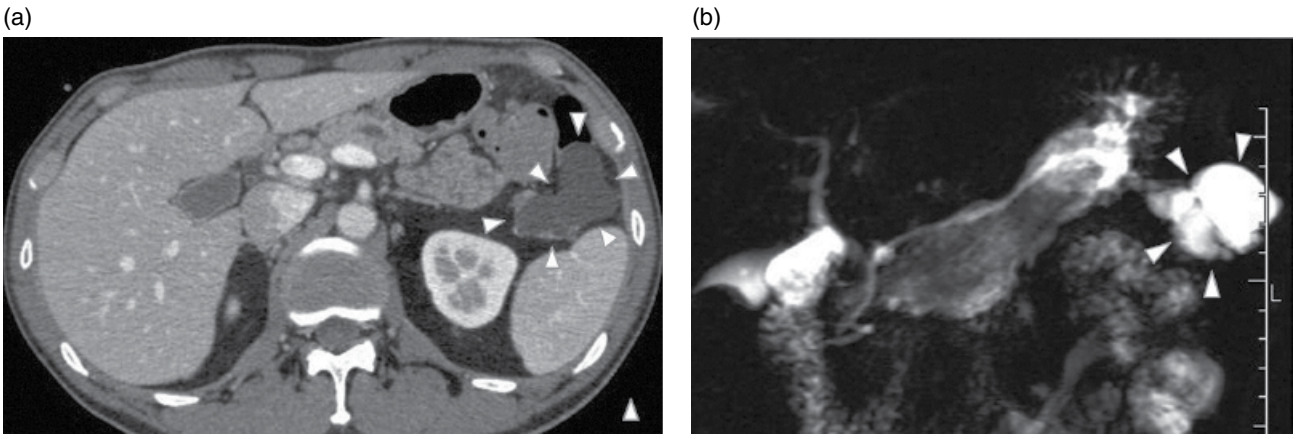


Figure 83.1 A 5.5 × 4.0-cm intraductal papillary mucinous neoplasm (arrowheads) in the pancreatic tail causing recurrent episodes of acute pancreatitis in a 51-year-old man. (a) Dynamic CT. (b) MRCP.

common bile duct may develop due to inflow of mucin when a large IPMN with invasive cancer invades and penetrates the bile duct wall, resulting in jaundice and/or cholangitis. However, the advent and wide availability of modern imaging technologies that promote early diagnosis of IPMN have made these symptoms very rare.

Mucinous Cystic Neoplasm

A vast majority of MCN have no connection with the main pancreatic duct. This feature has been regarded as one of the characteristics to distinguish MCN from BD-IPMN [2,5]. However, a recent study reported that 18.1% of 156 patients with MCN histologically proven by the presence of ovarian-type stroma had a communication between the cyst and pancreatic duct [6]. Unexpectedly, as many as 47% of 153 patients with MCN were symptomatic and 10 patients (6.6%) had a history of acute pancreatitis. Unfortunately, however, details of the clinical symptoms were not described and, moreover, the association of acute pancreatitis and the presence of communication to the pancreatic duct were not described in this study.

Xourafas et al. [7] compared clinical characteristics of 47 patients with noninvasive MCN and 87 patients with noninvasive IPMN. Those with MCN were more often female, significantly younger, more symptomatic, and had cysts more often located in the pancreatic tail. MCN may present with some clinical symptoms more frequently than previously thought.

The symptoms associated with MCN are usually caused by compression of nearby organs. Although compression on the common bile duct might cause jaundice, only one of 156 patients with MCN reported by Yamao et al. [6] had the tumor in the head of the pancreas. Other symptoms include a palpable mass, abdominal pain or discomfort, and rarely general fatigue and weight loss. Left pleural effusion may be associated with a large MCN (Fig. 83.2). Sperti et al. [8] reported two patients with MCN whose clinical presentation was an attack of acute pancreatitis and called attention to possible misdiagnosis as a pseudocyst. MCN should also be taken into consideration in a patient with a cystic formation in the body and tail of the pancreas after acute pancreatitis.

MCN exerts an adenoma–carcinoma sequence. Mucinous cystic carcinoma is usually large and has mural nodules within the cyst. It may present with nonspecific symptoms in the upper abdomen due to its large size. In the series of 156 patients with MCN reported by Yamao et al. [6], 3 patients did not provide the information. Of the remaining 153 patients, 7 (4.6%) had diabetes mellitus, similar to 3.8% previously reported by Thompson et al. [9]. This would be pancreatic diabetes secondary to parenchymal replacement by a large MCN or obstructive pancreatitis caused by an MCN. Very rarely, MCN contains gastrin-producing cells causing hypergastrinemia and Zollinger-Ellison syndrome as rarely seen in ovarian MCN as well [10,11].

Serous Cystic Neoplasm

Most of SCN grow very slowly and remain asymptomatic. A large series of 172 patients with SCN reported by a study group of the Japan Pancreas Society included 90 patients with resection and 82 under observation [12]. Thirty-nine percent of SCNs were located in the head, 35% in the body, and 22% in the tail of the pancreas. The mean size of SCN was 4.1 cm. Of these, only 20% were symptomatic. Small SCN invariably remain asymptomatic. The symptoms if any are largely nonspecific such as nausea, vomiting, and abdominal discomfort caused by mass effects and/or

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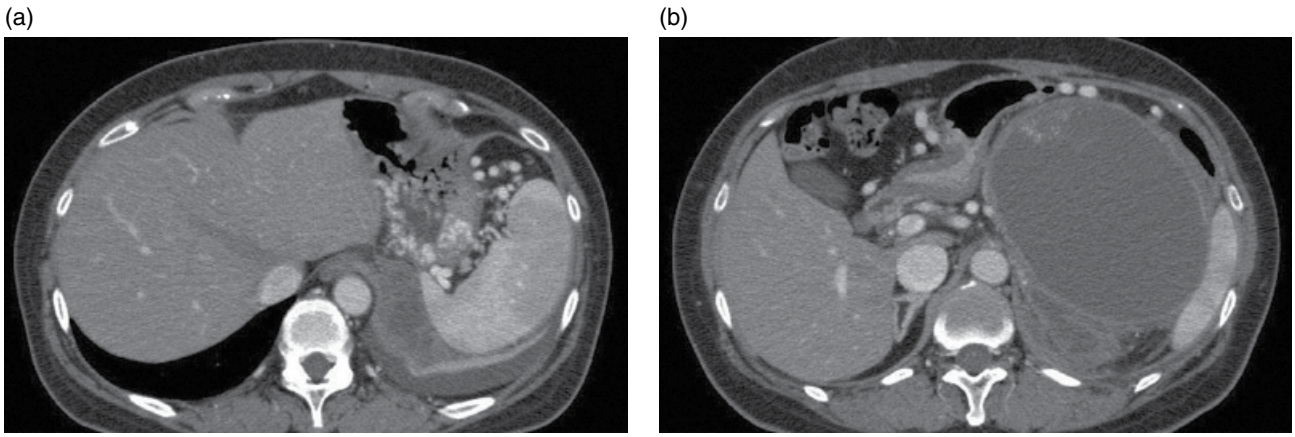


Figure 83.2 A 13-cm mucinous cystic carcinoma in a 56-year-old woman presenting with left pleural effusion. (a) Dynamic CT showing dilated perigastric collateral veins and gastric varices resulting from obliteration of the splenic vein. Left subphrenic fluid collection and pleural effusion are also observed. (b) Another image delineating a thick-walled huge cyst with an enhanced mural nodule.

compression to the main pancreatic duct. When the tumor grows huge, it may become palpable. It may also cause acute and/or chronic obstructive pancreatitis, or onset or deterioration of diabetes mellitus. Jaundice may occur when an SCN located in the head of the pancreas has enlarged and occluded the common bile duct; however, this is also a very rare event, occurring in only one of 172 patients [12]. In most cases, surrounding structures would detour as much as possible even if the SCN should grow large.

Solid Pseudopapillary Neoplasm

SPN is a benign or low-grade malignant neoplasm largely found in children or young women. Approximately 90% of patients are female, and the median age of all patients at diagnosis is 25–30 years. Although abdominal discomfort or dull pain may bring a patient with SPN to medical attention, most of the patients are diagnosed by chance on routine physical examination or imaging studies for a screening or other purpose. In symptomatic patients a palpable mass is the most common presentation (Fig. 83.3). Lee et al. [13] reported 62 patients with SPN. A mass was palpable in 60% of 15 pediatric patients and 40% of 47 adults. The tumor tended to be larger in children than in adults. Abdominal discomfort with or without dull pain was claimed in 58% of another series of 62 patients reported by Cai et al. [14]. A palpable mass was noticed in 15%. In a later series of 45 patients, Dai et al. [15] described clinical presentation in 44 female and 1 male patients with a mean age of 32.2 years. Abdominal pain was present in 37.8%, abdominal

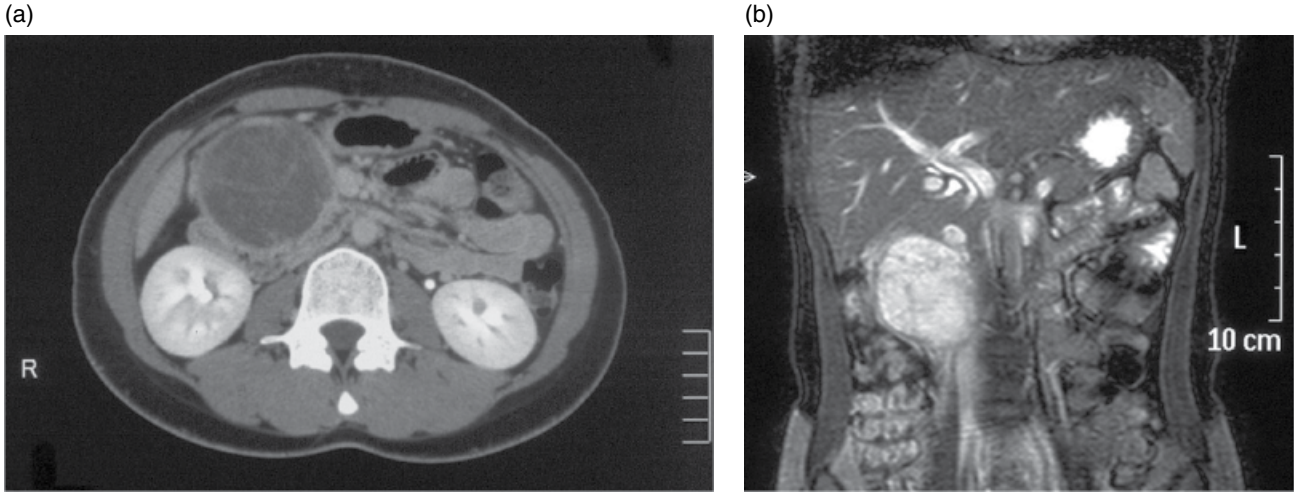


Figure 83.3 A solid pseudopapillary neoplasm in the pancreatic head in a 21-year-old female student. (a) Delayed phase of dynamic CT showing an 8.5-cm encapsulated cystic tumor with enhanced components. (b) Sagittal plane of T2 weighted MRI demonstrating heterogenous structure of the tumor.

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distension 31.1%, back pain 13.3%, and vomiting 8.9%. All four patients with the incidental diagnosis of an SPN were asymptomatic in their series.

The mass effect of SPN sometimes affects the main pancreatic duct and common bile duct; however, jaundice is very rare even when the tumor is in the head of the pancreas. Rupture of an SPN may occur very rarely, causing severe abdominal pain, hemoperitoneum, and hypotension [16,17].

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Evaluation of Cystic Lesions Using EUS, MRI, and CT

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Introduction

As imaging improves, pancreatic cysts are being incidentally detected with increasing frequency. Older studies found a prevalence of 2.6% with computed tomography (CT) and 3–13% of magnetic resonance imaging (MRI) studies [1,2], with more recent studies identifying pancreatic cysts in 49% of patients undergoing MRI [3]. However, the size and morphology of these cysts determine management. Pancreatic cysts represent a range of etiologies from benign cysts such as pseudocysts or serous cystadenomas, those with the potential for progressing to invasive carcinoma (IC), such as intraductal papillary neoplasms (IPMN), and mucinous cystic neoplasms (MCN), as well as those associated with a high risk of IC such as solid pseudopapillary neoplasms (SPN) or cystic degeneration of a neuroendocrine tumor (NET). The four most common types of pancreatic cysts seen are pseudocysts, IPMN, MCN, and serous cystadenomas (SCA), which account for over 90% of pancreatic cysts seen [4].

Imaging plays two critical roles. First, to identify the type of cyst, and second, to identify features associated with the presence of high-grade dysplasia (HGD) or IC in patients with IPMN and MCN, in whom surgical resection should be considered [5,6]. In this chapter we review the imaging features of different types of pancreatic cysts using CT, MRI, and endoscopic ultrasound (EUS).

Low-Risk Pancreatic Cysts

Pseudocyst

Pancreatic pseudocysts are inflammatory collections related to trauma, acute or chronic pancreatitis. They are well defined, and found either within, or adjacent to the pancreas, and can be single or multiple. Initially the wall is thin but may thicken as the pseudocyst matures. Pseudocysts appear as low-attenuation fluid collections on CT. MRI provides improved soft tissue resolution and helps better assess the contents of the fluid collections and integrity of the pancreatic duct. On T1 weighted (T1W) images, pancreatic pseudocysts have a hypointense center, with an enhancing wall. On T2 weighted (T2W) images pseudocysts appear hyperintense due to their fluid content. Blood products, necrotic or proteinaceous debris are commonly present in postnecrotic collections associated with necrotizing pancreatitis (walled-off pancreatic necrosis) and are seen as areas of increased signal on T1W images [7]. Similarly areas of decreased signal may be seen in postnecrotic collections or walled-off pancreatic necrosis due to the presence of debris [7]. In acute pancreatitis, peripancreatic fluid and stranding may be present, which correlates with the degree of inflammation present on the T2W fat-suppressed images [8]. Furthermore, magnetic resonance pancreatography (MRCP) sequences help delineate pancreatic ductal disruption and/or communication with the fluid to guide treatment. Presence of gas within the collection may be due to superimposed infection or fistulous communication with the adjacent bowel. Infected collections may be better assessed on diffusion weighted imaging (DWI) with visualization of a hypointense rim on the apparent diffusion coefficient (ADC) map [9]. On EUS, they appear as a well-defined, anechoic lesion. The wall may appear thickened, and debris can appear as irregular, echogenic material within the cyst (Fig. 84.1). Differentiating pseudocysts from IPMN can occasionally be difficult, as highlighted by surgical series in which pseudocysts account for between 3% and 6% of resected cases, and cyst fluid analysis can be helpful in these cases [4,10]. A very low cyst fluid amylase of <250 U/L excludes 98% of pseudocysts [11]. A CEA of <5 ng/mL has a high specificity (98%), but low sensitivity (50%) for a pseudocyst [11].

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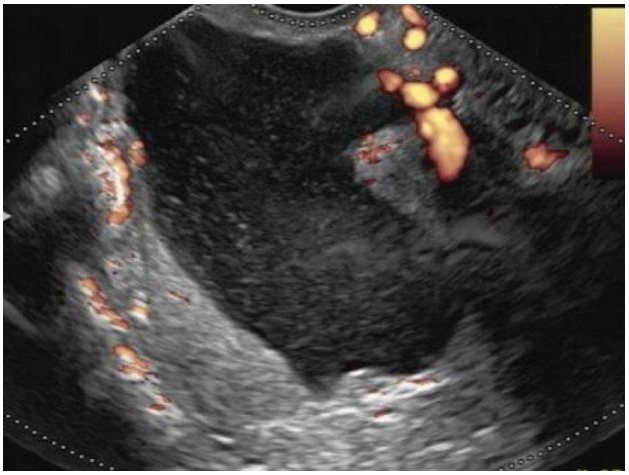


Figure 84.1 Pseudocyst. The features of a well-defined pseudocyst seen on EUS, with hyperechoic material within the cyst consistent with debris. *Source:* Copyright AML, by permission of the author.

Serous Cystadenoma

SCA are typically single cysts, and can occur in any location in the pancreas. The exception to this rule is von Hippel–Lindau disease, in which multiple SCA occur. Two-thirds occur in women, with a median age of presentation of 58 years [12]. They carry an exceptionally small risk (0.1%) of transformation into a cystadenocarcinoma [12]. Thus, differentiating these very low-risk cysts from other types of neoplastic cysts is extremely important for appropriate clinical management. Classical teaching is that SCA have a nondilated main pancreatic duct, which does not communicate with the cyst. Upstream dilation of the main pancreatic duct is an uncommon feature but may be seen due to mass effect [13]. The presence of a central scar, with or without calcification, is found in between 11% and 30% of SCA and is very specific [14]. A microcystic, or honeycomb, appearance is found in 45–58% of SCA, 32–35% have a macrocystic appearance, 18–28% a mixed macro or microcystic appearance, and 5–6% have a solid appearance (Fig. 84.2a–d) [12–14]. On

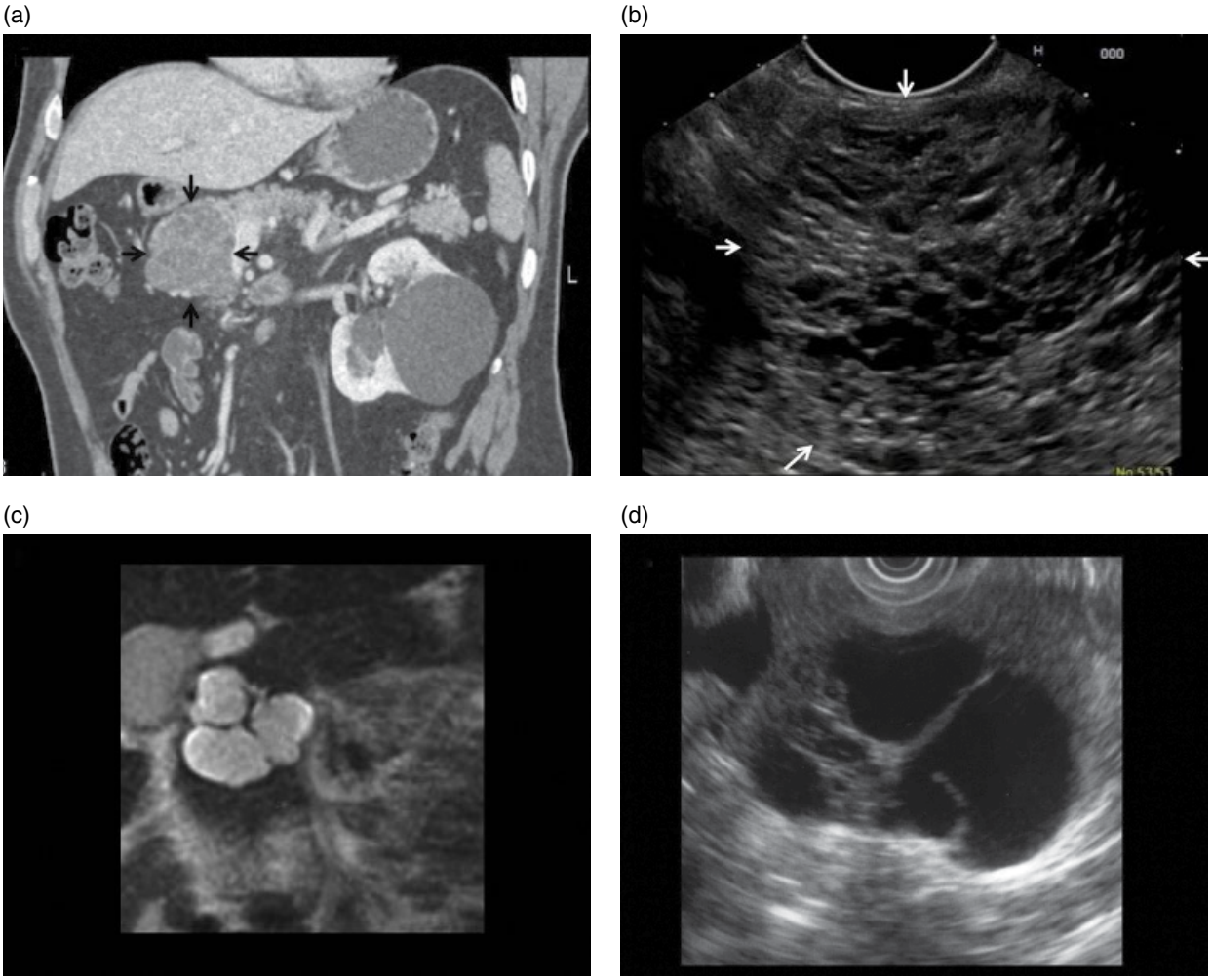


Figure 84.2 Serous cyst. Serous cysts (white arrows) have a range of appearances including microcystic (a, b), macrocystic (c), mixed macro and microcystic (d). They can occasionally have a solid appearance (e, f). In these cases MRI/MRCP is helpful in confirming the cystic, rather than solid nature of the cyst (g). *Source:* (a, b) Copyright AML, by permission of the author.

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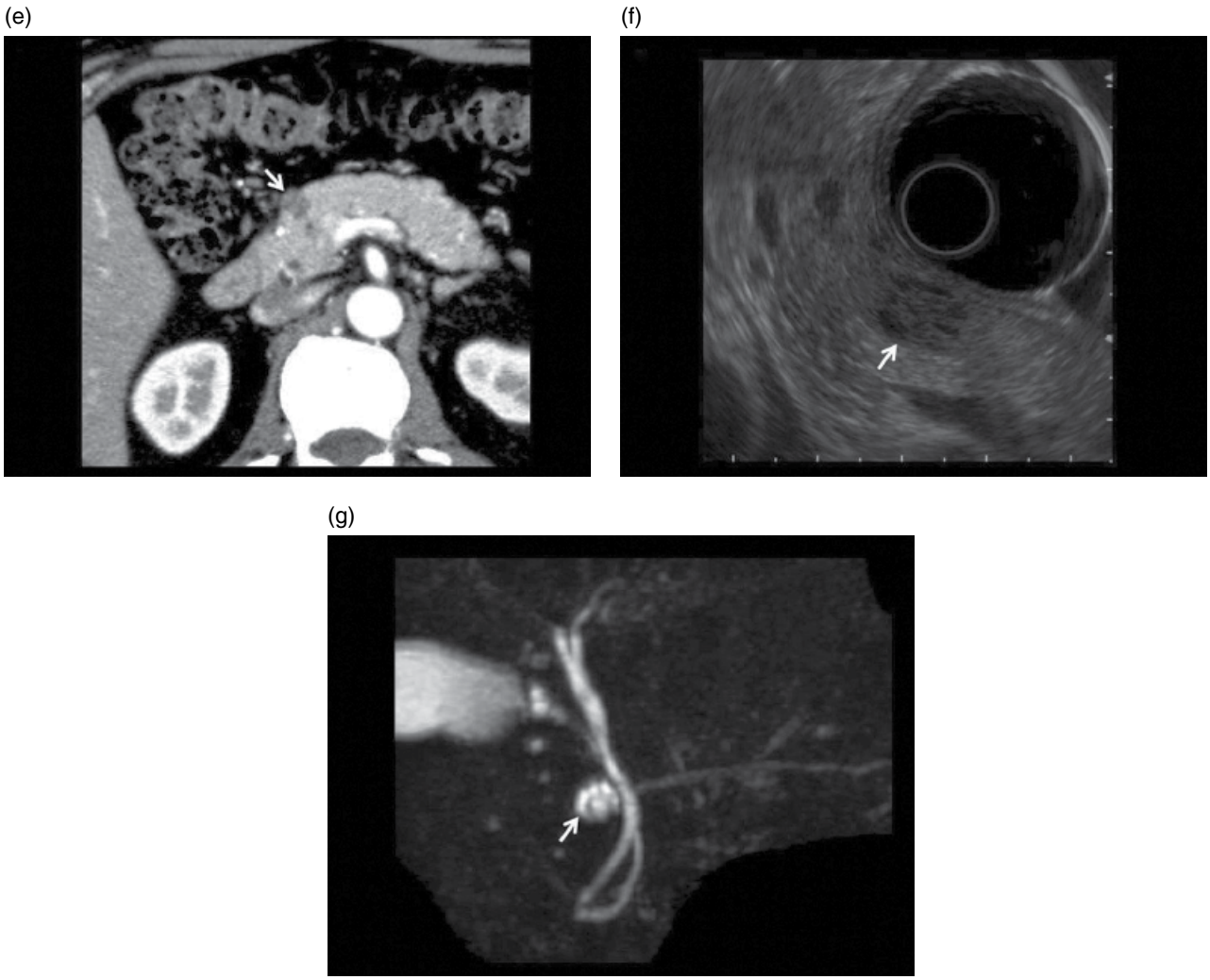


Figure 84.2 (Continued)

CT, the most common appearance is a lobulated conglomeration of small cysts that may exhibit a central scar with or without calcification [15]. The adjacent blood vessels may drape around the lesion and aggressive features such as invasion and vascular thrombosis are absent. On MRI they have a low intensity on T1W imaging, high signal on T2W imaging, with enhancement of the septations on contrast-enhanced T1W imaging with or without a central scar. In solid appearing SCA on CT, T2W imaging and MRCP is useful for confirming the cystic, rather than solid nature of the cyst (Fig. 84.2e–g). EUS can be useful in these cases in which classic imaging features are absent. It is superior for identifying a classic microcystic appearance to either CT or MRI [14], while the vascular nature of SCA is often seen with Doppler, or with contrast-enhanced EUS. A very low cyst fluid CEA, of <5 ng/mL, has 95% specificity, and 50% sensitivity for a SCA [11]. Almost 59% of SCA harbor a mutation in the Von Hippel–Lindau (*VHL*) gene or loss of heterozygosity (LOH) of chromosome 3 where the *VHL* gene is located [13]. The presence of a *VHL* mutation and the absence of mutations in *GNAS*, has 46% sensitivity and 100% specificity for SCA [13].

Lymphoepithelial Cyst

Lymphoepithelial cysts are rare, benign pancreatic cysts, which occur predominantly in middle-aged men (82%), with a mean age of presentation of 55 years [16]. They are single cysts, with almost 70% found adjacent, or outside of the pancreas [17]. Sixty percent are multilocular. The main pancreatic duct is normal, and unlike IPMN or pseudocysts, there is no communication between the cysts and the duct.

Lymphoepithelial cysts may have a mixed solid and cystic appearance, with a purely cystic or mainly solid lesion occurring in only 14% and 16% of cases, respectively (Fig. 84.3a, b) [16]. These cysts are low attenuation on CT and appear to abut the pancreatic parenchyma. On MRI, the lesions mostly appear hypointense on T1W, and hyperintense on T2W imaging. However, presence of

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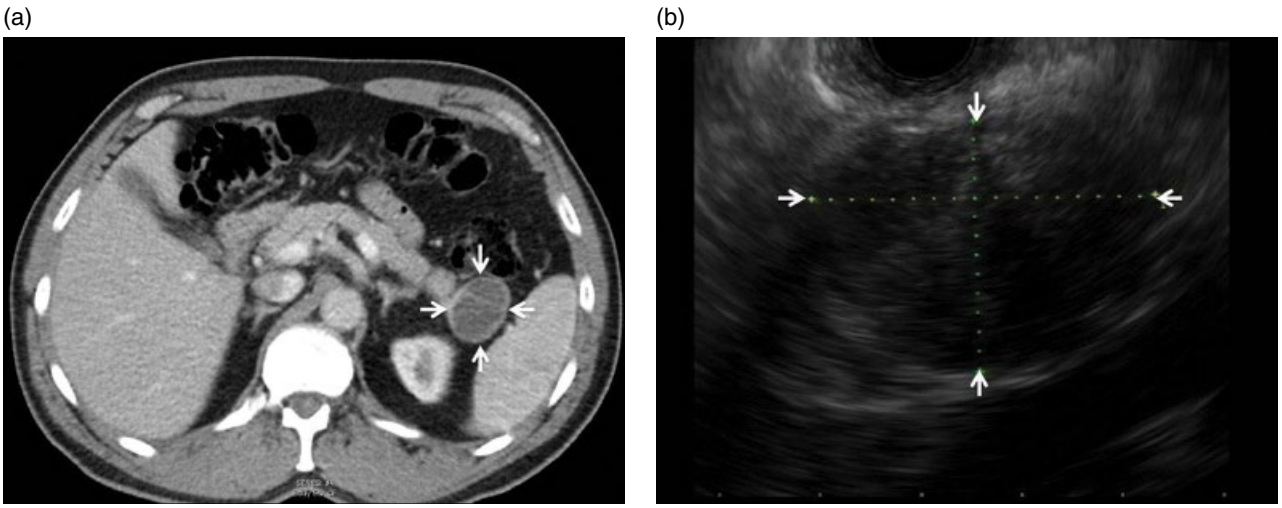


Figure 84.3 Lymphoepithelial cyst. The CT (a) and EUS (b) appearance. *Source:* Copyright AML, by permission of the author.

granular keratinized epithelium may cause them to appear high attenuation on CT, hyperintense on T1W imaging, and heterogeneous on T2W imaging due to the presence of fluid (high signal) and high keratin content (low signal) [16]. Furthermore, loss of signal on out of phase chemical shift imaging may be seen due to the presence of lipid content. These features are not classically seen in other cysts and may be helpful in identifying these lesions [16]. On EUS they are a solid-appearing, hypoechoic, heterogeneous lesion with posterior acoustic enhancement and may have evidence of debris within the cyst [17]. Cytology can be useful and identified 22% of lymphoepithelial cysts in a large series of 117 patients [16]. Cyst fluid CEA is >192 ng/mL in a third of patients [16].

Pancreatic Cysts with Malignant Potential

Mucinous Cystic Neoplasm

Mucinous cystic neoplasms (MCN) are single cysts, which occur almost exclusively in women (20:1 ratio), with a mean age of presentation of 53 years [18]. MCN are almost always located in the body or tail of the pancreas. Although MCN do not involve the main pancreatic duct, ductal abnormalities can be found. Main pancreatic duct dilation is found in up to 17% of MCN, which increases to 43% in the presence of HGD/IC. The absence of communication between the cyst and the main pancreatic duct is considered a classic feature used to differentiate MCN from IPMN [19]. Almost 40% of MCN are multilocular, and may have slightly thickened septations. The classic appearance of an MCN is a thickened wall which enhances on contrast-enhanced CT and MR imaging. This thick wall, or capsule, often has a "cyst within a cyst" appearance, which resembles an orange on CT or MRI (Fig. 84.4a, b). On EUS the cyst is unilocular with the "cyst within a cyst" seen within the wall (Fig. 84.4c). Calcification is located at the edge of the cyst creating an "eggshell" type appearance (Fig. 84.4d, e). In large surgical series between 15% and 25% of MCN have a mural nodule, increasing to 54–100% in MCN with HGD/IC [19,20]. This is seen on CT and MRI as intracystic enhancing soft tissue, or a hypoechoic, irregular area on EUS (Fig. 84.4f). Other features favoring malignancy include size >4 cm and thick irregular walls. Cyst fluid CEA (>192 ng/mL) and amylase are elevated. *KRAS* mutations are present in 35% of MCN [13].

Intraductal Papillary Mucinous Neoplasm

IPMN can involve the main pancreatic duct (MD-IPMN), branch duct (BD-IPMN), or both, in which case it is termed a mixed-type IPMN (Fig. 84.5a–c). This classification is important, as it determines the risk of malignant transformation, and the management of patients with IPMN. IPMN have an equal distribution in men and women, with a median age of presentation of 66 years [21]. They have a slight preponderance for the head of the pancreas, especially the uncinated process, but can occur anywhere. Over a third of individuals with IPMN have multiple cysts [21]. On imaging they may appear as a single or multiple small cystic lesions or as a cluster of small cysts with lobulated margins that appear as a "cluster of grapes." One of the classic features used to identify BD-IPMN is the presence of communication between the cyst and the main pancreatic duct (Fig. 84.5b). This is best assessed with MRI/MRCP, which have a very high reported sensitivity of 100% [22]. Cysts are usually well defined, with thin walls, can be unilocular or multilocular, and calcification is rarely present.

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Figure 84.4 MCN. Classic "cyst within a cyst" appearance of an MCN on CT and MRI (a, b). On EUS the cyst is unilocular, with the "cyst within the cyst" seen in the wall (c, arrow). A classic appearance of an MCN (a) with calcification at the edge (d, arrowheads). The EUS appearance showing calcification at the edge (e, arrowhead) with a thickened, irregular wall (f, arrowheads). *Source:* (c–f) Copyright AML, by permission of the author.

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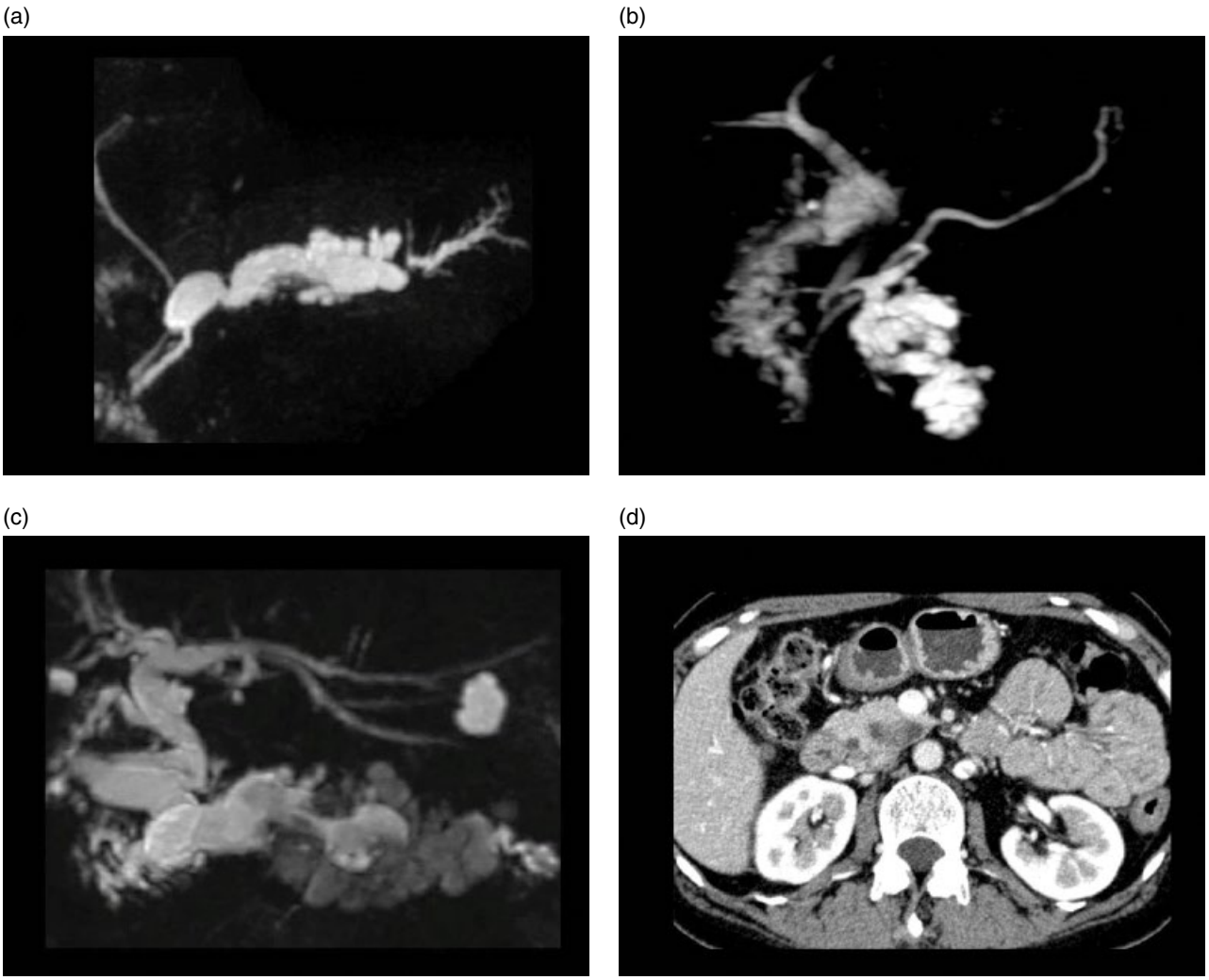


Figure 84.5 IPMN. The classic dilated main pancreatic duct seen in main-duct IPMN (a). In comparison there is a cyst but a normal pancreatic duct in a BD-IPMN (b, c), and a dilated main pancreatic duct and a cyst in a mixed-type IPMN (c). Mural nodules appear as soft tissue mass with contrast enhancement on CT and hyperechoic protruded lesion on EUS (d, e). Tissue harmonic echo (THE) shows a superior imaging compared with B-mode (f, g).

Main-duct involvement, which occurs in MD-IPMN or mixed IPMN, is defined as focal or diffuse dilation of the main pancreatic duct to >5 mm. They may appear cystic if only a short segment of the duct is involved. On endoscopy a gaping "fish-mouth" papilla extruding mucus is occasionally seen.

IPMN have the potential to progress to HGD or IC. There are a number of imaging features that are associated with an increased risk of HGD or IC including cyst size >3 cm (odds ratio [OR] 2.97), dilation of the main pancreatic duct (OR 2.4), and the presence of a solid component, or mural nodule (OR 7.7) [23]. Molecular marker evaluation of cyst fluid obtained at the time of EUS, is increasingly being used. The presence of a *TP53* or a *SMAD4* mutation is associated with an OR of 1.6 and 5.1, respectively, for the presence of HGD or IC [13], while another study found the presence of both a TP53 and PIK3CA mutation was associated with 79% sensitivity and 96% specificity for HGD or IC [24].

On CT and MRI a mural nodule appears as a soft tissue nodule protruding into mucin-filled dilated duct or cyst and shows enhancement following administration of intravenous contrast or as a hyperechoic, irregular lesion arising on EUS (Fig. 84.5d, e). The size of the mural nodule is associated with the risk of IC; however, the exact size is unclear and varies in studies from ≥3 mm to >10 mm, with the latter associated with IC in almost 90% of patients in one study [25,26]. Mucin appears as a hypoechoic lesion, with a hyperchoic, smooth rim on EUS, and is non-enhancing on CT or MRI. Contrast-enhanced EUS (CE-EUS) may demonstrate vascularity in mural nodules and is useful for differentiating a mural nodule from a mucin ball.

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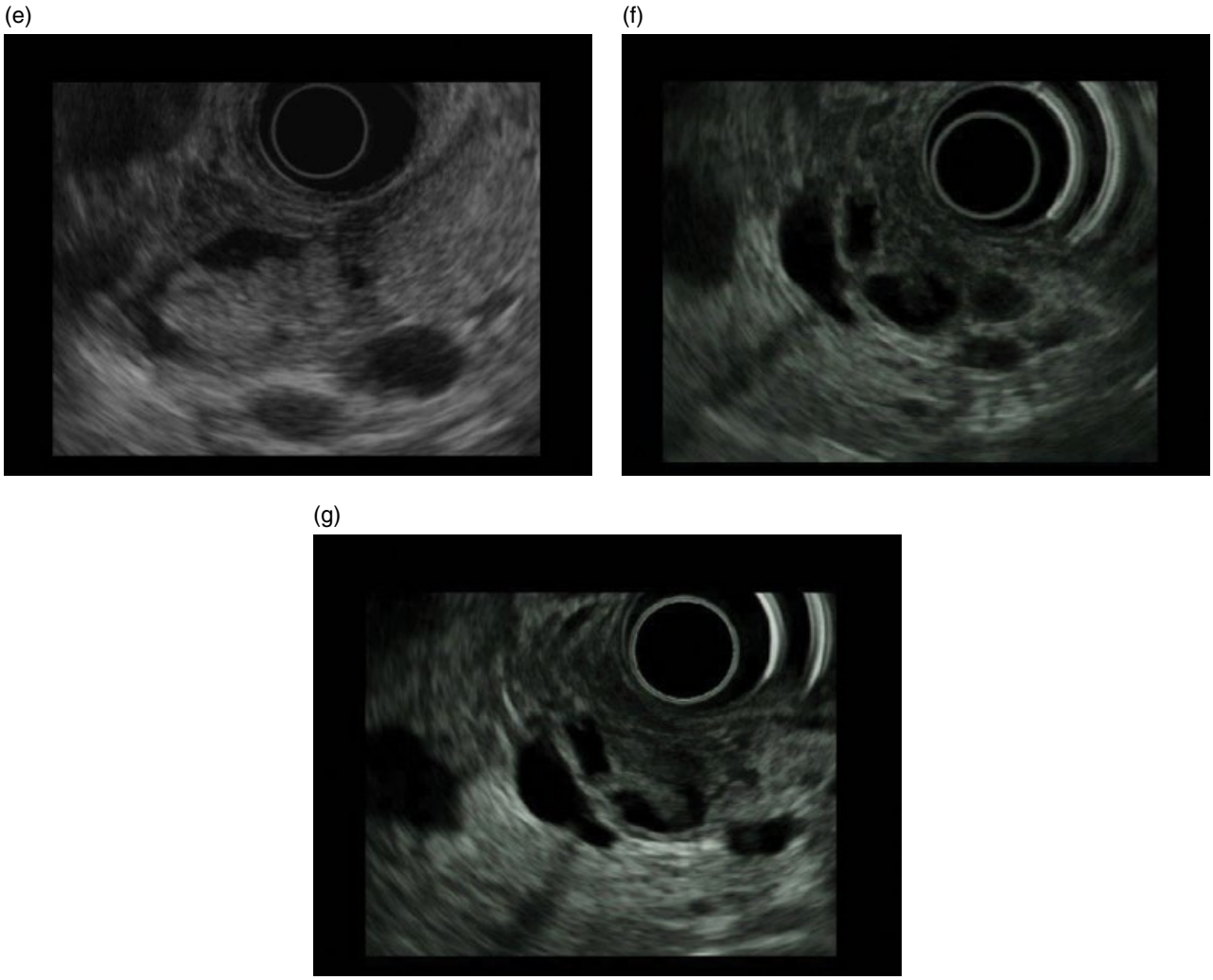


Figure 84.5 (Continued)

A prospective study found that CE-EUS correctly identified 75% of mural nodules with HGD or IC. Tissue harmonic echo (THE) imaging is a further development in EUS. Preliminary studies appear promising, and show superior image visualization of mural nodules compared with normal B-mode imaging (Fig. 84.5f, g) [27]. Individuals with IPMN can develop concomitant pancreatic adenocarcinoma in a region separate to the cyst, highlighting the importance of inspecting the entire parenchyma and not just the cyst. The cyst fluid analysis shows a high CEA (>192 ng/mL), and high amylase. The presence of either a *GNAS* or *KRAS* mutation has 85% to 100% sensitivity and 96% to 97% specificity for identifying an IPMN [13,24].

Solid Pseudopapillary Neoplasm

SPN are single cysts, with 60% located in the body or tail of the pancreas. Almost 90% occur in women, presenting at a mean age of 29 years [28]. The main pancreatic duct is normal, and does not communicate with the cyst. The cysts are well circumscribed, round or oval, with calcification present in almost half the cases [29]. In ~70% of cases, the imaging appearance is of a cystic and solid lesion, in 30% they are predominantly solid, and in rare cases are entirely cystic (Fig. 84.6a) [28,29]. The imaging appearance varies due to the cystic and solid nature of these neoplasms with areas of fluid appearing as low attenuation on CT and high signal intensity on T2W, and the solid components appearing higher attenuation on CT and mixed signal intensity on T2W imaging with weak enhancement within the solid components [30]. Areas of increased signal may be seen on the pre-contrast T1W imaging due the presence of hemorrhage within the lesions. A capsule with or without calcifications may also be present.

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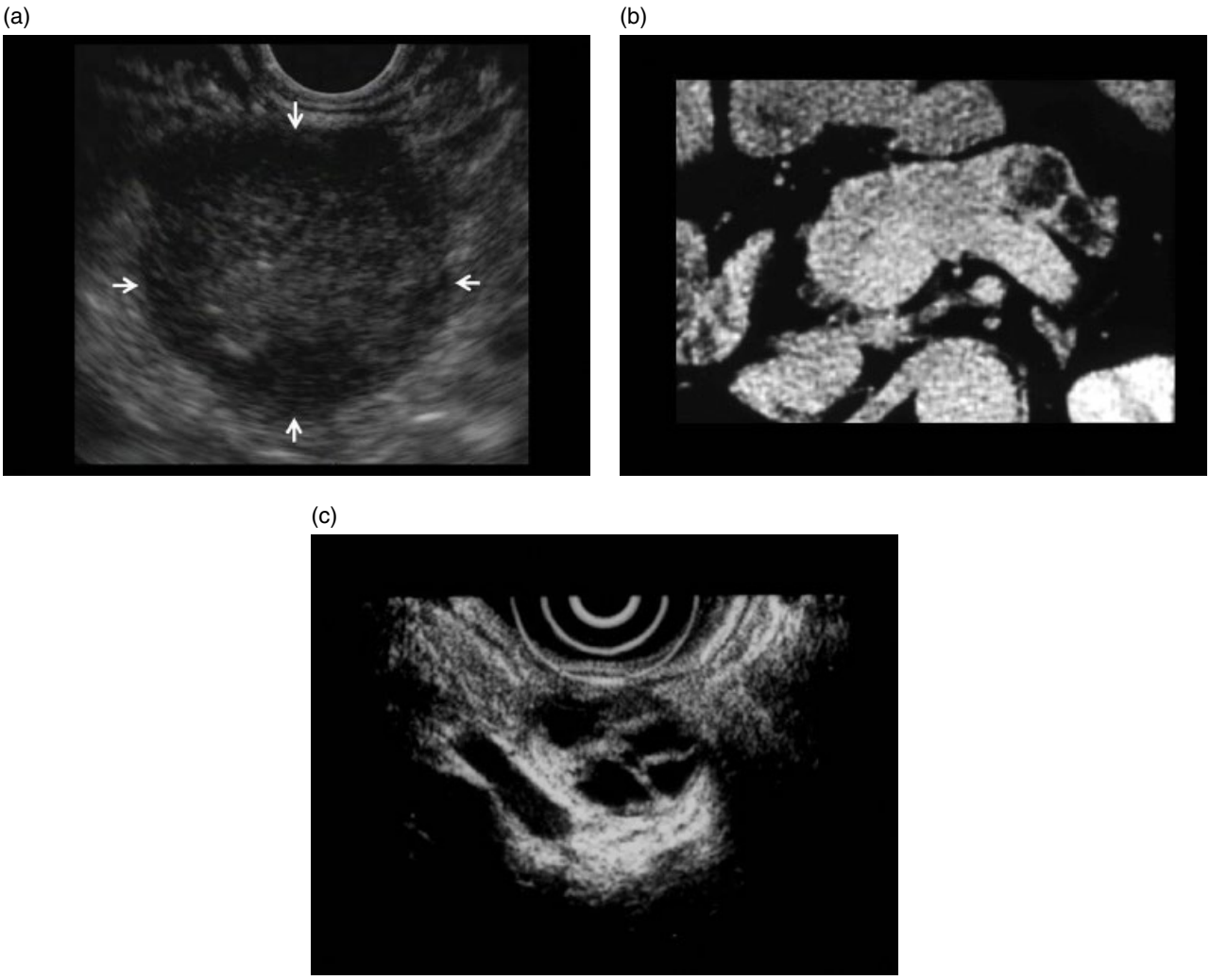


Figure 84.6 SPN and PanNET. Solid appearing SPN (a). Cystic PanNET showing enhancement of the rim and septum on CT (b). On EUS the appearance is of a solid component with cystic areas (c). *Source:* (a) Copyright AML, by permission of the author.

Cystic Neuroendocrine Tumor

Cystic degeneration of neuroendocrine tumors is rare, occurring in less than 20% of cases [31]. There is an equal distribution between genders, with a mean age at presentation of 53 years. These cysts are predominantly solid, with the cystic component due to degeneration of the tumor. They are round, usually well defined, with a rim of tissue that shows hyperenhancement on the arterial phase CT and MR imaging. Gallium 68–tetraazacyclododecane tetraacetic acid-octreotate PET/CT can help detect PNET with 93% sensitivity and 91% specificity and also helps in staging detection of recurrent and metastatic disease [32]. On EUS they appear as a well-defined, round, hypoechoic lesion, with an anechoic cystic area (Fig. 84.6b, c). They often have a vessel running around the edge of the lesion. Cyst fluid CEA and amylase levels are low.

Future Technology

In the field of medical imaging, recent work in radiomics has shown promising results in the diagnosis and risk stratification of the pancreatic cystic lesions, which utilizes extra information such as shape, texture, and grayness stored in various imaging modalities such as CT or MRI that is beyond human visual perception. Radiomic features have shown promising results in differentiating IPMN, MCN, and SCA with an accuracy, in one study, of up to 83.6%, and predicting IPMN with an accuracy of up to 96% using CT [33]. In another study, a combined model with radiomic and CT features outperformed the CT features alone in differentiating macrocystic SCA from MCN [34]. Some work has also been done to predict high-grade dysplasia or adenocarcinoma within IPMN with predictive nomograms diagnosing cancer

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preoperatively. In one such study, a combination of multiple radiomic features with CA 19-9 levels and main pancreatic duct size helped predict high-grade disease with AUC of up to 0.876 [35]. The use of radiomic features as a tool for genetic profiling (radiogenomics) may further help improve high-risk patient characterization and outcome prediction. This is a rapidly evolving field, with clinical trials and research at big academic centers showing an immense potential in the accurate diagnosis and risk prediction of pancreatic cystic lesions.

Needle-based confocal endomicroscopy (nCLE) is a relatively new technology in which a very thin microscope is passed through a 19-gauge EUS-FNA needle into a cyst and creates a real-time optical biopsy of the cyst. Initial studies found that different types of cysts had specific imaging features, such as a superficial vascular network in SCA, or papillary projection in IPMN. To date there have been seven prospective trials enrolling between 18 and 144 patients and reporting a sensitivity of between 59% and 100%, and specificity of between 94% and 100% in differentiating IPMN from other types of pancreatic cysts [36–42], and is more accurate than cyst fluid CEA and cytology. One limitation is that almost all the studies are in patients with a large cyst of at least 2 cm in diameter and this technique is probably not applicable to smaller cysts.

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85

Cytologic Evaluation of Cystic Neoplasms: The Role of Liquid Biopsy

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Introduction

In the era of highly sensitive imaging modalities, most pancreatic cystic lesions (PCL) are incidentally discovered during screening for unrelated presentations. Detection rates range from 2.4% to 49.1%, creating a major management problem, requiring noninvasive diagnostic tests to stratify risk and management [1,2].

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or liquid biopsy is frequently used to sample pancreatic lesions. It shows variable sensitivity (60–96%) but high specificity in diagnosis [3,4]. However, when assessing PCL, EUS-FNA performance is significantly challenged. Accurate diagnosis of PCL requires integration of clinical and radiologic information, biochemical and molecular analysis of cyst fluid, and cytology.

Types of Pancreatic Cystic Lesions

Pancreatic cysts are either nonneoplastic or neoplastic. Most nonneoplastic PCL arise secondary to postinflammatory sequelae of acute and/or chronic pancreatitis, and include pseudocysts (the most frequently encountered [75%] nonneoplastic PCL), paraduodenal cysts, lymphoepithelial cysts (LEC), and squamoid cysts of pancreatic duct (SCOPD). Neoplastic cysts are low-risk (serous cystadenoma) or high-risk (mucinous and nonmucinous cystic/intraductal lesions, solid pseudopapillary neoplasm [SPN]). Intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) constitute the majority of neoplastic PCL. Other nonmucinous cystic intraductal lesions include intraductal oncocytic papillary neoplasm (IOPN) and intraductal tubulopapillary neoplasm (ITPN) [5,6]. Serous cystadenoma (SCA) and SPN are nonmucinous, nonductal cystic neoplasms. Solid pancreatic tumors (ductal adenocarcinoma, neuroendocrine neoplasms, and acinar cell carcinoma) may undergo cystic degeneration and should be considered in the differential.

Reporting Terminology for Pancreatobiliary Cytology Specimens

In 2014, the Papanicolaou Society of Cytopathology (PSC) proposed standardized reporting for pancreatobiliary cytology [7]. This includes six categories: I. Nondiagnostic, II. Negative, III. Atypical, IV. Neoplastic (benign or other), V. Suspicious, and VI. Positive for malignancy. Nonneoplastic pancreatic cysts are classified as negative. Serous cysts are "neoplastic: benign," while mucinous/intraductal nonmucinous cysts (IPMN, MCN, IOPN, and ITPN) and SPN are in the "neoplastic: *other*" category. Cystically degenerated ductal adenocarcinoma and acinar cell carcinoma are malignant (see Table 85.1). Risk of malignancy (ROM) increases with each category (7.7% for nondiagnostic; 1% for negative; 28% for atypical; 0% for neoplastic: *benign*; 30.3% for neoplastic: *other*; 90.0% for neoplastic: *other* with high-grade atypia [HGA]; to 100% for suspicious; and 100% for positive) [8].

Assessment of Pancreatic Cystic Lesions: A Multimodal Approach

The primary goal of preoperative assessment of PCL is to exclude malignancy, and then to distinguish low-risk from high-risk cysts. An integrated, multidisciplinary approach that incorporates clinical, radiologic, and

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Table 85.1 Cytologic terminology and reporting system of pancreatic cystic lesions.

Diagnostic category	Diagnostic entity
Negative	Pseudocyst Paraduodenal cyst of groove pancreatitis Lymphoepithelial cyst (LEC) Squamoid cyst of pancreatic duct (SCOPD)
Neoplastic: Benign	Serous cystadenoma
Neoplastic: Other	Intraductal papillary mucinous neoplasm (IPMN) Mucinous cystic neoplasm (MCN) Intraductal oncocytic papillary neoplasm (IOPN) Intraductal tubulopapillary neoplasm (ITPN) Pancreatic neuroendocrine tumor (PanNET) Solid pseudopapillary neoplasm (SPN)
Positive/ Malignant	Solid malignancy with cystic degeneration • Adenocarcinoma • Lymphoma • Sarcoma • Metastatic malignancies • Neuroendocrine carcinoma • Acinar cell carcinoma

cytologic findings with (chemical/molecular) cyst fluid analysis and ancillary studies, is necessary to ensure accurate preoperative classification [9].

Radiologic and Clinical Assessment

Detailed radiologic assessment of PCL is beyond the scope of this text. However, some radiologic and clinical findings should prompt consideration of specific entities. For middle-aged patients with a single or multiple PCL involving the main and/or branch pancreatic ducts and associated with leakage of thick mucin from the ampulla of Vater, the main differential is IPMN. This contrasts with MCN, SCA, LEC, pseudocysts, paraduodenal/groove cysts, and SPN, which do not involve pancreatic ducts. For perimenopausal/postmenopausal females with multilocular tail cysts the main differential is MCN. In elderly females with circumscribed multiloculated cysts, an associated central stellate scar and no duct involvement, the main differential is SCA. For young females in the second to third decade with tail cysts, SPN is the main differential.

Use of Rapid Onsite Evaluation (ROSE) in the Analysis of Pancreatic Cysts

During rapid onsite evaluation (ROSE) a cytopathologist can assess cyst viscosity, which in mucinous cysts is greater than that of serum [10]. Mucinous cysts yield thick, mucoid material that is difficult to express from needles. Nonmucinous cysts only rarely show high viscosity. Use of ROSE in cytologic evaluation of PCL risks wasting limited fluid that should be prioritized for carcinoembryonic antigen (CEA) and amylase quantification, and molecular studies. ROSE can be used to assess a solid component in IPMN or MCN.

Biochemical Analysis of Pancreatic Cyst Fluid

Measurement of cyst fluid CEA is the mainstay of biochemical analysis of PCL. It requires approximately 0.5 mL of fluid and has a higher sensitivity, specificity, and accuracy than cytology or EUS-FNA alone [11]. Values of 192 ng/mL and higher (range 110–200 ng/mL) have high accuracy (80%), sensitivity (75%), and specificity (84%) for mucinous cysts [11]. Lower values do not completely exclude mucinous cysts, and individual laboratories must establish thresholds. CEA alone cannot distinguish IPMN from MCN, nor identify malignant mucinous cysts [12]. CEA is rarely elevated in nonmucinous cysts (pseudocysts, SCOPD, SCA, LEC), and should not be interpreted in isolation [11,12].

Cyst fluid amylase can distinguish pseudocysts and mucinous cysts (IPMN and MCN) from SCA, which typically has low amylase. Pseudocysts have the highest amylase (>1000 ng/mL) but low CEA levels. In fact, an amylase level below 250 U/L excludes a pseudocyst [12]. High amylase plus high CEA favors IPMN or MCN, but cannot distinguish between them [13].

Vascular endothelial growth factor-A (VEGF-A) has high sensitivity (100%) and specificity (97%) for SCA and is incomparably higher in SCA than pseudocysts, IPMN, and MCN [14]. Cyst fluid glucose <50 mg/dL is more sensitive than CEA >192 ng/mL (93.6% vs. 54.8%; $P = 0.003$) in diagnosing mucinous cysts, but with similar specificity (96% vs. 100%; $P = 1$) [15].

Molecular Analysis of Pancreatic Cyst Fluid

Different cyst types have specific molecular alterations that show high concordance with resection [16,17]. *VHL* mutations have been identified in SCA cyst fluid, while *KRAS* mutations and loss-of-heterozygosity (LOH) in tumor suppressor genes *CDK2NA*, *RNF43*, *SMAD4*, and *TP53* have been identified in mucinous cysts and distinguishes them from nonmucinous cysts [13,16–19]. Aneuploidy in mucinous cysts is linked to malignant transformation [13,16,17,20]. *PRKACA* and *PRKACB* fusions are seen in cyst fluid of pancreatic/biliary IOPN and their invasive counterparts [21]. Molecular alterations in specific cyst types are discussed in detail below.

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Cytologic Analysis of Pancreatic Cyst Fluid

The primary goal of cytologic assessment of PCL is to identify malignancy and distinguish innocuous neoplastic and nonneoplastic cysts from high-risk cysts prone to harboring or progressing to carcinoma. Low-risk cysts are typically only resected if patients are symptomatic or definitive cytologic or imaging diagnosis is impossible. In contrast, because high-risk cysts have a high risk of harboring carcinoma they should ideally be resected in suitable surgical candidates. Resection of high-risk cysts depends on clinical confounders, cyst size, pancreatic duct diameter, mural nodule, and cytologic and/or molecular findings suggestive of malignancy [22].

Mucinous Pancreatic Cysts

Mucinous pancreatic cysts include MCN and IPMN, which are lined by mucin-producing epithelium with villi formation, variable cytoplasmic mucin, and a spectrum of dysplasia (low- or high grade). Some harbor invasive ductal adenocarcinoma (approximately 30% of IPMN and 17% of MCN).

IPMN accounts for 3–5% of all pancreatic tumors and comprises ~40% of all resected primary pancreatic cystic neoplasms. IPMN tend to affect older males (mean age 68 years) and the majority involve the head. IPMN cysts are larger than 1.0 cm and arise from, and involve, main and/or branch ducts. There are three epithelial subtypes: gastric, intestinal, and pancreatobiliary. Gastric-type IPMN has villi lined by gastric-type epithelium that is often low grade. Intestinal-type IPMN forms larger, complex cystic lesions and morphologically resembles colonic villous adenoma. Invasive carcinoma is seen in a third of intestinal-type IPMN and is most frequently colloid type. Pancreatobiliary-type IPMN has villi that are lined by cuboidal or columnar cells with high-grade dysplasia.

In contrast, MCN is a mucin-producing cyst that does not involve the duct system, and is defined by ovarian-type stroma (OTS) in its wall. OTS has all the features of ovarian cortex and expresses estrogen and progesterone receptors. MCN occurs almost exclusively (>97%) in the tail/body of perimenopausal women (mean age 48 years) and presents as multilocular cysts [23]. Invasive carcinoma is seen in approximately 17%.

Preoperative assessment of suspected mucinous cysts is used to identify high-grade cytologic atypia (encompassing high-grade dysplasia and/or invasive carcinoma). This is based on clinical information, imaging, cytology, and biochemical and molecular analysis of cyst fluid. The 2017 revised international consensus Fukuoka guidelines for IPMN management define "high-risk" stigmata (worrisome for, or supportive of, malignancy) as an associated solid component, main pancreatic duct diameter ≥10 mm, cyst size >= 3 cm (with thick walls/mural nodules), main duct size 5–9 mm (a worrisome feature), suspicious or positive cytology, and abrupt pancreatic duct caliber change with distal atrophy, among others [22]. If worrisome features are present, EUS-guided cytology is recommended and if "*neoplastic with high-grade atypia, or suspicious/positive for malignancy*" then surgery is recommended [24].

Cytologic Findings in Neoplastic Mucinous Cysts

Because the entity-defining OTS of MCN is rarely sampled on FNA, cytologic distinction between IPMN and MCN is practically impossible. In fact, the cytologic findings in IPMN and MCN are essentially identical, hence their combined classification under the umbrella term "neoplastic mucinous cyst." Aspirates from neoplastic mucinous cysts yield abundant thick, ropey colloid-like mucin in a background of neoplastic mucinous epithelium. Viscous mucin is magenta on Diff Quik and greenish-pink to orange on Papanicolaou stain (Fig. 85.1). Aspirates contain flat/folded/branching sheets, papillae, and clusters of mucinous cells (Figs 85.1 and 85.2). Less complex mucinous cysts may yield only thick acellular mucin, which in the appropriate clinical/radiologic setting, is diagnostic of a neoplastic mucinous cyst, if associated with elevated CEA.

Neoplastic cells in neoplastic mucinous cysts have well-defined cell walls (Figs 85.1 and 85.2). Gastric-type IPMN resembles normal gastric epithelium, intestinal-type resembles intestinal epithelium, and pancreatobiliary-type resembles pancreatobiliary adenocarcinoma (Figs 85.1 and 85.2). Gastric-type IPMN shows branching sheets and papillae comprised of cells with abundant cytoplasmic mucin (Fig. 85.1), and may be impossible to distinguish from normal gastric epithelium, which is usually sampled as the endoscopic needle traverses the gastric wall during aspiration of pancreatic body/tail lesions. Gastric foveolar epithelium typically contains U-shaped cytoplasmic mucin cups that fill the superficial third of the cell (Fig. 85.3). Gastric-type IPMN with low-grade atypia can be distinguished from gastric epithelial contaminants by correlating with cyst fluid CEA and amylase levels, which are elevated in IPMN and normal/low in gastric epithelial contaminants. If CEA and amylase are unavailable/inconclusive, then a diagnosis of "*Atypical findings. See comment*" is recommended with a comment stating that "If truly aspirated from a cyst, then this may represent a gastric-type IPMN." Other contaminants in EUS-FNA include watery extracellular GI tract mucin, and duodenal epithelium, which is usually sampled when the needle traverses the duodenal wall during sampling of pancreatic head/uncinate process cysts. Duodenal epithelium forms sheets of enterocytes and goblet cells, the nuclei of which are surrounded by a halo of mucin-rich cytoplasm (Fig. 85.3). Intestinal-type IPMN yields papillae

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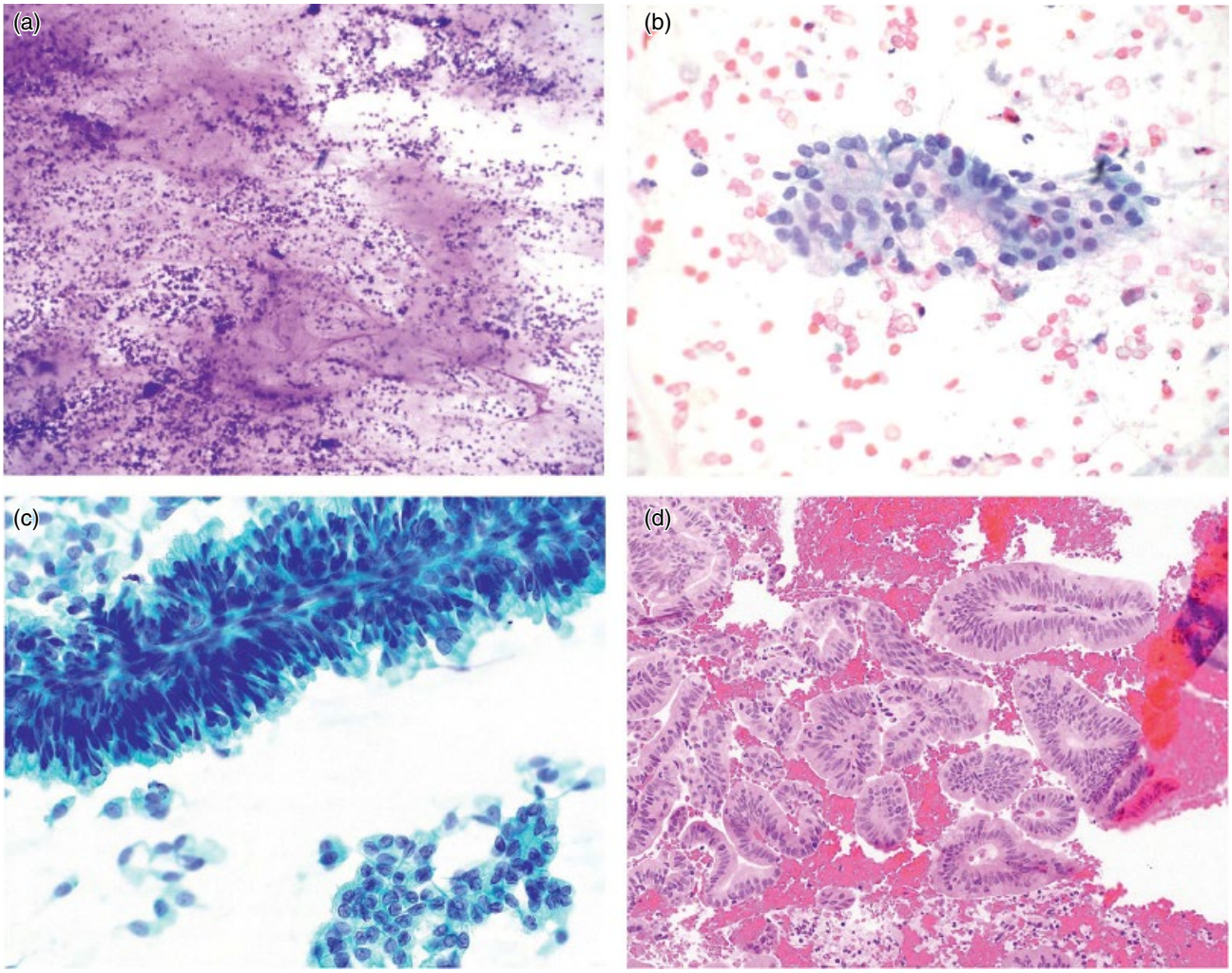


Figure 85.1 Neoplastic mucinous cyst. (a) Thick colloid-like ropey magenta-colored mucin in smear background (Diff Quik stain, 40×). (b) Neoplastic mucinous cyst with low-grade atypia has sheets of neoplastic columnar cells with low nuclear-to-cytoplasmic ratio, well-defined cell borders, pink cytoplasmic mucin, and rounded nuclei (Papanicolaou, 400×). (c) Neoplastic mucinous cyst with high-grade atypia has papilla (upper half of image) with central fibrovascular core and sheet of neoplastic cells (lower half of image) with high nuclear-to-cytoplasmic ratio and irregular hyperchromatic nuclei (Papanicolaou, 400×). (d) Cell block from part (c) shows multiple papillae lined by pseudostratified pancreatobiliary epithelium (H&E, 200×).

covered by pseudostratified columnar cells, with pencillate nuclei. Tumor cells are positive for intestinal markers MUC2, CDX2, and CK20. Pancreatobiliary-type IPMN show high-grade cytology (3-dimensional clusters and papillae with overlapping high nuclear-to-cytoplasmic ratio cells) and positivity for MUC1 (Fig. 85.2). Aspirates of MCN contain mucinous epithelial cells with variable atypia, in thick background mucin (Fig. 85.1).

Grading of Atypia in Neoplastic Mucinous Cysts (IPMN and MCN)

A 2-tiered classification system (low- vs. high-grade dysplasia) was proposed for precursor pancreatobiliary lesions IPMN, MCN, and pancreatic intraepithelial neoplasia (PanIN) [25]. Mild to moderate/intermediate dysplasia is classified as low grade, while severe dysplasia/carcinoma-in-situ is considered high grade, has a strong association with invasion, and warrants intervention [25]. In neoplastic mucinous cysts with low-grade atypia (equivalent to low-grade dysplasia) mucinous epithelium is bland, has a low nuclear-to-cytoplasmic ratio, polarized nuclei, even chromatin and inconspicuous nucleoli (Fig. 85.1). Gastric-type IPMN are usually low grade.

The cytologic term "high-grade atypia" in neoplastic mucinous cysts encompasses both high-grade dysplasia and invasive adenocarcinoma since cytology material typically lacks the required stromal component necessary to assess invasion [7,26]. Cytologic features of high-grade atypia include crowded or drunken honeycomb sheets, papillae, and 3-dimensional clusters of high nuclear-to-cytoplasmic

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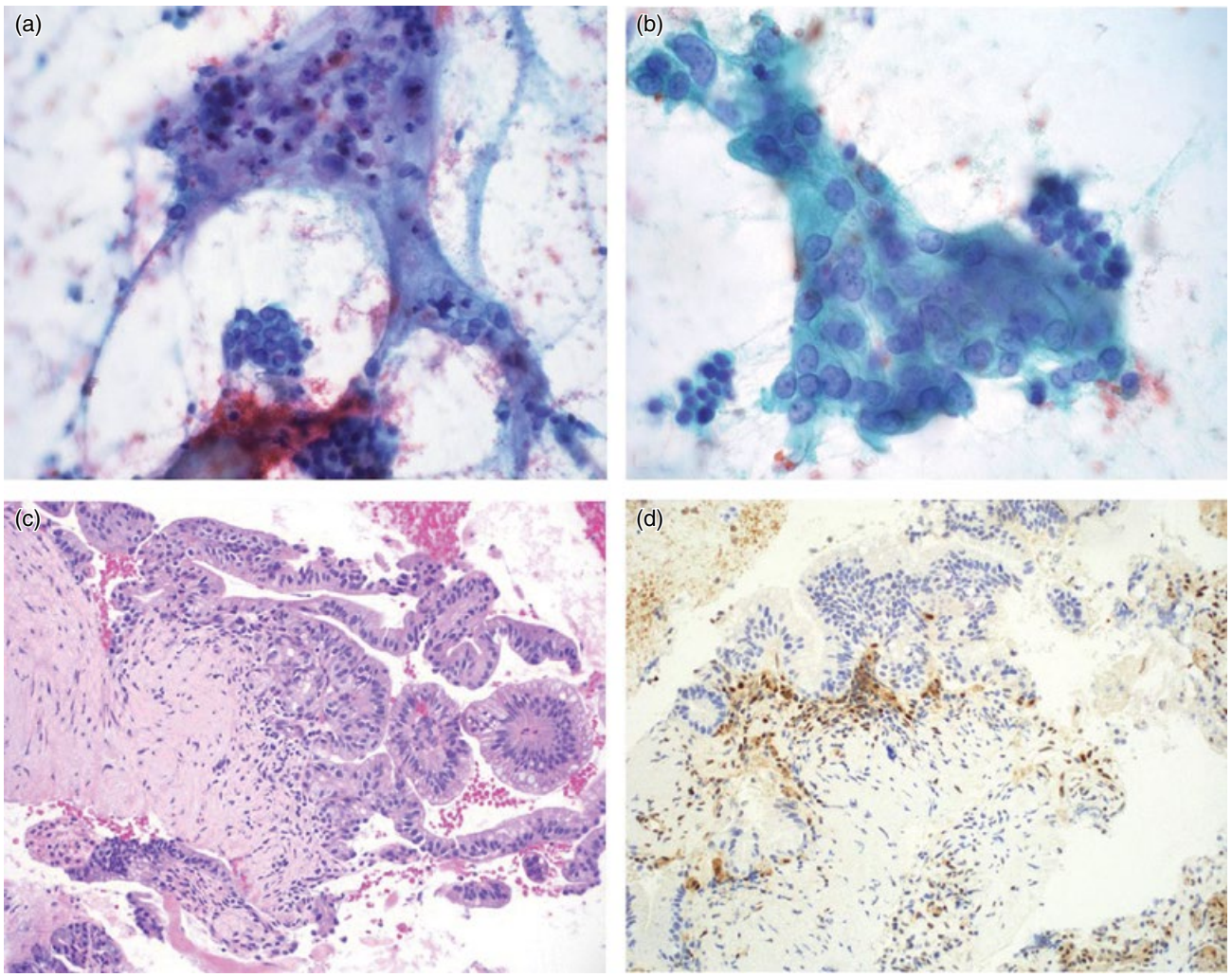


Figure 85.2 Neoplastic mucinous cyst with high-grade atypia. (a) Clusters of oncotic and high nuclear-to-cytoplasmic ratio cells in ropey mucin (Papanicolaou, 400×). (b) Neoplastic cells have high nuclear-to-cytoplasmic ratio, pale chromatin, and irregular nuclei (Papanicolaou, 400×). (c) Corresponding cell block shows cyst's fibrous wall lined by fused papillae covered by pancreatobiliary epithelium (Papanicolaou, 400×). (d) Papillae show SMAD4 loss (positive internal control in stromal cells).

ratio cells with irregular nuclei, change in chromatin (hyperchromasia and/or hypochromasia) and prominent nucleoli (Figs 85.1 and 85.2). Single high nuclear-to-cytoplasmic ratio cells, rounded cytoplasmic mucin vacuoles (Figs 85.1 and 85.2), and single cell or coagulative necrosis may also be seen (Fig. 85.2). By definition, pancreatobiliary-type IPMN is high grade, while intestinal-type IPMN may show low- or high-grade atypia (Fig. 85.2).

Immunohistochemical markers that can potentially identify high-grade cytologic atypia include placental S100 (S100P), insulin-like growth factor II messenger RNA binding protein-3 (IMP-3), and pVHL (von Hippel–Lindau protein). IMP-3 and S100P show nuclear and cytoplasmic positivity in high-grade atypia, while pVHL is negative and SMAD4 (an immunohistochemical surrogate for *SMAD4/DPC4* mutation) is lost (Fig. 85.2) [27].

Molecular Alterations in Neoplastic Mucinous Cysts (IPMN and MCN)

More than 90% of IPMN have either *GNAS* or *KRAS* mutations, and almost half show both [17,28]. *KRAS* mutation has a sensitivity and specificity of 54% and 100%, respectively, for ductal adenocarcinoma, IPMN, and MCN [18,29]. *GNAS* mutations are seen in up to 60% of IPMN, with intestinal-type showing the highest prevalence [17]. Somatic *RNF43* mutations are also seen in IPMN and MCN [18,28]. A commercially available molecular kit used to assess *KRAS* mutation, LOH, DNA quality, and DNA quantity in PCL had 83% sensitivity and 100% specificity for malignancy [30]. Other PDAC-related driver gene mutations (*TP53*, *p16/CDKN2A*, *SMAD4/DPC4*) may occur in IPMN and MCN, particularly those with high-grade dysplasia or invasion [13].

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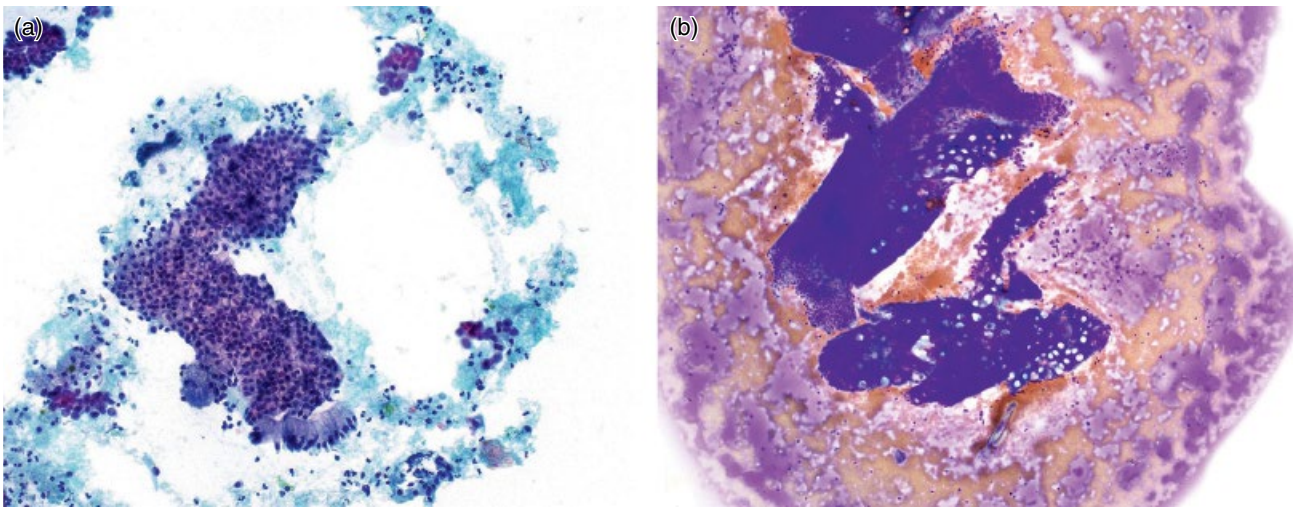


Figure 85.3 (a) Gastric epithelium with low nuclear-to-cytoplasmic ratio, basal bland nuclei (Papanicolaou, 40×). (b) Normal duodenal epithelium has small enterocytes and pale goblet cells. Note watery background gastrointestional tract mucin (Diff Quik, 200×).

Intraductal Oncocytic Papillary Neoplasm (IOPN)

IOPN is a cystic intraductal mucin-depleted tumor of the pancreatic/bile ducts [5,31]. IOPN was formerly considered as an IPMN subtype but is now classified separately [5,31,32]. Cysts are lined by complex branching or fused papillae covered by pseudostratified, multilayered oncocytic epithelium with brisk mitoses and oval or slightly irregular vesicular nuclei, and prominent macronucleoli. IOPN has an excellent prognosis with 10-year survival of over 95%.

The cytologic features of IOPN are quite distinctive [33]. Aspirates are usually hypercellular but background mucin is usually scant. Architecturally complex sheets and papillae are seen, lined by large, polygonal cells with low nuclear-to-cytoplasmic ratios, distinct cell membranes, dense granular eosinophilic cytoplasm, round or slightly irregular nuclei with vesicular chromatin and slightly eccentric, prominent nucleoli (Fig. 85.4). Cell blocks show papillae with edematous and/or hyalinized cores lined by two to five layers of pseudostratified oncocytic cells with interspersed rounded spaces, and scant mucin. Atypical mitoses and necrosis may also be seen. By definition, IOPN are high grade and are classified in the "neoplastic: *other*" category of the Papanicolaou Society cytologic guidelines (Table 85.1) [31].

IOPN is positive for MUC6, MUC5AC, and MUC1 and negative for MUC2, CK20, and CDX2. Unique molecular alterations were recently identified including *PRKACA* and *PRKACB* fusions (*DNAJB1-* and *ATP1B1-PRKACA*) [32]. IOPN may express the hepatocellular marker HepPar, but arginase is negative.

The differential diagnosis of IOPN includes pancreatic neuroendocrine tumors (PanNET), particularly oncocytic PanNET, and acinar cell carcinoma. Oncocytic PanNET have abundant granular oncocytic cytoplasm and may contain papillae resembling IOPN [34]. However, the eccentric nuclei, salt-and-pepper chromatin, and neuroendocrine marker expression should facilitate diagnosis of PanNET. Acinar cell carcinoma also shows abundant granular cytoplasm and oval nuclei with macronucleoli resembling IOPN. Unlike IOPN, acinar cell carcinoma expresses trypsin, chymotrypsin, and BCL10 [35].

Intraductal Tubulopapillary Neoplasm (ITPN)

ITPN is a relatively rare (<2%) complex, cystic or partially solid intraductal neoplasm of the pancreatic or bile duct. It forms polypoid intraductal neoplasms with back-to-back tubules, minimal papillae and no mucin production [6]. Tubules are lined by mucin-depleted cuboidal cells with high-grade cytology. Invasive pancreatobiliary tubular type carcinoma is common (~70%) [6].

Cytologic preparations of ITPN are composed of branching sheets or clustered mucin-depleted cells with high-grade cytology. Back-to-back tubules may also be seen (Fig. 85.4). Mitoses and necrosis are frequent but cytoplasmic/extracellular mucin is typically absent [9,36,37]. On cell block tubules may contain luminal mucin or proteinaceous eosinophilic concretions resembling enzymatic concretions of acinar cell carcinoma.

Tumor cells are positive for CK7, CK19, MUC1, and MUC6, and negative for MUC2 and MUC5AC. ITPN

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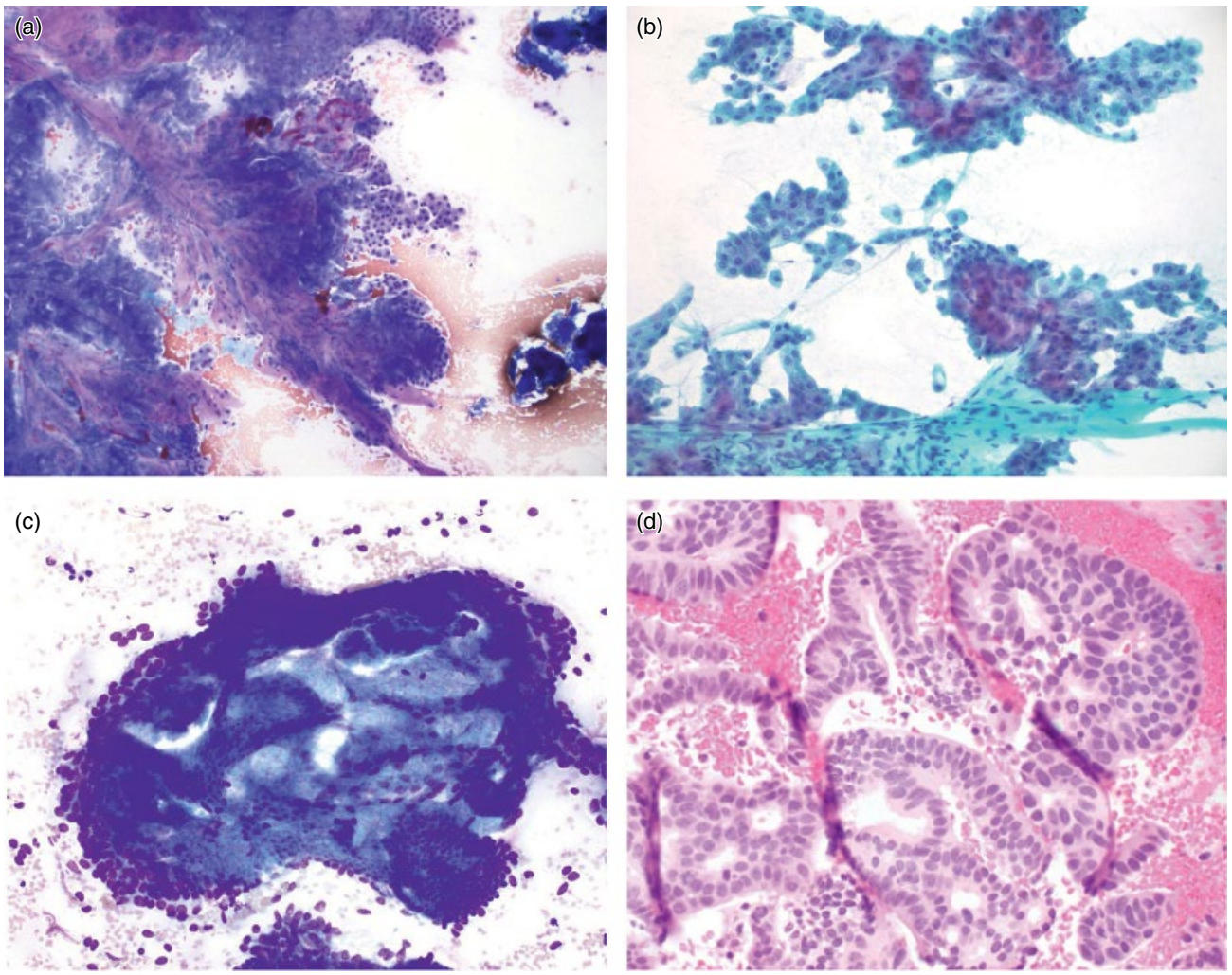


Figure 85.4 (a–b) Intraductal oncocytic papillary neoplasm (IOPN). (a) Hypercellular smear with magenta-colored broad fibrovascular cores (Diff Quik, 200×). (b) Branching papillae covered by oncocytic cells with abundant granular cytoplasm, low nuclear-to-cytoplasmic ratio and oval nuclei with vesicular chromatin and prominent nucleoli (Papanicolaou, 400×). (c–d) Intraductal tubulopapillary neoplasm (ITPN). (c) Crowded sheets of back-to-back tubules (Diff Quik, 200×). (d) Cell block from same case shows fused back-to-back tubules lined by pancreatobiliary epithelium with high nuclear-to-cytoplasmic ratio, no cytoplasmic mucin, and occasional abnormal mitoses (H&E, 400×).

may show phosphatidylinositol 3-kinase (*PIK3CA*) mutation, a potential diagnostic and therapeutic target. *P16/CDKN2A* mutations may also be seen.

Differential diagnosis for ITPN includes neoplastic mucinous cysts with high-grade atypia (particularly pancreatobiliary-type IPMN) and acinar cell carcinoma. Neoplastic mucinous cysts usually have cytoplasmic mucin and lack the back-to-back cribriform tubules of ITPN. Acinar cell carcinomas may be cystic/intraductal and have tumor cells containing dense granular cytoplasm with red zymogen granules, large nuclei and cherry-red nucleoli, reminiscent of ITPN. However, unlike ITPN, acinar cell carcinoma is positive for trypsin, chymotrypsin, and BCL10 [35].

NONMUCINOUS CYSTIC NEOPLASMS OF PANCREAS

Serous Cystadenoma (SCA)

SCA is a benign nonmucinous tumor of centroacinar cells and the second most common cystic pancreatic neoplasm. It predominantly occurs in elderly females (70%), frequently involves the body/tail and resection is curative [38]. Radiologically, SCA form sponge-like microcystic masses with a soap-bubble appearance. Oligocystic/unicystic variants may be misdiagnosed as IPMN or MCN. SCA often have high VEGF-A [14], but viscosity, CEA, and amylase levels are usually low [11].

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SCA aspirates are predominantly bloody and hypocellular, with scant hemorrhagic/serosanguinous fluid, scattered hemosiderin-laden macrophages, stromal fragments and only rare tumor cells (Fig. 85.5). Tumor cells are bland with PAS-positive glycogen-rich clear cytoplasm, distinct cell membranes, and oval hyperchromatic nuclei [39].

SCA tumor cells are positive for pancytokeratin, PAS (with diastase digestion), inhibin, and glucose uptake and transporter-1 (GLUT1) (Fig. 85.5) [38]. *VHL* mutations and chromosome 3p aneuploidy have been reported in SCA cyst fluid [17].

Solid Pseudopapillary Neoplasm (SPN)

SPN are rare pancreatic tumors that arise in the pancreatic tail of young women in the third decade. Tumors present as large (mean 8–10 cm) solitary, circumscribed, cystic/cystic and solid lesions [40]. Prognosis is excellent after resection but they may rarely invade adjacent organs or metastasize to lymph nodes or distant sites.

Smears are hypercellular with complex papillae containing delicate branching fibrovascular cores covered by dense myxoid stroma (magenta-colored on Diff Quik and blue-green on Papanicolaou stain) (Fig. 85.6) [41]. Tumor cells are bland and discohesive with scant cytoplasm, coffee-bean nuclei, longitudinal nuclear grooves, open chromatin, and small peripheral nucleoli (Fig. 85.6).

SPN display *CTNNB1* or ß-catenin mutation in 95–100% which leads to nuclear and cytoplasmic ß-catenin positivity (Fig. 85.6). *CTNNB1* is part of the Wnt signaling pathway, which also includes transcription factor for immunoglobulin heavy-chain enhancer-3 (*TFE3*) and lymphoid enhancing binding factor-1 (LEF1)

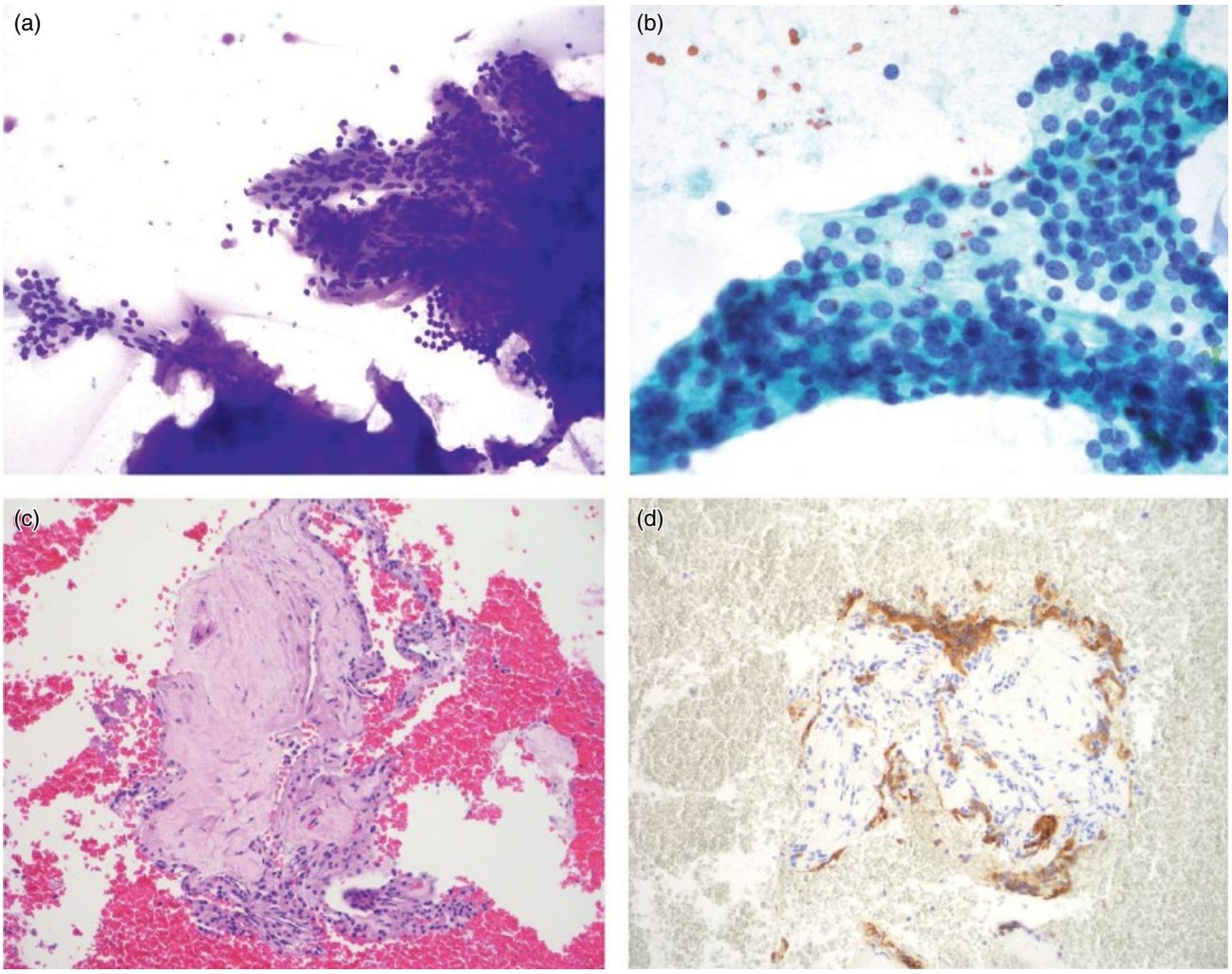


Figure 85.5 Serous cystadenoma (SCA). (a) Syncytial bland tumor cells hug adjacent fibrotic stroma (Diff Quik, 200×). (b) Bland cells in sheets have round to oval nuclei (Papanicolaou stain, 400×). (c) Cell block shows fibrotic stroma covered by a single layer of clear cells with low nuclear-to-cytoplasmic ratio (H&E, 200×). (d) Tumor cells are inhibin-positive.

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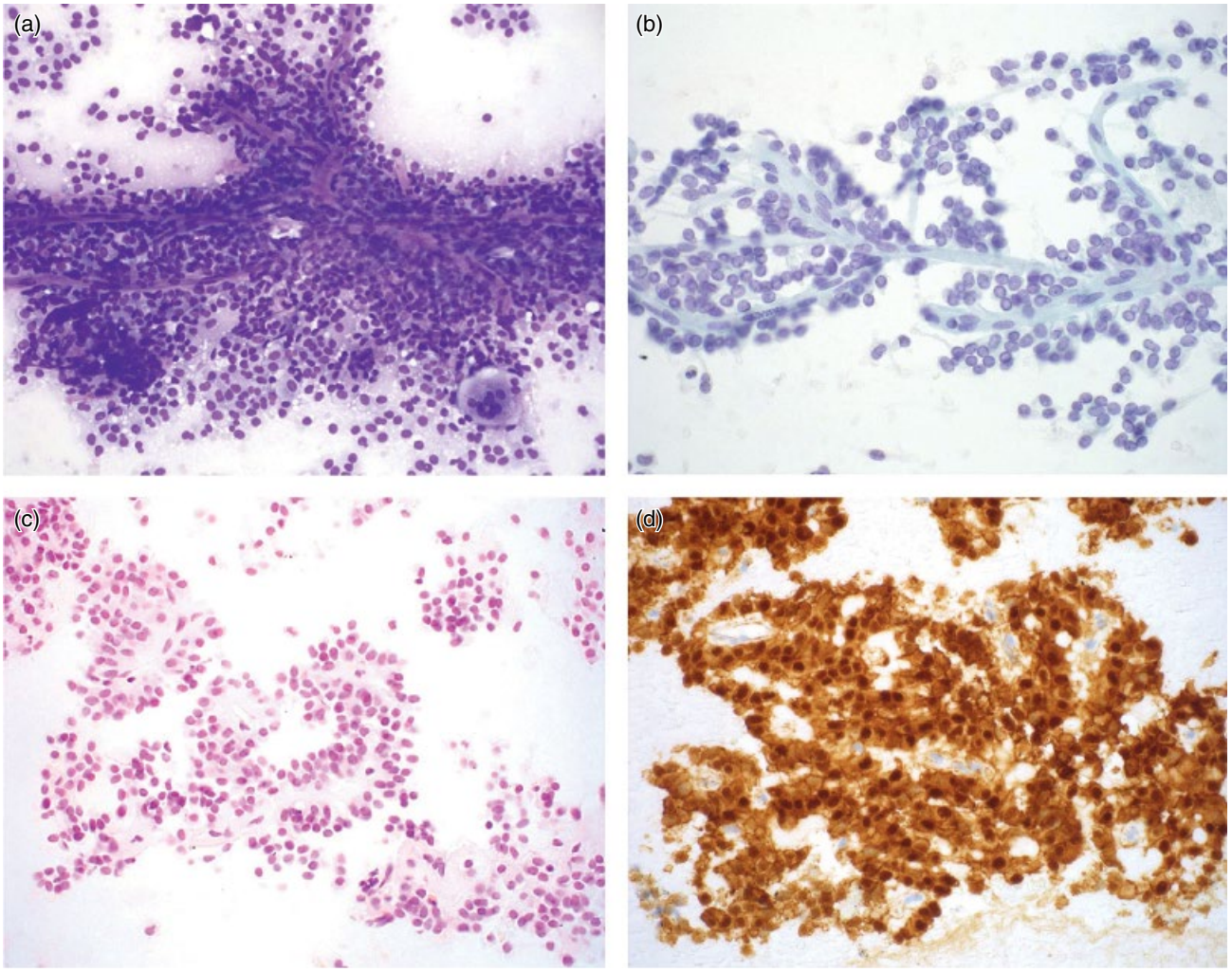


Figure 85.6 Solid-pesudopapillary neoplasm (SPN). (a) Hypercellular smear with delicate branching fibrovascular cores covered by magenta-colored myxoid stroma and lined by bland epithelioid cells, some with plasmacytoid features. (b) Fibrovascular cores covered with pale blue myxoid stroma and lined by bland epithelioid cells with high nuclear-to-cytoplasmic ratio, pale chromatin and grooved nuclei with small peripheral nucleoli (Papanicolaou stain, 200×). (c) Cell block with branching papillae (H&E, 200×). (d) Tumor cells show aberrant nuclear and cytoplasmic positivity for ß-catenin immunostain.

and results in nuclear positivity for TFE3 and LEF1 immunostains [42]. E-cadherin loss may also be seen. SPN is usually negative or only focally positive for pancytokeratin. Other positive markers include androgen and progesterone receptor, cyclin D1, CD99, and synaptophysin (but chromogranin is usually negative) [42].

SPN differential includes PanNET, IPMN, and IOPN. PanNET is characterized by clusters and single plasmacytoid cells with coarse salt-and-pepper chromatin, while SPN has pale chromatin and is negative for pancytokeratin and chromogranin. SPN papillae may resemble those in IPMN and IOPN, but SPN lacks the cytoplasmic and thick background mucin of IPMN, and oncocytic cytoplasm of IOPN. SPN cyst fluid consistently shows *CTNNB1* mutation, unlike IPMN and IOPN. *VHL*, *GNAS*, *RNF43*, and *PRKAC* alterations are not usually seen in SPN [17].

Cystic Degeneration of Solid Tumors

All solid pancreatic tumors may undergo cystic degeneration. Up to 8% of pancreatic ductal adenocarcinomas (PDAC) may show cystic change, especially large duct type, colloid and undifferentiated carcinoma, and those with squamous differentiation. Acinar cell carcinoma and neuroendocrine neoplasms may also undergo cystic change. Cystic PDAC yields malignant cells with three- to fourfold anisonucleosis, and cytoplasmic vacuoles. Well-differentiated PDAC may show drunken honeycomb sheets with overlapping nuclei and minimal pleomorphism (Fig. 85.7). Colloid carcinoma yields thick mucin and epithelial cells with high-grade cytology (Fig. 85.7). Cystic PanNET yields plasmacytoid cells, with eccentric oval nuclei and salt-and-pepper

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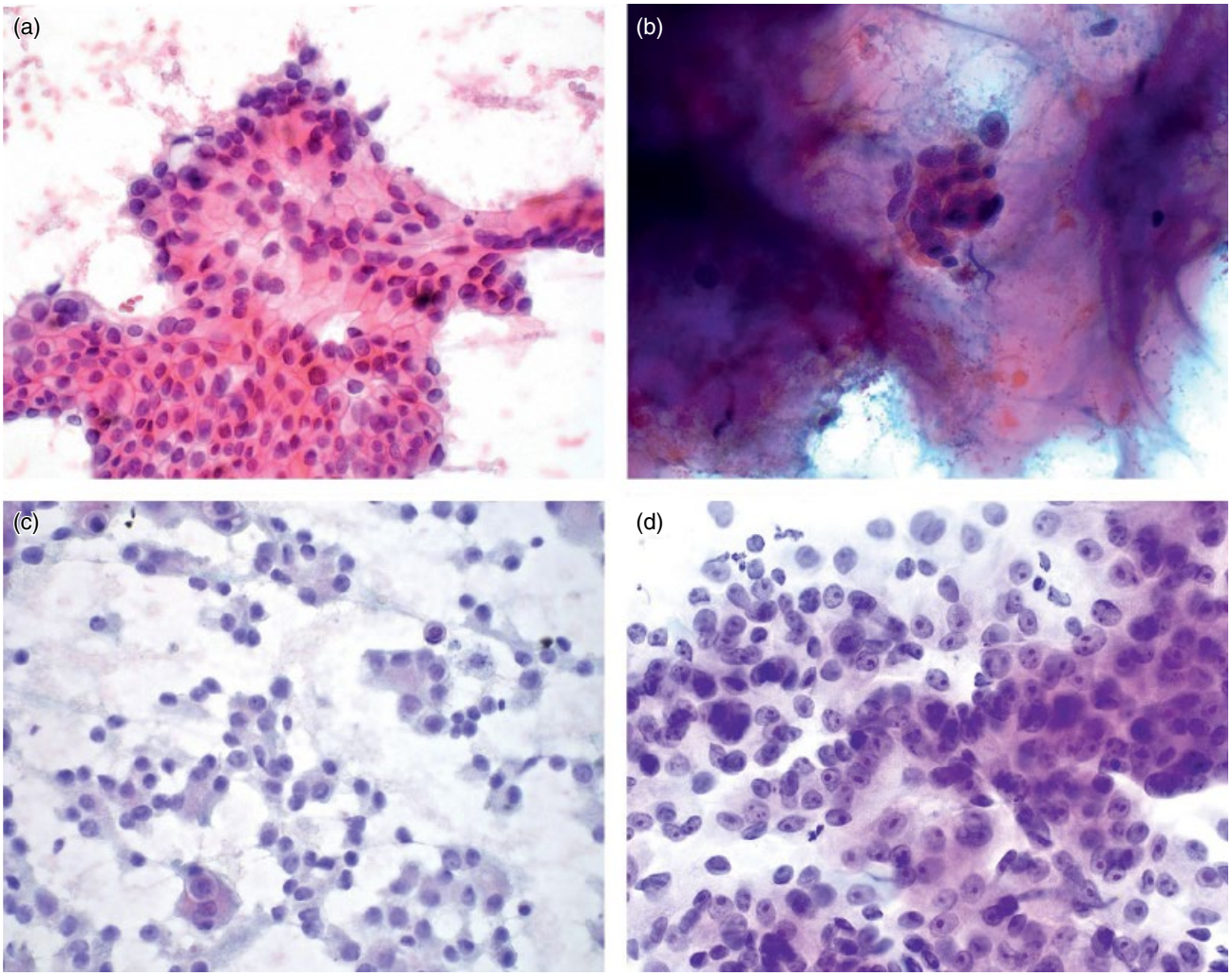


Figure 85.7 (a) Well-differentiated ductal adenocarcinoma with drunken honeycomb sheets of crowded foamy cells with well-defined cell walls and relatively low nuclear-to-cytoplasmic ratio (Papanicolaou, 400×). (b) Colloid carcinoma with 3-dimensional cluster and single pleomorphic high nuclear-to-cytoplasmic ratio cells in abundant thick mucin (Papanicolaou, 400×). (c) Well-differentiated neuroendocrine tumor with clustered and single plasmacytoid cells, vague rosettes, eccentric nuclei, and coarse chromatin (Papanicolaou stain, 400×). (d) Acinar cell carcinoma with crowded tumor cells, acinar arrangement, high nuclear-to-cytoplasmic ratio and macronucleoli (Papanicoloau stain, 400×).

chromatin (Fig. 85.7). Cystic acinar cell carcinoma yields large tumor cells with hypo- or hyperchromatic nuclei, prominent cherry-red nucleoli, and abundant zymogen-rich granular cytoplasm (Fig. 85.7).

NONNEOPLASTIC CYSTS OF THE PANCREAS

1-Lymphoepithelial Cyst of Pancreas (LECP)

LECP is the most common squamous-lined pancreatic cyst. Most arise in men and present radiologically as peripancreatic cysts. LECP cyst fluid is usually yellow-white and cheesy. Cysts may have high CEA and amylase levels which should not be mistaken for mucinous cysts [43]. Cytologic preparations contain keratinaceous debris, anucleated bland squamous cells and cholesterol crystals (Fig. 85.8). Lymphocytes are usually scant because the cyst wall (where they are most abundant) is often not sampled.

2-Squamoid Cyst of the Pancreatic Duct (SCOPD)

SCOPD represent nonneoplastic cystically dilated pancreatic ducts with squamoid metaplasia [44,45]. They are radiologically small cysts (<3 cm) but may be confused with mucinous cysts. Cysts are typically lined by multilayered transitional epithelium, with a basal layer of

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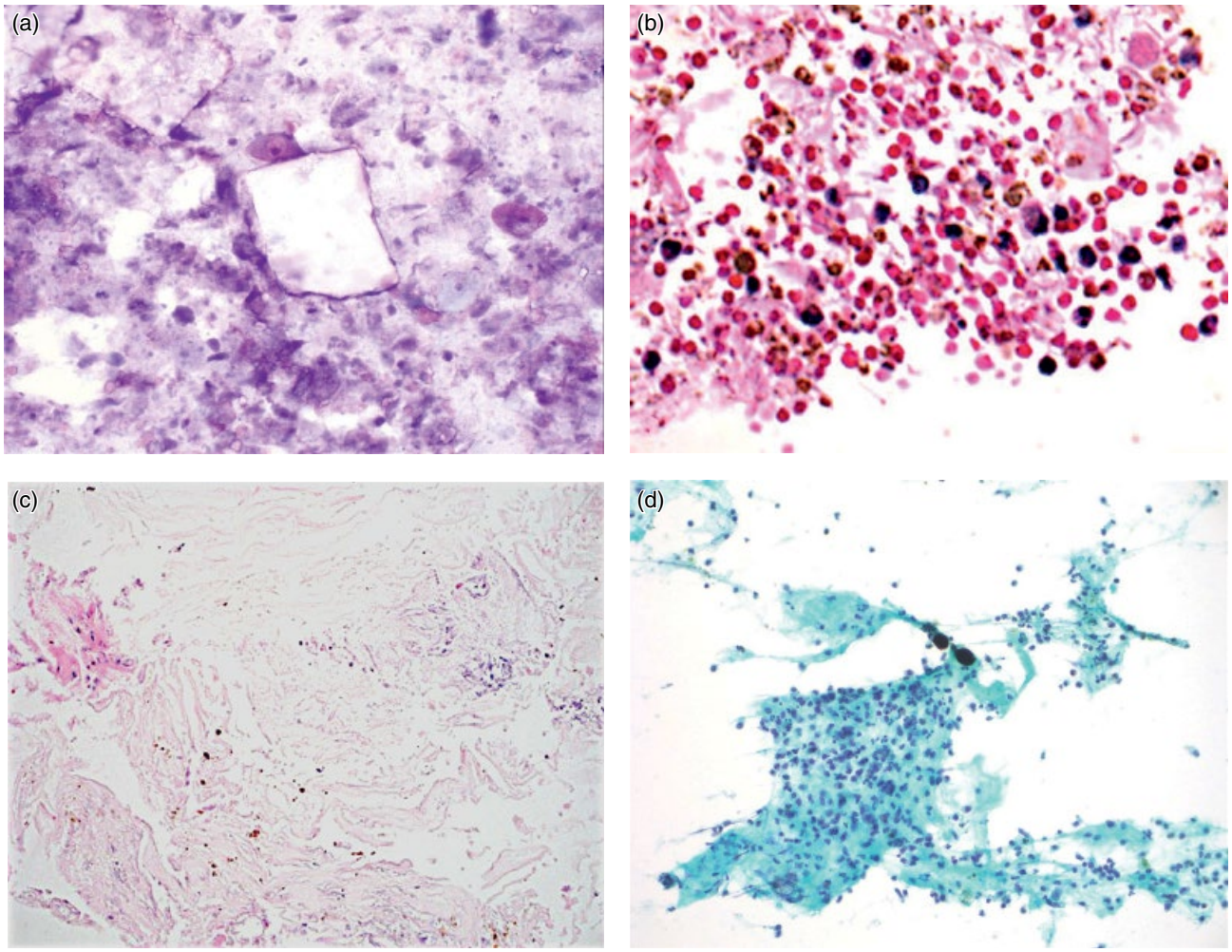


Figure 85.8 (a) Lymphoepithelial cyst with anucleated squamous cells and cholesteral crystal in debris (H&E, 400×). (b–c) Pseudocyst cell block with granular debris, pigment, and rare stromal fragments (H&E, 100×). (d) Groove pancreatitis with bland spindle cells and background inflammatory cells (Papanicolaou stain, 100×).

polygonal nonkeratinizing p40/p63-positive squamoid cells, and a luminal columnar cell layer. The cytologic features of SCOPD include polygonal squamoid cells with dense eosinophilic cytoplasm with bland columnar cells with or without cytoplasmic mucin [9,44]. Cyst fluid CEA and amylase may be high raising the differential of IPMN or MCN but thick ropey mucin is not a common feature [9,44].

3-Pancreatic Pseudocyst

Pancreatic pseudocysts are the most common nonneoplastic pancreatic cysts. They lack a true epithelial-lining and commonly develop as a postinflammatory complication of pancreatitis. Aspirated fluid is dark, brown to green and turbid. Chemical analysis of cyst fluid often reveals extremely high amylase but low CEA [3,11]. Cytologic preparations are paucicellular with predominantly blood, pigmented macrophages, debris, and pigment (Fig. 85.8).

4-Paraduodenal Wall Cyst (Paraduodenal or Groove Pancreatitis)

Paraduodenal wall cysts occur in the paraduodenal groove/pancreatic head region as a result of chronic inflammation (groove pancreatitis). This causes formation of paraduodenal wall cysts on the pancreas-facing duodenal wall surface, and they are often detected in men (fifth or sixth decade) with history of smoking or alcoholic abuse [46]. Smears consist of bland spindle cells (proliferating myofibroblasts), acute and chronic inflammatory cells, multinucleated giant cells, and amorphous proteinaceous debris from

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Table 85.2 Cytomorphologic features, immunohistochemistry, biochemical and molecular findings in common pancreatic cystic lesions.

Type of cyst	Cytologic features	Immunohistochemical stain	Biochemistry	Molecular
Pseudocyst	Brown pigment Amorphous debris Inflammatory cells including macrophages	N/A	High amylase usually >1000 units/LLow CEA levels	None
LECP	Nucleated and anucleated squamous cells Cholesterol crystals Keratinaceous debris	N/A	CEA increased Amylase increased	None
SCA	Paucicellular sample Scant background mucin Bland cuboidal cells with oval nuclei Smooth nuclear membranes Pale to clear cytoplasm Hemosiderin-laden macrophages Fibrotic stromal fragments	Keratin+ MUC6 + Inhibin + GLUT1+	CEA low Amylase low	*VHL* Chr 3p
SPN	Branching papillae Fibrovascular cores with myxoid stroma Coffee-bean-shaped nuclei, nuclear grooves, pale chromatin Small peripheral nucleoli	Keratin-/focally+ ß-catenin + (nuclear and cytoplasmic) LEF1+ TFE3+	N/A	*CTNNB1*
MCN	Thick colloid-like mucin Oncotic debris Neoplastic cells with cytoplasmic mucin	N/A	CEA high Amylase variable	*KRAS*
IPMN	Thick colloid-like mucin Oncotic debris Neoplastic cells with cytoplasmic mucin	MUC5AC+ gastric MUC2, CK20, CDX2+ intestinal MUC1+ pancreatobiliary	CEA high Amylase variable	*KRAS* *RNF43* *GNAS*
IOPN	Branching papillae lined by pseudostratified oncocytic cells	MUC6+ HepPar+	CEA high	*PRKACA* and *PRKACB* fusion

CEA: carcinoembryonic antigen; IOPN: intraductal oncocytic papillary neoplasm; IPMN: intraductal papillary mucinous neoplasm; LECP: lymphoepithelial cyst of pancreas; MCN: mucinous cystic neoplasm; N/A: not applicable; SCA: serous cystadenoma; SPN: solid pseudopapillary neoplasm.

pancreatic enzymatic concretions (Fig. 85.8) [47,48]. Cyst fluid amylase and CA19-9 may be high, but CEA is normal [48].

The cytologic, immunohistochemical, biochemical and molecular alterations in specific cyst types are summarized in Table 85.2.

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Natural History of Cystic Neoplasms: IPMN, MCN, SCN, and SPN

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Introduction

In recent years, cystic lesions of the pancreas have been identified with a rising incidence, due to the extended use of modern abdominal cross-sectional imaging modalities and due to an increasing awareness [1,2]. All types of cystic lesion or pancreatic branch-duct alteration are found in up to 25% of the elderly general population, increasing up to a 50–70% prevalence in people aged >70 years [3,4].

For adequate diagnosis and management of cystic pancreatic lesions, it is crucial to correctly differentiate between pancreatic pseudocysts and pancreatic cystic neoplasms (PCNs). In the past, inflammatory pseudocysts were thought to account for the majority of all cystic pancreatic lesions. With increasing awareness, it has become clear that PCNs are far more common than pancreatic pseudocysts, particularly in patients without a previous history of pancreatitis. While pseudocysts are benign residual lesions that occur after acute or recurrent chronic pancreatitis, PCNs display a certain potential for malignant transformation.

The most common cystic neoplasms of the pancreas are intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs), and solid-pseudopapillary neoplasms (SPNs). As these different entities are associated with a distinct potential for malignant transformation, ranging from almost no to high risk, and their radiologic differentiation is not always precisely possible, it is challenging for clinicians to balance their decisions between the risk of surgical overtreatment and the error of keeping a malignant lesion under surveillance. Accordingly, it is important to know the natural history of PCNs.

Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms are the most common cystic pancreatic lesions, making up approximately 35% of PCNs. IPMNs are characterized by mucin production as well as intraductal and papillary growth of the duct epithelium. Due to their association with the pancreatic duct system, they are classified into main-duct, branch-duct, or mixed-type IPMN, involving both the main duct and its major side branches [1,5]. It remains controversial whether mixed-type IPMN arises from the main pancreatic duct or from side branches and whether it represents a distinct subtype of IPMN [6]. Besides pancreatic intraepithelial neoplasms, IPMNs are the best described precursors of pancreatic ductal adenocarcinoma (PDAC) arising from the cyst itself. Furthermore, they also increase the risk of a syn- or metachronous additional PDAC elsewhere in the gland [7].

Main-duct and mixed-type IPMNs are characterized by dilation of the main pancreatic duct of >5 mm, segmentally or diffusely, without any other cause of obstruction [8]. The neoplastic epithelial cells produce abundant mucin with a high viscosity which cannot be drained sufficiently and leads to obstruction and secondary dilation of the affected parts of the duct system [9]. In contrast, branch-duct IPMNs occur as cysts >10 mm communicating with the main pancreatic duct without its dilation (Fig. 86.1) [2]. Although most IPMNs are basically noninvasive, they progress over time following an "adenoma–carcinoma" sequence via four grades (low-grade, borderline, high-grade dysplasia, and invasive cancer).

Recently, molecular profiling in a series of patients with coexistent high-grade dysplasia IPMN and invasive

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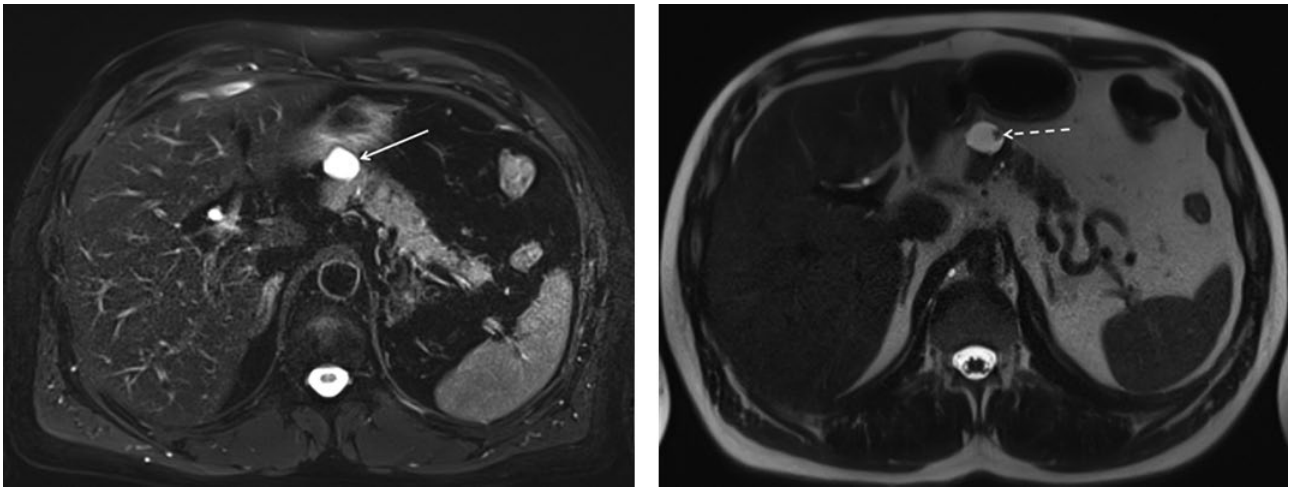


Figure 86.1 Natural history of branch-duct IPMN. A 54-year-old male patient with initial MRI finding of a branch-duct IPMN, serum CA 19-9 negative, no worrisome or high-risk features, diameter 22 mm (white arrow, left side). MRI control eight months later with development of a mural nodule (broken white arrow, right side). Indication for laparoscopic distal pancreatectomy, histopathology: branch-duct IPMN, oncocytic subtype, pTis, N0 (0/12), R0.

PDAC unveiled more tumorigenic pathways according to the proportion of shared sequence variation [10]. The malignant progression can originate from a single aberrant cell clone developing first IPMN and afterwards PDAC (the sequential subtype), from similar clonal origin with later divergence (the branch-off subtype), or from two separate sequence-variation profiles causing either IPMN or PDAC (the *de novo* subtype). The natural history of potential malignant transformation is still not well understood, and the clinical management of IPMN therefore represents a particular challenge.

Four major aspects determine the natural history of IPMN patients:

- morphologic type (main-duct, branch-duct or mixed-type IPMN)
- age at the time of diagnosis and time course of the disease
- histologic subtype (intestinal, pancreaticobiliary, oncocytic, gastric differentiation)
- grade of dysplasia at diagnosis (low-grade, borderline, high-grade dysplasia, invasive cancer).

Morphologic Type (Main-Duct, Branch-Duct or Mixed-Type IPMN)

Main-duct and mixed-type IPMNs have been reported as harboring invasive carcinoma in 11–81%, whereas the rate of invasive branch-duct IPMNs is only about 6–38% [2,11]. Lesions with high-grade dysplasia can also be regarded as "malignant" due to the consideration that this may reflect a "5-to-12" situation with a very short time to invasive cancer progression [12,13]. The dynamic of progression for the different morphologic IPMN types is not completely understood, as especially for main-duct and mixed-type IPMNs—which are basically resected by the time of diagnosis—no reliable data are available (Fig. 86.2). Furthermore, it has to be considered that radiologically defined findings of branch-duct IPMN may reveal themselves as mixed-type lesions in the histologic workup when they are resected [14]. This underlines the difficulty of evaluating an individual patient's risk on the basis of merely morphologic characteristics.

Age at Time of Diagnosis and Time Course of the Disease

Significant differences in the median age of patients presenting with benign IPMNs compared to malignant IPMNs have been reported in cohort studies of 140 and 136 resected main-duct and mixed-type IPMNs [15,16]. From both studies, the age-dependent progression to invasive IPMN can be estimated at 5–6 years as patients with benign IPMNs showed a median age of 61 and 63 years, compared to 67 and 68 years for patients with malignant findings [16]. This can be regarded as a surrogate parameter for an already longer subclinical course of preceding IPMN development by the time of diagnosis, which might be an indirect indicator for disease progression and malignant transformation over time [15,16]. A corresponding observation is the correlation between duct diameter and the risk of malignancy in main-duct IPMNs, underlining that a potentially longer disease course reflected by increased duct size leads to a higher proportion of malignant findings [17].

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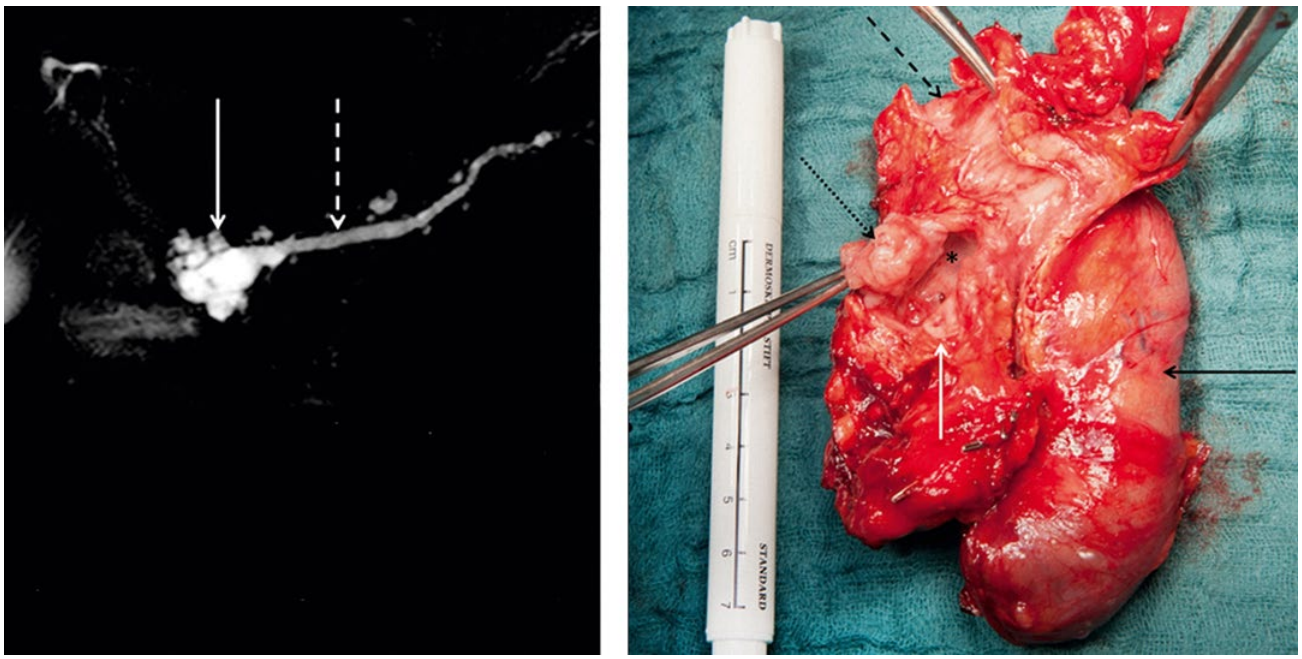


Figure 86.2 Mixed-type IPMN of the pancreatic head. MRI imaging (left side) showing branch-duct components (white arrow) and the dilation of the main duct which extends towards the pancreatic neck. Diameter of the main duct in the body of the pancreas 6 mm (broken white arrow). Partial pancreatoduodenectomy specimen of the same patient (right side). The specimen (dorsal view, black arrow: duodenum) shows macroscopic aspects of IPMN progression: dilated main duct without dysplasia at the resection margin (broken black arrow), papillary epithelium with borderline dysplasia (dotted black arrow), invasive cancer (white arrow). Histopathology: PDAC based on mixed-type IPMN, pT1, N0 (0/21), R0.

Time-dependent progression rates in patients with branch-duct IPMN, who were observed due to the lack of worrisome features, have been reported in larger studies by Sahora et al. [18] and Maguchi et al. [19]. In these studies, which included 411 and 349 patients, signs of progression occurred in 18% of the patients during median follow-up times of 26 months and 44 months, respectively. Malignant histologic features after resection were finally found in 9% and 15% of the patients. Furthermore, both studies demonstrated the development of "remote" lesions, both IPMN as well as PDAC, distant from the index lesion during observation. This underlines the hypothesis that IPMN-bearing pancreata may harbor a "field defect" of the entire gland [20].

Another aspect in this context is the synchronous occurrence of multiple branch-duct IPMNs [21]. As patients with these multifocal lesions are generally older than those with solitary IPMN findings, the "field defect" theory seems reasonable and the progression from solitary to multifocal IPMNs can be regarded as the natural course of this disease [21].

Although multiple lesions are likely to increase the long-term risk of malignant transformation, it remains controversial whether this risk has clinical relevance compared to unifocal lesions [21]. The additional risk of IPMN patients developing concomitant PDAC ranges between 3% and 9% during a 10-year period [22,23]. Whether the IPMN might play a promoting role in the development of PDAC remains unclear and the prognosis in these patients is certainly always determined by the PDAC component.

Histologic Subtypes

The differentiation of histologic subtypes (intestinal, pancreaticobiliary, oncocytic, gastric) [24] has a relevant prognostic impact. The intestinal subtype reveals a phenotype that resembles villous polyps of the colon with neoplastic epithelial cells expressing MUC2, MUC5AC, and CDX2. A recent study focused on 173 main-duct IPMN demonstrated that most main-duct IPMNs were of intestinal type with invasive components in 50% and overall invasiveness of 39% [22]. Invasive carcinomas that arise in association with an intestinal-type IPMN are usually colloidal carcinomas and show a better median survival compared to patients with PDAC (107 versus 20 months) [9,25]. The pancreatobiliary subtype is composed of branched papillary epithelia with high-grade atypia. In immunohistochemistry, it is positive for MUC1 and MUC5AC and has an associated invasive component in 90% of all cases. The associated invasive tubular adenocarcinomas are very similar to PDAC in

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morphology and prognosis [9,26,27]. The oncocytic subtype is characterized by eosinophil cytoplasm, goblet cells and complex branched papillary epithelia expressing MUC1 and MUC6. This subtype is rare as well as a malignant transformation into an oncocytic carcinoma which shows a prognosis similar to patients with a colloid carcinoma [25–27].

Branch-duct IPMNs usually are of the gastric subtype. The typical morphology is multiple small cysts with foveolar gland epithelium, similar to the glands of the gastric antrum. A tubular adenocarcinoma can eventually arise from these IPMNs and is associated with a rather poor prognosis with a mean survival of only 45 months [9,28].

Grade of Dysplasia (Low-Grade, Borderline, High-Grade Dysplasia, Invasive Cancer)

Data on outcome with referral to the grade of dysplasia are available from various larger cohorts of surgical patients [5,22,29]. As these results always reflect the grade of dysplasia at the time of resection, a valid estimation of the time intervals between the distinct grades remains difficult. Patients post resection of IPMNs harboring noninvasive IPMN with a range of low-grade to high-grade atypia show an excellent overall and disease-specific survival prognosis of 95–100% in a follow-up of 10 years in both main-duct and branch-duct IPMN [5,22]. In invasive IPMN, poor prognosis is closely related to disease stage, potentially positive resection margins, and a potentially positive N status [22,29]. While early stages including pT1 and pN0 show a much more favorable prognosis compared to sporadic PDAC, this advantage vanishes in more advanced stages (pT2–pT4) and also positive lymph nodes in any stage result in a prognosis which is similar to PDAC [29].

In addition to the above-mentioned aspects determining the natural history and malignant potential of IPMNs, more advanced approaches enable better discrimination, although such approaches have not yet been introduced in clinical practice. Among others, a recent serum protein signature discriminating low- and high-risk IPMN patients was identified in a cohort study using an antibody microarray platform to analyze the serum proteome via a noninvasive simple blood test. Combinations of established clinical features and the newly identified serum biomarkers correctly distinguished low- and high-risk IPMNs in 93% on 1000-fold crossvalidation which enables risk stratification of IPMN patients [30]. However, larger validation studies are needed to enable more rational decision making in clinical management of IPMN patients.

As all types of IPMN must be considered as a chronic and life-long disease (unless a total pancreatectomy has been performed), the natural course of these entities requires surveillance and follow-up. Surveillance and management strategies have been determined in the International Association of Pancreatology consensus guidelines published in 2006 and updated in 2012 and 2017 [2,8,11], as well as the 2013 European evidence-based guidelines [31] and the 2015 American Gastroenterological Association guidelines [32]. These guidelines are partly conflicting not only with regard to surgical and nonsurgical management but also regarding surveillance and follow-up diagnostics and intervals after resection of IPMNs which precludes accurate clinical decision making.

A recent cohort study including patients with pathologically proven IPMN who received a pancreatic resection and were evaluated preoperatively obtained images and medical history regarding signs of progression and/or malignant features [33]. In this study, the timeliness of resection was stratified into too early (adenoma and low-grade dysplasia), timely (intermediate-grade dysplasia and *in situ* carcinoma), and too late (invasive cancer). Of 1439 patients, 438 (30.4%) were assigned to the too early group, 504 (35.1%) to the timely group, and 497 (34.5%) to the too late group. Accordingly, one-third of IPMNs reached the cancer stage before resection. Radiologic criteria for malignant conditions were detected in 53 of 382 patients (13.9%), 149 of 432 patients (34.5%), and 341 of 385 patients (88.6%) in the too early, timely, and too late groups, respectively. Of the 497 patients in the too late group, 124 (24.9%) had a previous history of watch-and-wait care [33]. These data show that a watch-and-wait policy should be applied with caution, until the biology and progression patterns of IPMN are clarified. Furthermore, follow-up data show that in a cohort of 381 resected invasive and noninvasive IPMN, 17% had recurrence of the IPMN after a median of 17 months [23]. Within this study, 33 patients had only partial resection of multifocal disease with branch-duct IPMN left in the pancreatic remnant. The residual branch-duct IPMNs with a median size of 10 mm at the date of resection grew within a median follow-up of five years to a median size of 13 mm.

In a cohort of 130 patients who had undergone partial pancreatic resections for noninvasive IPMNs, He et al. showed that 17% developed lesions suspicious for new or progressive IPMN within a median time of 46 months [34]. Within this disease progression cohort, some patients developed high-grade dysplasia and invasive cancer. Another 12% of the cohort showed neither new IPMN nor progression in known residual IPMNs.

Within the literature, the recurrence rates vary between 8% and 57% [15,23,34,35]. However, even patients with noninvasive IPMN might have an estimated

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average recurrence rate of 25% of remote IPMN and 7% for developing pancreatic cancer within five years after resection, which underlines the importance of structured and long-term follow-up.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms generally occur in perimenopausal women with a median age of 48 years. MCNs are often located in the distal body or tail of the pancreas (>90%) with a mean size of 6.5 cm in diameter at diagnosis. Macroscopically, MCNs show a uni- or multicystic pattern with a thick wall and potentially solid components without any communication to the pancreatic duct system. An ovarian-like stroma is typical and pathognomonic for the histology of MCNs [36].

Similar to IPMNs, most MCNs are noninvasive, but show a risk of an "adenoma–carcinoma" sequence over time. In 15–20% of all cases, MCNs harbor, at least focally, an invasive component [37]. As data show that patients with an invasive MCN are significantly older (median 3–10 years) than those with a noninvasive MCN, a time-dependent tumor progression is suggested, comparable to that in IPMN [2]. It has been suggested that ectopic ovarian stroma in the pancreatic tail might release hormones and growth factors that stimulate endodermally derived epithelium to progress and form PCNs. This hypothesis is supported by the fact that rapid growth of pancreatic MCNs was seen in women during pregnancy. It has been reported that mural nodules on imaging, lesion size >6 cm and calcification of the cyst wall are associated with the presence of a tubular-type invasive carcinoma very similar to PDAC [38–41].

Since nearly all reported MCNs have been resected, the natural history of MCN is still unknown and recommendations are based on findings from resection specimens revealing the above-mentioned malignancy rates. When an MCN is diagnosed, a distal pancreatectomy is indicated in most cases due to the young age of the patients and the inability to differentiate securely between a benign and malignant lesion. For most patients with noninvasive MCNs, complete resection is curative as these lesions are solitary and show no recurrence [2]. Postoperative surveillance is not mandatory and would require life-long high-resolution imaging associated with high costs without any advantages for the patients [2,42]. In contrast, follow-up after resection of invasive MCN should be performed similar to PDAC [42]. The five-year survival of patients presenting with invasive MCN has been described to be as high as 62%, being worse for elderly patients and for patients with more advanced tumor stages [43].

Serous Cystic Neoplasms

Serous cystic neoplasms are typically located in the pancreatic body and tail and show no significant potential for malignant transformation. The incidence of SCNs is slightly higher in women than in men, with a peak at the age of 60 years. In abdominal imaging, SCNs have a micro- or macrocystic appearance with a spongy structure. In some cases, they also present with a solid growth pattern. On histopathology, they typically are composed of cysts lined by a single layer of cuboid epithelial cells filled with glycogen [36,44]. A preoperative distinction of SCN from MCN is feasible in most cases due to significant differences in imaging. SCNs are usually sporadic, but some arise in patients with von Hippel–Lindau (VHL) syndrome. In patients with VHL syndrome, SCNs are commonly multiple. These patients show a loss of heterozygosity of the VHL gene [45,46]. Sporadic SCNs have a somatic mutation of the VHL gene in up to 50%, with inactivation of the VHL tumor suppressor protein [45–47], and often show a mutation in the *TBC1D3* gene, also known as *PRC17*, but no mutations in the genes typically mutated in mucin-producing neoplasms, such as *KRAS*, *RNF43*, or *TP53* [45,47].

At diagnosis, micro- and macrocystic SCNs have a mean size of 4–6 cm and approximately 50% of all patients are asymptomatic [44,48]. Depending on localization and size of the lesion, symptoms including abdominal pain, discomfort, jaundice or fatigue are reported. Malignant transformation of SCN with the occurrence of a serous cyst adenocarcinoma is very rare and has only been described in a few case reports [49]. Thus, for asymptomatic patients with a SCN of <4 cm in diameter and without criteria for malignancy on preoperative imaging, surveillance is indicated rather than surgical resection.

The natural course of SCN is characterized by a gradual increase in diameter (0.6 cm/year on average). The growth rate seems to depend on the initial tumor size as small SCN (<4 cm) show a significantly slower growth rate of 1–2 mm/year than larger lesions (>4 cm) in which annual growth rates of up to 2 cm can be observed [48]. Consequently, besides the size, growth rate during surveillance may have an influence on the decision for surgery to avoid local complications of compression. Following resection, recurrence risk is extremely low and no structured follow-up is recommended [42].

Solid-Pseudopapillary Neoplasm

The SPN, also known as a Frantz tumor, was first described in 1959. SPNs are rare cystic neoplasms that account for approximately 1–2% of all pancreatic tumors [50]. They

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usually occur in women with a median age of 30 years and are most frequently located in the tail of the pancreas. SPNs are classified as malignant due to the potential for lymphatic spread, recurrence, and distant metastases [51]. As all reported series include mainly patients who underwent resection, the natural history of SPN without resection (i.e., growth dynamics) cannot be determined. Anecdotal reports on nonsurgical treatment have shown that both long-term survival with locally limited tumor manifestation and also aggressive systemic spread with short survival times are possible [52].

At diagnosis, SPNs have a mean size of 8 cm and are located in the body and tail of the pancreas in 60% of patients [51,53]. Their macroscopic morphology varies from pure solid to entirely cystic [54]. Tissue analysis of resection specimens has shown that characteristic mutations in exon 3 of the β-catenin gene occur in 83–100% of SPNs [55,56]. Moreover, the absence of other common mutations, such as *KRAS*, *SMAD4* or *TP53*, distinguishes SPNs from other neoplasms of the pancreas [56,57].

Following complete surgical resection, the long-term outcome of SPN is excellent although approximately 6% of patients show locally advanced tumors (vascular involvement, lymph node metastases) and 8% present with distant metastases [51]. The most comprehensive review including 2285 resected patients demonstrated that 95.6% of the patients are disease free during long-term observation. The time to recurrence in the remaining 4.4% is more than four years and final tumor-related mortality is 1.5% [51].

Despite this overall favourable prognosis, SPN must be considered as a tumor entity with a basically malignant course and complete surgical resection is indicated in all patients who qualify for surgery. Furthermore, life-long follow-up (i.e., annually) is mandatory [42].

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Surveillance or Surgical Treatment in Asymptomatic Cystic Neoplasm

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Introduction

Our knowledge regarding cystic lesions of the pancreas has evolved since the initial publication of this chapter half a decade ago, and now offers a safer and more individualized approach to most patients. In cystic neoplasms, such as solid pseudopapillary neoplasms, mucinous cystic neoplasms, cystic neuroendocrine tumors, and main-duct IPMN, the accepted approach is still surgical resection if the patient is a suitable candidate [1,2]. Otherwise, observation for serous cystic neoplasms (SCN) and main-branch IPMN has proved to be safe [3].

However, in a majority of patients with small lesions, identification of the cyst subtype is either not feasible or uncertain. Based on observational data, several treatment algorithms have been proposed for these unclassified cystic lesions, facilitating the decision on whether to operate or observe [4–6]. Most of these recommendations are based on patient symptoms and morphologic cyst characteristics. Symptomatic patients should strongly be considered for surgery, while in the absence of symptoms, observation is recommended in lesions without suspicious morphologic features.

Further aspects such as age, comorbidities, quality of life, and assumption of costs by the local healthcare system should also be considered when counseling a patient with an asymptomatic cystic lesion of the pancreas. A recent review of three decades from our department at the Massachusetts General Hospital showed how noticeably the diagnostic work-up and indications for surgery have changed over time [7]. With greater availability of endoscopic ultrasound (EUS) over the decades, the concordance between preoperative and final histopathologic diagnosis increased from 45% to 68%, and is currently 80%.

Over time, resections for mucinous cystic neoplasm (MCN) and SCN have decreased significantly, while the number of resected cystic neuroendocrine tumors doubled. The frequency of pancreatic resections for purely benign lesions decreased from 37% to 16%, with a low surgical mortality of 0.9%. Moreover, diagnosis of MCN became less frequent and the number of IPMN more dominant over time.

Rationals for Surveillance or Surgery in Asymptomatic Cystic Neoplasm

After an early period of radical resection of all pancreatic cystic tumors, growing evidence from larger case series caused a transition towards a more selective and observational approach. The rationales behind selective surveillance in asymptomatic patients with a pancreatic cyst are: (i) some cystic lesions, such as SCN of the pancreas, never progress into malignant tumors; (ii) in others that can become malignant, an adenoma–carcinoma transformation takes many years or may never occur; and (iii) cystic lesions with malignant potential normally exhibit suspicious features that can distinguish them from those that are benign. Overall, it can be assumed that the risk that a cystic lesion is malignant at the time of diagnosis does not exceed 0.01%, but it is greater for cysts >2 cm [8]. Further estimation based on collective data from large case series suggests that the percentage of patients developing an invasive carcinoma is approximately 0.24% per year [5].

A recent population-based study from Germany of 1077 healthy individuals who underwent MRI screening showed that 46% harbored cystic lesions of at least 2 mm [9]. The prevalence was associated with higher

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age, higher body mass index (BMI), and diabetes mellitus. Thirteen percent of primary cyst-free patients developed a pancreatic cyst within a five-year follow-up, otherwise a cyst was no longer detectable in 1.6% and none of the cyst-harboring patients developed pancreatic cancer. Likewise, a dual-center retrospective analysis from Medical University Vienna and the Verona Pancreatic Center of 376 incidentally discovered and 10-year nonobserved small cysts of the pancreas demonstrated that the risk for associated pancreatic cancer was low (1.6%) [10]. In both studies, cyst size was moderately small (<15 mm). However, other authors claim the risk of malignancy in pancreatic cystic lesions, especially IPMN, should not be underestimated. In a large surgical series from Heidelberg, 9% of patients already had invasive carcinoma at the time of surgery and had been under surveillance for at least one year [11].

Ideally, patients should only be recommended for pancreatic surgery if this would prevent death from pancreatic cancer or if resection is required for relief of symptoms. In patients with a high comorbidity burden (measured by an Charlson comorbidity score of ≥7), an analysis from our institution demonstrated that the absolute majority of patients with unsuspicious cystic lesions, assumed to be branch-duct IPMN, died from causes other than IPMN carcinoma [12]. Therefore, it is reasonable to question whether further surveillance should be limited only to those patients who can benefit from major pancreatic surgery should the lesion develop concerning features.

Treatment Guidelines for Asymptomatic Cystic Neoplasms

The 2017 revised International Association of Pancreatology (IAP) guidelines for the management of IPMN and MCN of the pancreas [4,6,13], the American Gastroenterological Association (AGA) guidelines on management of asymptomatic neoplastic pancreatic cysts [5] and the 2018 European evidence-based guidelines on pancreatic cystic neoplasms (ESG) [14] have been adopted by most physicians. At the Massachusetts General Hospital and the Medical University Vienna, surveillance of asymptomatic cystic neoplasm of the pancreas is conducted according to IAP guidelines (Fig. 87.1). There are several differences between these proposed algorithms (Table 87.1).

Primarily, the AGA guidelines have been designed for asymptomatic cysts in general, while the IAP and ESG algorithm focuses on the management of branch-duct IPMN. All the guidelines established a list of concerning or worrisome features on which further diagnostic workup, surveillance or surgery is recommended. The IAP and ESG guidelines agree on most points regarding relative and absolute surgical indications, while the AGA only suggests upfront surgery if a solid mass with associated main duct dilation is present. The IAP recommends further evaluation by EUS ± fine needle aspiration (FNA) if any worrisome feature is present. If a definitive mural nodule/solid component and/or main duct involvement is confirmed by EUS, surgery should be considered in all fit patients according to the IAP guidelines. These guidelines also recommend surgery if the EUS shows concerning features or the cytology shows high-grade dysplasia or more. The AGA guidelines, by contrast, only recommend surgery if two concerning features are present and the cytologic analysis of the fluid or cyst wall (obtained by EUS) is either malignant or suspicious for high-grade dysplasia. The ESG guidelines only recommend EUS if the results are expected to change clinical management and only if the diagnosis is not established by cross-sectional imaging.

While this direct relation between cyst size and the risk of malignancy has been investigated and described in numerous studies, the relative meaning of cyst size change over time has been given less attention. In 2017 and 2018, the revised IAP and European evidence-based guidelines on pancreatic cystic neoplasms introduced a rapid growth rate >5 mm/two years as a worrisome feature (relative surgical indication) and favored resection in young patients or observation at very short intervals by EUS and/or magnetic resonance imaging (MRI) (3–6 months) [13–15].

For further surveillance, the AGA proposed an annual interval once after diagnosis, followed by a two-year interval and end of surveillance after five years. By contrast, the IAP surveillance frequency is based on cyst size: <1 cm, 2–3 years; 1–2 cm, yearly for two years, then longer if no change; 2–3 cm, EUS in 3–6 months, then longer interval alternating MRI with EUS as appropriate; ≥3 cm, close follow-up with EUS every 3–6 months. ESG guidelines recommend an initial follow-up after six months, followed by yearly clinical evaluation with Ca 19-9 and MRI/EUS in patients without an absolute or relative surgical indication. As proposed by the AGA guidelines, discontinuation of follow-up in stable unsuspicious cysts after five years may be a cost-effective approach but is not recommended in surgically fit patients. A retrospective analysis of our cyst database revealed that the risk for malignancy is still 5.5% beyond five years of surveillance and size-stable cysts can still progress into invasive cancer [14]. Of note, cystic lesions that were 1.5 cm or less and remained so for more than five years had a very low risk of malignancy that was no different from that of the general population.

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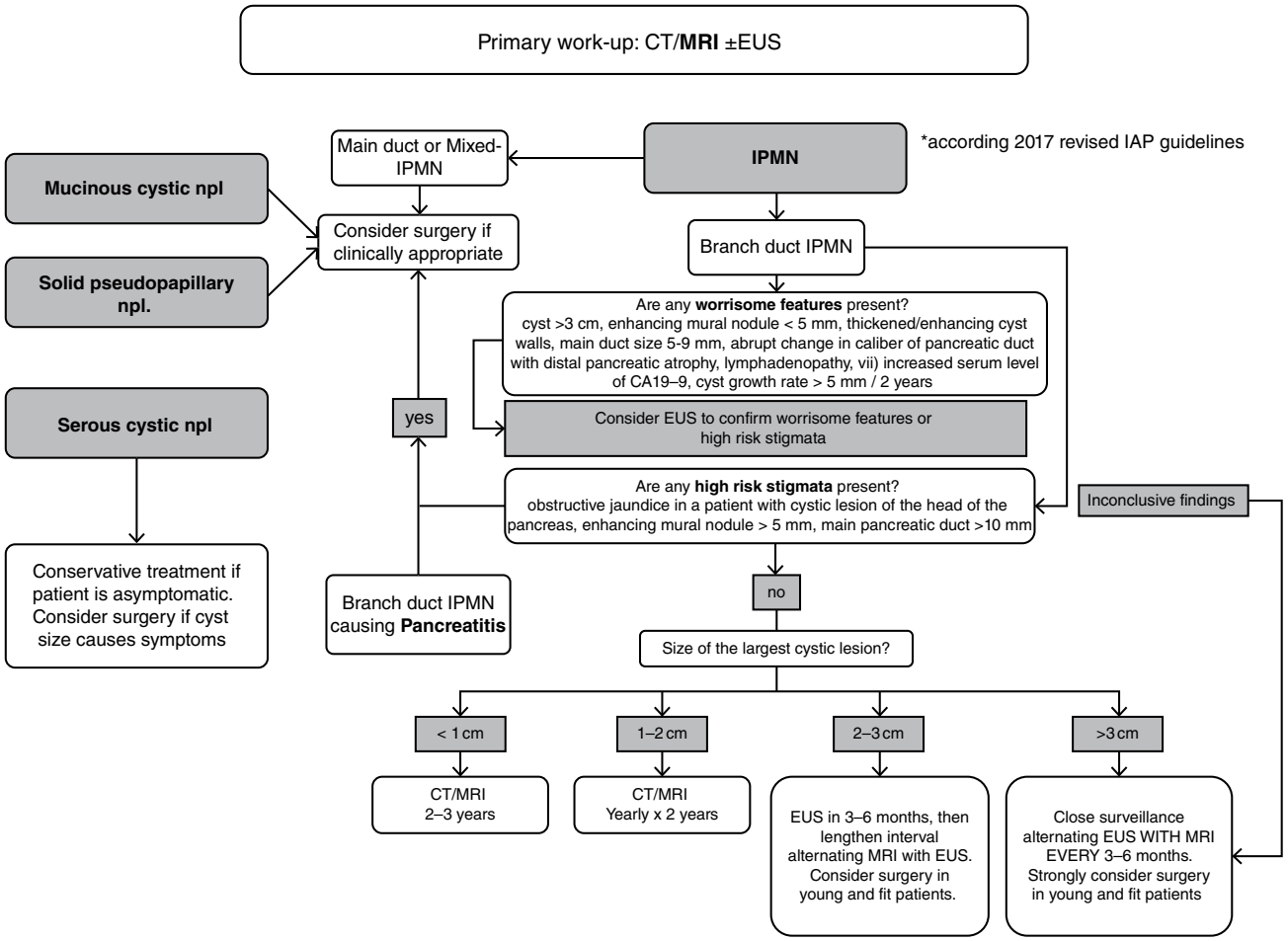


Figure 87.1 Recommended approach in patients with cystic neoplasms. IPMN, intraductal papillary mucinous neoplasms; npl, neoplasm; EUS, endoscopic ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.

Table 87.1 Comparison of current guidelines.

IAP 2017	European Study Group 2018	AGA
High-risk stigmata—absolute surgical indication		
Obstructive jaundice, enhancing mural nodule >5 mm, main pancreatic duct >10 mm	Positive cytology for malignancy or high-grade dysplasia, solid mass, jaundice, enhancing mural nodule >5 mm, main pancreatic duct >10s>mm	Dilated main pancreatic duct **with associated** solid component
Worrisome features—relative surgical indication		
Pancreatitis, cyst >3 cm, enhancing mural nodule <5 mm, thickened/enhancing cyst walls, main duct size 5–9 mm, abrupt change in caliber of pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum level of CA19-9, cyst growth rate >5 mm/2 years	Pancreatitis, cyst >4 cm, enhancing mural nodule <5 mm, main duct size 5–9 mm, increased serum level of CA19-9, cyst growth rate >5 mm/2 years, new-onset diabetes	>3 cm, a dilated main pancreatic duct, associated solid component EUS with FNA recommended

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Surveillance in "Surgically Unfit" Patients

There is only limited information regarding the natural course in frail patients, who are not good surgical candidates, undergoing surveillance with worrisome features or high-risk stigmata. In a multicenter analysis of 281 conservatively managed patients harboring worrisome features or high-risk stigmata (median follow-up 51 months), IPMN-Ca mortality was only 4% in branch-duct IPMN with worrisome features versus 43% in those with main-duct IPMN and high-risk stigmata [16]. Overall, 57 patients (20%) died, but only 12% had progression towards IPMN carcinoma and IPMN-related mortality was only 9%. A recent study showed that cystic lesions with a single stable worrisome feature have a relative low risk of malignancy, while those developing an additional worrisome feature or high-risk stigmata under observation are likely to harbor high-grade dysplasia [17].

Quality of Life: Surgery versus Surveillance

The major objective in treating a patient with an asymptomatic and unsuspicious cystic neoplasm is to prevent or detect the development of pancreatic malignancy. There is controversy over whether or not this should include high-grade dysplasia (what we previously referred to as carcinoma *in situ*) or only invasive cancer. Given the poor prognosis of invasive cancer, most clinicians in the field feel that the goal of surveillance should be the detection of high-grade dysplasia. Repeating imaging studies, invasive diagnostic procedures and major pancreatic surgery are indispensable requirements to maintain this aim.

However, the majority of case series and actual guidelines often neglect issues relating to quality of life, patient preference or postsurgical functional status. In a unique analysis, Weinberg et al. used decision analysis with Markov modeling to compare competing management strategies in a patient with pancreatic head cysts [18]. In their study, they found that surgery remains the superior strategy for maximizing quality of life in patients who are between 65 and 75 years of age with cysts ≥3 cm, but concluded that patients >85 years have improved quality of life when managed with surveillance. They assume that poor quality of life experienced postoperatively often outweighs the minimal benefit derived from surgery in this population. Analogous consideration has been reported regarding prostate cancer in the elderly, where "watchful waiting" is often more appropriate than radical prostatectomy [19]. Van der Gaag et al. reported that after cyst resection, long-term quality of life is equal to healthy references and concluded that the excellent long-term overall outcome justifies proceeding with surgery once an indication for resection has been made [20]. Equally, evaluation of Italian patients with branch-duct IPMN under observation revealed that their quality of life did not deviate from the normal population. Further psychologic questionnaires conducted at basal evaluation and during follow-up demonstrated that the majority of patients showed no signs of anxiety or depression [21].

Cost-Effectiveness of Each Approach

In the light of continuously increasing healthcare costs and a restrictive compensation policy by insurance companies, optimal cost-effective management of asymptomatic pancreatic cystic neoplasm is increasingly relevant. Repeated costly MRI imaging studies for patients under surveillance must be weighed against a more aggressive surgical approach and follow-up with any intervention or stop of surveillance in selected patients. Yet, only a view studies have focused on cost-effectiveness in the management of pancreatic cystic neoplasm.

Das et al. used a Markov model with a third party payer perspective, comparing follow-up without any specific intervention with an aggressive surgical approach and initial EUS with FNA with cyst fluid analysis for risk stratification and resection of all mucinous cysts [22]. The strategy based on risk stratification of malignant potential by EUS with FNA and cyst fluid analysis was the most cost-effective and yielded the highest quality-adjusted life-years. Researchers from our own institution reviewed the cost-effectiveness of the IAP consensus guideline implementation in the management of branch-duct IPMN [23]. Three scenarios based on 60-year-old patients with branch-duct IPMN were analyzed: surveillance using consensus guidelines for surgical resection (surveillance strategy), surgical resection based on symptoms without surveillance (no surveillance strategy), and immediate surgery (surgery strategy).

Surveillance according to the IAP guidelines is a cost-effective strategy in the management of branch-duct IPMN in the head of pancreas when compared to no surveillance or immediate surgery. However, given the large number of patients who are found to have incidental pancreatic cysts, and the lack of endpoint in surveillance, there is a clear need for additional triage strategies to identify groups of patients with higher risk and those with negligible risk, where potentially surveillance could be stopped early on. These potential strategies include

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analysis of cyst fluid for unique markers and identification of circulating tumor cells, exosomes, or free DNA. For example, mAb Das-1, a monoclonal antibody against a colonic epithelial phenotype investigated at our institution, showed high reactivity, both in EUS-FNA cyst fluid samples (sensitivity 89%, specificity 100%) and histologic specimens from resected high-grade IPMN (sensitivity 85%, specificity 95%) [24,2]. Recently, a cost-effective preoperative nomogram for predicting grade of dysplasia in IPMN with a strong objective predictive power (c-index 0.82) was proposed [26]. Combination of this nomogram with cyst fluid protein analysis resulted in increased discrimination of low- versus high-grade lesions (c-index 0.84) [27].

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Artificial Intelligence in the Detection and Surveillance of Cystic Neoplasms

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Introduction

Pancreatic cysts are often incidentally detected on cross-sectional imaging, from approximately 2% of abdominal computed tomography (CT) to 20% of magnetic resonance imaging (MRI) exams [1]. These pancreatic cysts represent a spectrum of pathologies ranging from benign (e.g., serous cystadenoma [SCA], pseudocyst), cysts with malignant potential (e.g., mucinous cystic neoplasm [MCN], intraductal papillary mucinous neoplasm [IPMN]), to cystic or necrotic appearance of overt malignancies (e.g., pancreatic ductal adenocarcinoma [PDAC], pancreatic neuroendocrine tumor [PNET]). These pancreatic cysts can have overlapping clinical and imaging features and can be difficult to diagnose accurately [1]. Cysts with high-risk features such as mural nodules, wall thickening, and main pancreatic duct dilation are often referred for endoscopic ultrasound (EUS) and fine needle aspiration (FNA) and/or surgical resection [1,2]. Current management guidelines recommend serial monitoring of cysts with low-risk characteristics for five years [3] or even 10 years [1], which can be a significant economic burden to the healthcare system [4] and source of patient distress.

There is much optimism that artificial intelligence (AI) may be able to extract digital clinical and imaging data that can lead to earlier disease diagnosis, more accurate disease classification, and the identification of prognostic markers to optimize patient management. This chapter will provide a brief overview of AI, review current AI applications in pancreatic cysts, and discuss future directions for the role of AI in the management of pancreatic cysts.

Brief Overview of Artificial Intelligence

Artificial intelligence can be broadly defined as the computer systems that perform tasks that ordinarily require human intelligence [5,6] (Fig. 88.1). AI can help automate the relatively mundane tasks in medicine (e.g., data entry, lesion measurement) and allow physicians to focus on higher level cognitive tasks that fully utilize their expertise. AI can also decipher patterns in large volumes of multidimensional data, which may not be fully appreciated by humans, and this additional insight may potentially improve human performance.

Machine learning is a subset of AI that trains the algorithms to perform tasks by learning patterns from the data, instead of by explicit programming [6]. The machine learning algorithms can be trained using supervised or unsupervised learning methods. In supervised learning, the algorithm is provided with annotated "ground truth" labels, which is used as feedback to improve the algorithm in an iterative process. The ground truth is the reference standard, which can range from normal versus abnormal at the individual patient level, to detailed slice-by-slice labeling of medical images. In unsupervised learning, the algorithm determines how to classify the data into groups, without the assistance of ground truth labels [6].

Deep learning is a subset of machine learning. It uses convolutional neural networks (CNNs), which are composed of layers of interconnected nodes, inspired by the architecture of biologic neural networks. The principles for deep learning were first developed in the 1950s, but the early applications were limited by computer hardware. The convergence of powerful parallel computing hardware, abundance of medical and nonmedical

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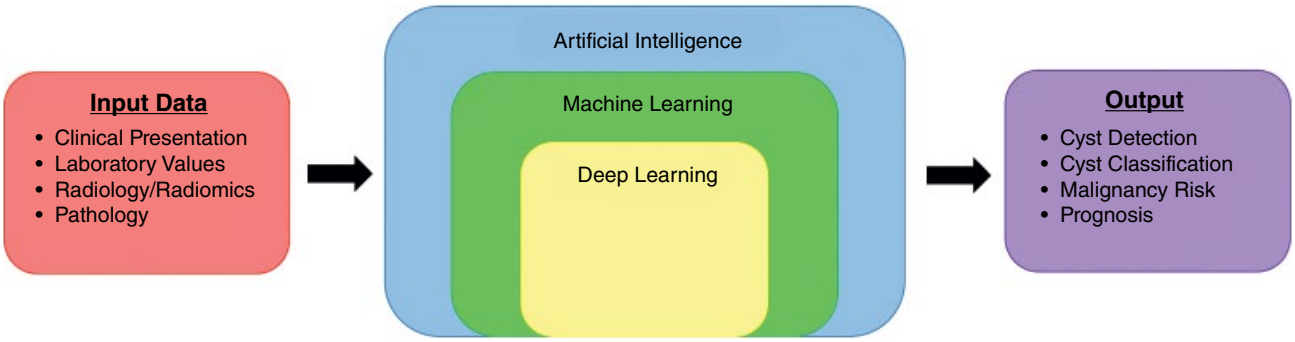


Figure 88.1 Potential role of artificial intelligence in pancreatic cystic neoplasms. Deep learning and machine learning are subsets of artificial intelligence (middle column) that can build models based on diverse sources of input data (left column), and generate output prediction on cyst detection, classification, and prognostication (right column).

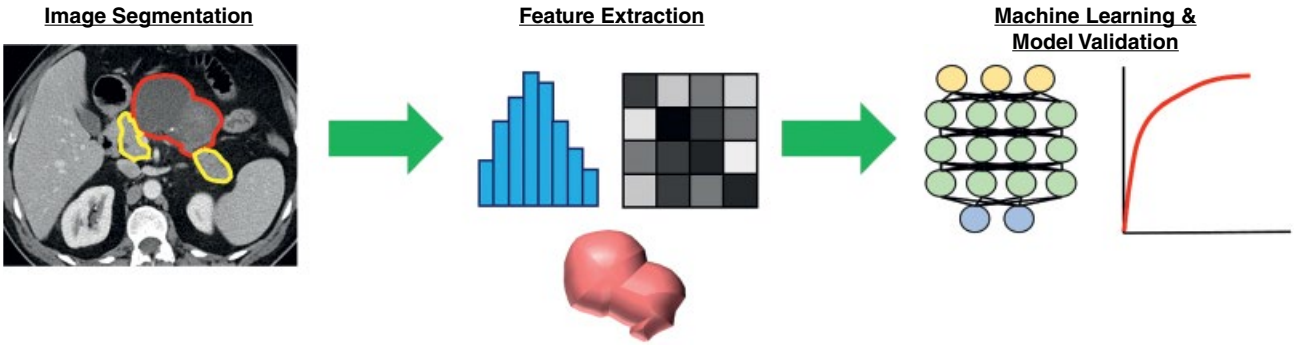


Figure 88.2 Process of radiomics. The radiologic images are first manually segmented to define the region of interest (left column). Quantitative image features, including signal intensity, texture, and shape (middle column), are extracted from these regions of interest. These quantitative features are analyzed with machine learning techniques for model development and validation (right column).

training data, and improvements in network architectures and training techniques has significantly improved the performance of these deep neural networks [5,6].

The input data for machine learning can be derived from various sources, including patient demographics, clinical presentation (e.g., presence or absence of specific symptoms), laboratory values, medical images (e.g., radiology, pathology), and disease diagnosis. Many current AI applications involving radiologic images employ a quantitative feature extraction step before analysis with machine learning. Radiomics is a feature extraction method that converts images into high-dimensional mineable quantitative features [7] (Fig. 88.2). The radiologic images are first manually segmented to define the region of interest (ROI), which is a labor-intensive process that requires expertise in imaging anatomy and pathology. Quantitative image characteristics, including signal intensity, shape, texture, and higher-order features, are then extracted from these ROIs [8]. Signal intensity features are derived from histogram distribution of individual voxel signal intensities and include measures of central tendency and the shape of the distribution. Shape features are extracted from three-dimensional surface masks of the ROI. Texture features take into account the correlation of voxel signal intensities in relation to surrounding voxels in all three dimensions. Higher-order statistics add a filtration step prior to feature extraction [9]. This process typically generates hundreds of features, and a feature reduction step is performed to eliminate redundant features and identify the most relevant ones.

Pancreatic Neoplasm Detection

Computed tomography is one of the first-line imaging modalities for suspected pancreatic pathologies, but imaging features of these pancreatic pathologies can be subtle and overlooked by the radiologist at the time of interpretation. There are a few preliminary reports demonstrating the potential role of deep learning in facilitating automatic detection of pancreatic cancer (Table 88.1), analogous to how computer-aided detection (CAD) in mammography assists radiologists in breast cancer detection (10).

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Table 88.1 Representative peer-reviewed studies of machine learning in the detection of pancreatic pathology.

Study	Study population	Imaging modality	Machine learning and validation	Clinical accuracy or AUC of best model	Machine learning accuracy or AUC of best model
Liu [11]	752 PDAC 490 controls	CT	CNN Split sample External validation	94.4	98.6 (0.997) EV: 83.2 (0.920)
Ma [12]	222 PDAC 190 controls	CT	CNN Crossvalidation	92.2	95.5

AUC, area under the curve; CNN, convolutional neural network; CT, computed tomography; EV, external validation; PDAC, pancreatic ductal adenocarcinoma.

Liu *et al*. trained a CNN from CT images obtained from 752 patients with pancreatic cancer and 490 healthy controls, and showed that the CNN model was 97.3–99.0% sensitive, 98.9–100% specific, and 98.6–98.9% accurate in the differentiation of pancreatic cancer from healthy controls [11]. The CNN model achieved superior sensitivity in pancreatic cancer detection compared to radiologists who originally interpreted the studies (97.3–99.0% vs 91.7–94.4%), and it was able to correctly identify 11/12 (92%) of the pancreatic cancers that were missed by the original radiologists' interpretation. The authors validated their model on external test set, which demonstrated 79.0% sensitivity, 97.6% specificity, and 83.2% accuracy, with the caveat that the pancreatic cancer cases and the healthy control cases came from different institutions, which could affect the performance of the model.

Ma *et al*. similarly constructed a CNN to differentiate between CT images obtained from 222 patients with pancreatic cancer and 190 healthy controls, and showed that the CNN achieved superior accuracy in a 10-fold crossvalidation (95.5%), compared to gastroenterologists (92.2%) and trainees (73.6%) [12].

These promising results obviously need to be further validated in future studies, but they support the potential role of AI to serve as a "second reader" to decrease the number of early, potentially curable cancers that are missed. This may be especially important in rural or resource-poor settings where access to pancreatic imaging expertise may not be readily available, and these AI programs may help elevate the performance of an average clinician to the level of an expert. Such deep learning-based strategies can be adapted to facilitate the automatic detection of pancreatic cysts [13], and surveillance of these pancreatic cancer precursors may lead to earlier pancreatic cancer detection.

Classification of Pancreatic Cysts

Pancreatic cysts may share overlapping clinical and imaging features and studies have shown that AI can potentially improve the classification accuracy of pancreatic cysts. Studies have employed different strategies in pancreatic cyst classification (Fig. 88.3, Tables 88.2, 88.3):

- multi-class approach differentiating each type of pancreatic cyst
- binary classification differentiating benign cysts from cysts with malignant potential
- binary classification of high-grade versus low-grade dysplasia in mucin-producing cysts.

Dmitriev et al. reported that a multi-class machine learning model based on 134 pancreatic cystic masses could differentiate SCA, IPMN, MCN, and SPN (solid pseudopapillary neoplasm) with an accuracy of 83.6% in a 10-fold crossvalidation [14]. Shen et al. developed a model from 164 pancreatic cystic masses and achieved an accuracy of 79.6% in differentiating three types of cysts, including SCA, MCN, and IPMN [15]. Other studies used a binary classification to differentiate SCA from other pancreatic cystic neoplasms, with accuracy ranging from 69.2% to 94.7% (see Table 88.2). The combination of the radiomics machine learning model and the clinical model could further increase the diagnostic accuracy to 76.9–98.2% [16–21]. The rationale for this strategy to differentiate SCA from other pancreatic cystic neoplasms is that increased confidence in the diagnosis of SCA, a benign entity, can safely reassure patients and avoid any unnecessary clinical and imaging follow-ups, biopsies or surgeries, and can reduce healthcare costs.

Another important AI application is the prediction of dysplasia grade in mucin-producing cysts. Our current IPMN management guidelines are designed to emphasize the sensitivity of malignancy detection [2], at the expense of specificity. A recent 15-year multi-institution study showed that only 25% of branch-duct IPMN and 66% of main-duct IPMN in patients who underwent surgical resection had high-grade dysplasia or invasive carcinoma [22]. Therefore, better assessment tools are needed for IPMN risk stratification and to appropriately triage patients who require surgical resection.

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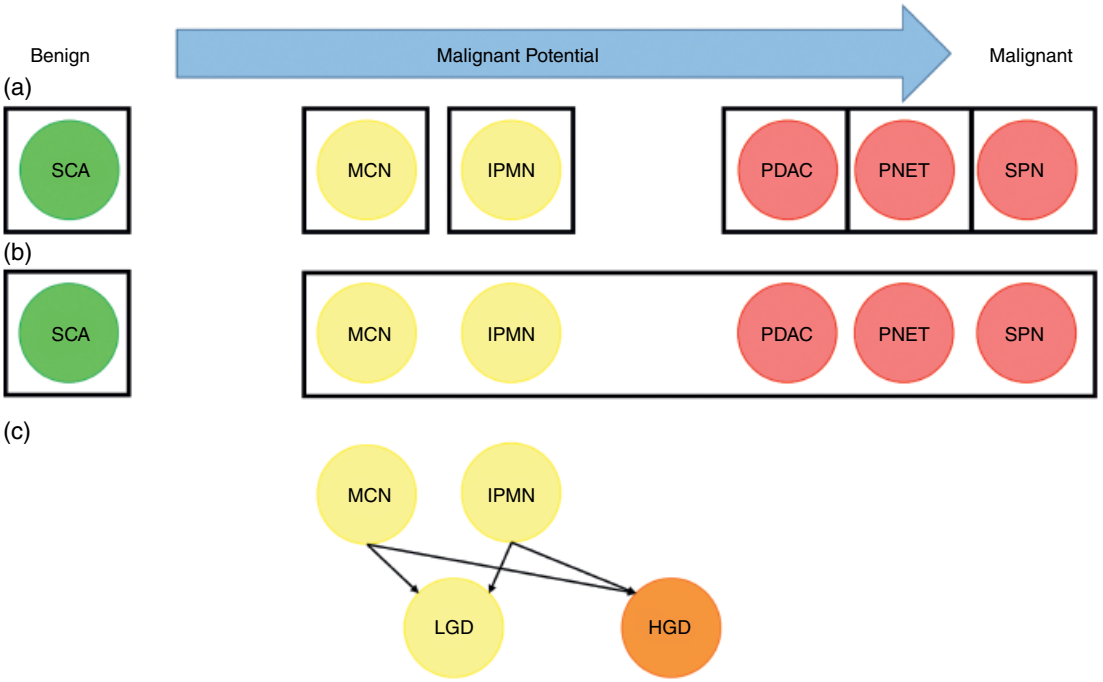


Figure 88.3 Current artificial intelligence strategies in the classification of pancreatic cysts. Row A illustrates the strategy of predicting each individual class of pancreatic cysts, where each cyst type (colored circle) is bounded by separate black boxes. Row B illustrates the strategy of differentiating pancreatic serous cystadenoma (SCA) from all other cyst types (grouped in black rectangle). Row C illustrates the risk assessment of mucin-producing into low-grade dysplasia or high-grade dysplasia. HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MCN, mucinous cystic neoplasm; PDAC, pancreatic ductal adenocarcinoma; PNET, pancreatic neuroendocrine tumor; SCA, serous cystadenoma; SPN, solid pseudopapillary neoplasm.

Table 88.2 Representative peer-reviewed studies of machine learning in the classification of pancreatic cyst type.

Study	Pancreatic cyst types	Imaging modality	Machine learning and validation	Clinical accuracy or AUC of best model	Machine learning accuracy or AUC of best model	Combined accuracy or AUC of best model
Dmitriev [14]	74 IPMN 14 MCN 29 SCA 17 SPN	CT	CNN Crossvalidation	N/A	83.6	N/A
Shen [15]	76 SCA 40 MCN 48 IPMN	CT	Radiomics + SVM, RF, and CNN Split sample	N/A	79.6	N/A
Yang [16]	53 SCA 24 MCN	CT	Radiomics + RF, LASSO Split sample	N/A	83.0 (0.75)	N/A
Wei [17]	102 SCA 74 IPMN 35 MCN 49 SPN	CT	Radiomics + SVM Split sample	0.774	0.837	0.837
Xie [18]	31 MCN 26 SCA (macrocystic)	CT	Radiomics	77.2 (0.775)	94.7 (0.989)	98.2 (0.994)
Chen [19]	31 SCA 30 IPMN 28 MCN	CT	Radiomics LASSO Split sample	65.4 (0.683)	69.2 (0.817)	76.9 (0.869)
Nguon [20]	59 MCN 49 SCA	Endoscopic US	CNN Split sample	N/A	82.8 (0.88)	N/A
Yang [21]	63 SCA 47 MCN	CT	CNN RF Split sample	N/A	92.6 (0.98)	N/A

AUC, area under the curve; CNN, convolutional neural network; IPMN, intraductal papillary mucinous neoplasm; LASSO, least absolute shrinkage and selection operator; MCN, mucinous cystic neoplasm; RF, random forest; SCA, serous cystadenoma; SPN, solid pseudopapillary neoplasm; SVM, support vector machine; US, ultrasound.

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Table 88.3 Representative peer-reviewed studies of machine learning in the classification of dysplasia grade in intraductal papillary mucinous neoplasms.

Study	IPMN dysplasia grade	Imaging modality	Machine learning and validation	Clinical accuracy or AUC of best model	Machine learning accuracy or AUC of best model	Combined accuracy or AUC of best model
Hanania [23]	19 LGD 34 HGD	CT	Radiomics Crossvalidation	64.0	(0.96)	N/A
Permuth [24]	20 LGD or MGD 18 HGD or invasive CA	CT	Radiomics Crossvalidation	(0.84)	(0.77)	(0.93)
Attiyeh [25]	76 LGD 27 HGD	CT	Radiomics Crossvalidation	(0.67)	(0.76)	(0.79)
Chakraborty [26]	76 LGD 27 HGD	CT	Radiomics + RF, SVM Crossvalidation	(0.68)	(0.77)	(0.81)
Polk [27]	22 LGD 29 HGD or invasive CA	CT	Radiomics Crossvalidation	(0.817)	(0.871)	(0.90)
Tobaly [28]	181 LGD 128 HGD 99 Invasive CA	CT	Radiomics LASSO Crossvalidation + external validation	N/A	CV: (0.84) EV: (0.71)	CV: (0.83) EV: (0.75)
Corral [29]	31 Normal 48 LGD 20 HGD 40 Invasive CA	MRI	CNN Crossvalidation	(0.769)	(0.783)	N/A
Kuwahara [38]	27 LGD or MGD 23 HGD or invasive CA	EUS	CNN Crossvalidation	(0.560)	(0.940)	N/A

AUC, area under the curve; CA, cancer; CV, crossvalidation; EUS, endoscopic ultrasound; EV, external validation; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LASSO, least absolute shrinkage and selection operator; LGD, low-grade dysplasia; MGD, moderate-grade dysplasia; RF, random forest; SVM, support vector machine.

Several radiomics and machine learning studies have focused on predicting the dysplasia grade in IPMNs (see Table 88.3). These studies, heterogeneous in design, differed in the type of imaging modality (CT, MRI, endoscopic US), type of cysts (inclusion or exclusion of main-duct IPMN, cases with invasive carcinoma), and validation methods. Despite their methodologic variations, these studies support the notion that radiomics with machine learning (AUC range 0.76–0.96) were superior to guideline-based clinical features (AUC range 0.56–0.84), and the combination of the two (AUC range 0.79–0.93) may offer the best performance in distinguishing between low-grade dysplasia and high-grade dysplasia or invasive carcinoma [23–29]. Such models could help refine the selection criteria for surgical resection, reduce unnecessary surgery, and tailor the surveillance interval based on the risk profiles of individual patients.

These preliminary studies have shown that machine learning trained solely on imaging data can achieve superior performance compared to current guideline-based features. However, imaging data only account for a fraction of the risk profile. The addition of clinical features, laboratory values, and cyst fluid analysis to the imaging data could further refine the risk assessment [30,31]. Springer et al. developed a machine learning *CompCyst* model that incorporated patient characteristics, imaging findings, and cyst fluid molecular analysis from 862 patients, and they used this model to predict pancreatic cyst type as well as appropriate management based on the underlying pathology [30]. In the validation cohort of 426 patients, 53 patients had benign cysts that could be safely discharged, 140 patients had mucin-producing cysts without invasive cancer or high-grade dysplasia that were appropriate for surveillance, and 152 patients had malignant cysts suitable for surgical resection. The machine learning model achieved superior accuracy in triaging patients into discharge and surveillance groups compared to current clinical management and could have avoided unnecessary surgery in 60% of patients in the validation cohort, while maintaining comparable sensitivity for identifying patients in whom surgery was indicated (91% vs 89%) [30]. Incorporation of multidimensional data in these machine learning models may be able to assist clinicians to better assess risk and optimize patient management.

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Challenges and Future Directions

Artificial intelligence has the potential to revolutionize how we manage pancreatic cysts, but there are a few challenges limiting its translation into clinical practice. Firstly, most published reports are single-center retrospective studies with small sample sizes (less than a few hundred participants). Machine learning can be susceptible to overfitting, and the observations based on limited datasets may not be generalizable. It is estimated that the development of generalizable AI algorithms may require hundreds of thousands or even millions of cases to train [32]. This is problematic because curation of quality medical datasets is an expensive and labor-intensive process.

One potential solution is to apply natural language processing (NLP), a linguistic application of AI, to retrospectively identify patients with pancreatic cysts who may be eligible for research studies. Although our medical records have been in electronic format for at least the past 10–20 years, our clinical notes and radiology reports are still mostly composed of unstructured text. NLP can sift through these unstructured medical records to identify patients with pancreatic cysts [33,34] to help build large-scale longitudinal pancreatic cyst registries, which can provide the amount of data necessary to validate AI models. In addition, AI can be used to generate synthetic data to aid in model training. Generative adversarial networks (GANs) are composed of a pair of generator and discriminator deep networks, and through serial iterations, these paired deep networks are trained to produce realistic synthetic data [32]. However, it remains unclear whether these synthetic data are representative of the broad spectrum of variations that are present with real data.

Ideally, AI models should be validated on data from different institutions. Data acquisition and annotation should also be standardized across institutions to facilitate data compatibility. However, data sharing among institutions is often hindered by data security and patient confidentiality concerns. The National Cancer Institute and other organizations have initiated efforts to host central data repositories that allow member institutions to access the pooled resources from other institutions and strengthen inter-institution collaboration [35]. As an alternative to transferring patient data among various institutions, AI algorithms could be shared among institutions through federated learning [36]. With federated learning, patient data remain protected behind the firewall of each local institution. The AI model is trained and tested on each local dataset and sends feedback to update the central AI model [36]. This central AI model can leverage the power of each local dataset while alleviating concerns with data security.

Secondly, many publications, especially in the computer science literature, focus on comparing the performance of the study algorithm with the "state-of-the-art" benchmark. In order to be clinically relevant, AI performance should be compared to human experts, to evaluate if the AI would provide any additional value. These AI models also should integrate different sources and layers of clinical data to build comprehensive models (Fig. 88.4). Based on clinical presentation, past medical history, family history, and any known genetic mutations,

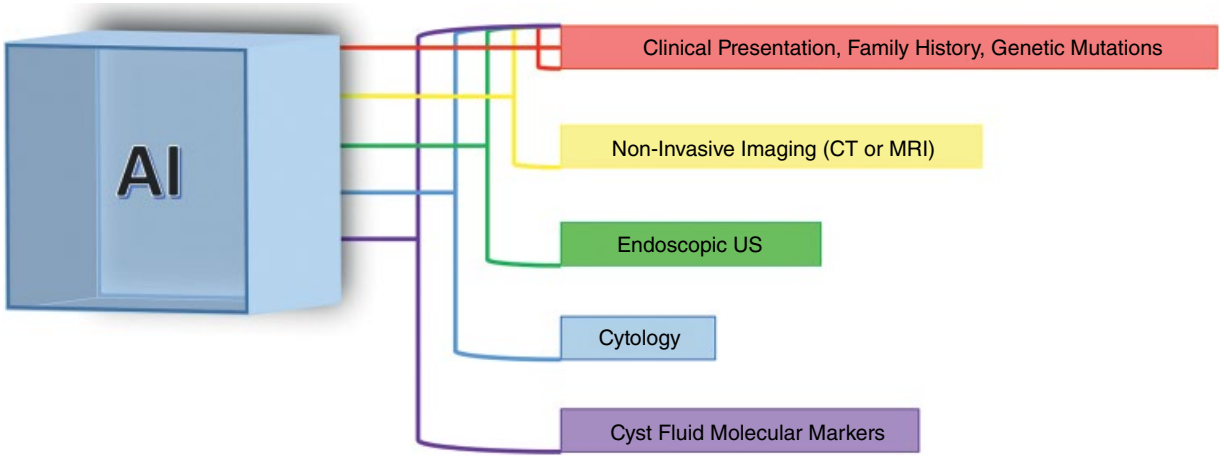


Figure 88.4 Artificial intelligence models have the opportunity to integrate various sources of data and provide clinical decision support during different stages of the patient's journey. Initial models may integrate clinical presentation, family history, and any known genetic mutations (red box) to assess the pretest probability of pancreatic neoplasm and determine if the patients require noninvasive imaging (yellow box) for further evaluation. The next layer of models will integrate both the clinical presentation and imaging data to determine if the patients require endoscopic ultrasound (green box). The final layer of models will integrate cytology (blue box) and cyst fluid molecular markers (purple box, if available) with the clinical presentation and imaging data to provide individualized patient management support.

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AI can determine subsets of patients who require noninvasive imaging (CT or MRI) for further evaluation. Additional AI models that incorporate imaging features and clinical features could determine who should proceed to endoscopic ultrasound and tissue sampling. Then a comprehensive model, analogous to the CompCyst model [30], should incorporate all clinical features, imaging features, and cyst fluid molecular markers, to provide clinical decision support in determining whether patients require surgical resection or periodic surveillance, or can be safely discharged. The validated AI models should be packaged with user-friendly interfaces and integrated seamlessly into clinical workflow, so that clinicians in both academic and private practice would be able to use these models and make a real impact in clinical care.

Thirdly, it is difficult to understand how AI makes decisions due to its black box nature. It can be problematic for clinicians to reconcile any disagreements between human and AI interpretation without understanding the rationale for the AI decision support. There has been active research to improve the transparency and explainability of the AI models and move from "black box AI" to "glass box AI" [37]. Glass box AI allows us to review the variables that are the main drivers for the AI prediction, allowing humans to ascertain whether these variables make biological sense. This may also help us gain better insight into which imaging or laboratory tests are high value, so that we can focus on accurate and cost-effective diagnostic tests for future patients.

Conclusion

Artificial intelligence has the potential to improve the detection of pancreatic pathology from medical images, which can lead to earlier pancreatic cancer diagnosis. It also has the potential to improve the diagnostic accuracy in pancreatic cyst classification and assessment of malignancy risk. These promising results must be validated in large-scale multi-institutional clinical trials. Future comprehensive AI models should integrate numerous sources of clinical data and can provide clinical decision support at various stages to determine the next most appropriate diagnostic test or management strategy.

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Oncologic Resection of IPMN and MCN: Open Approach—Results

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Introduction

Pancreatic cystic neoplasms (PCNs) are common. A recent prospective study showed a prevalence of pancreatic cystic lesions of 49.1% in the general population [1]. Some PCNs are considered benign, for example serous cystic neoplasms of the pancreas, as they present almost no risk for progression to cancer [2]. In contrast, other PCNs, like intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), can progress to cancer [3].

The clinical management of PCNs is extremely challenging for two primary reasons. First, even though their biologic behavior and histologic characteristics are different, these lesions are hard to differentiate using conventional radiology. Some studies suggest that the diagnostic accuracy of PCNs, even at tertiary, high-volume referral centers, is no higher than 60–70% [4]. More recently, endoscopic ultrasound (EUS) with fine needle aspiration (FNA) has been proposed as a valid method of differentiating mucinous (e.g., IPMNs and MCNs) from nonmucinous (e.g., SCN) neoplasms. The presence of a CEA concentration $\geq$192 ng/mL in the cystic fluid has an accuracy of 75% in diagnosing mucinous lesions [5]. However, even assuming that differential diagnosis between mucinous and nonmucinous lesions is possible, determination of the level of dysplasia (or cancer) associated with the lesion and the need for, and proper timing of, surgical resection is rarely possible preoperatively. Since 2006, several scientific society guidelines have been published to try to guide the management of cystic lesions of the pancreas. However, we are not yet able to reliably identify the ideal timing for surgical intervention.

High-grade dysplasia (HGD) in mucinous cystic neoplasms should be considered the optimal target for surgical resection. However, considering that we don't have methods to reliably identify this level of progression, an unsolved question is: is it better to overtreat or undertreat? For example, is it better to resect some low-grade dysplasia (LGD) in order to catch the maximum number of HGD lesions or to minimize surgery in LGD lesions, at the risk of missing some HGD lesions? This question has no evidence-based answer. However, in the authors' opinion, the morbidity and mortality risk of pancreas cancer outweighs the risk of surgery in many carefully selected patients. Therefore, the risk of missing a lesion with HGD or a cancer is carefully weighed. In this chapter, we will focus our attention on the oncologic surgical management of mucinous cystic tumors of the pancreas.

Principles of Oncologic Resection in Mucinous Tumors of the Pancreas

Mucinous tumors of the pancreas should be treated surgically when there is a suspicion or proof of HGD and/or malignancy. For this reason, oncologic resections are most commonly performed.

While parenchyma-sparing procedures have been proposed for the treatment of mucinous neoplasms of the pancreas, the authors' opinion is that this approach was more appropriate in the past when many more low-risk lesions were being resected. Previously, surgery was often offered in cases of "innocent" appearing lesions and there was less knowledge of the biology of these diseases.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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In the case of IPMNs, surgery cannot be considered a diagnostic tool or a strategy to discontinue surveillance. Even in cases of a single branch duct (BD)-IPMN, there is a risk of future development of other IPMNs in the pancreatic remnant and an increased risk of pancreatic cancer. Therefore, surveillance should be continued after resection. This differs from MCNs, where radical excision of a noninvasive lesion corresponds with cure.

Surgical Indications

IPMNs

IPMNs are classified morphologically into three different groups. In branch duct IPMNs (BD-IPMNs), the disease macroscopically affects "only" the side branches of the pancreas. These lesions are frequently multiple and characterized radiologically by communication with the main pancreatic duct. The risk of malignant transformation is lower than the other types. In published series, this risk ranges from 11% to 30% [3]. Main-duct IPMNs (MD-IPMN) are IPMNs exclusively involving the main duct. Mixed-type IPMNs (MT-IPMN) exhibit involvement of both the main duct and branch ducts. When the main pancreatic duct is involved, the risk of malignant progression seems to be higher, with reported rates between 36% and 100% [3].

For this reason, in cases of MD-IPMNs or MT-IPMNs, surgical resection should be considered in patients fit for surgery. There is broad agreement that surgery is indicated for main pancreatic duct (MPD) dilation over 10 mm, but this is debated for MPD dilation between 5 and 10 mm [6,7]. Recent studies emphasize the importance of a surgical evaluation starting at 5 mm diameter of the MPD. These data from surgical series have shown a correlation between MPD dilation over 5 mm and the risk of IPMNs associated with HGD and/or invasive cancer [8-10].

For BD-IPMN, the diameter of the cyst (> of 3 or 4 cm) was historically considered the main indication for surgery [11,12]. More recently, the role of measurements alone has been reevaluated and found to be less important [8]. For this reason, the new evidence-based European guidelines on cystic tumors of the pancreas consider the diameter of the cyst measuring over 4 cm to be only a relative indication for surgery [6]. These guidelines define absolute indications for surgery as the presence of cytology positive for malignancy/HGD, solid masses, jaundice caused by the lesion, enhancing mural nodules (≥5 mm), and MPD dilation over 10 mm. Relative indications for surgery are fast growth of the cyst (≥5 mm/year), serum Ca 19.9 levels greater than 37 U/mL, dilation of the MPD between 5 and 10 mm, cyst diameter greater than 4 cm, enhancing mural nodules (<5 mm), and symptomatic lesions (i.e., IPMN-related acute pancreatitis or new-onset diabetes) [6]. The introduction of the concept of "relative indications" in the European evidence-based guidelines on cystic tumors of the pancreas is innovative because it gives the clinician discretion to personalize the management based on the patient's characteristics (i.e., expectancy of life or performance status).

MCNs

In the past, all patients with MCN were recommended for resection. However, beginning in 2013 and more recently in 2018, the European guidelines on cystic tumors of the pancreas introduced the possibility of surveillance in patient with small (<4 cm) MCNs [6,12]. The safety of this approach has been supported by retrospective data [13,14]. In general, in cases of suspected malignant MCN, a "radical" operation should be performed. A distal pancreatectomy with splenectomy is the most common operation performed, as the usual location of this disease is the body and/or tail of the pancreas. A Whipple procedure is recommended for surgical treatment of pancreatic head lesions.

Oncologic Resection of IPMN and MCN

Given the topic of this chapter, our attention will be focused on "radical" resection in cases of suspected invasive disease. As a general consideration, we must acknowledge that if surgery for IPMN and MCN is ideally done only in cases of suspected invasive cancer and/or HGD, there is a very limited role for local resection. Although the general approach to open procedures is described below, these resections can also be accomplished laparoscopically and robotically.

Preoperative Work-up

Radiological diagnosis and staging guide surgical intervention in patients affected by IPMNs and MCNs. Preoperative cross-sectional imaging (CT scan and/or MRI) should be available. Many patients undergo EUS + FNA. Preoperative histologic diagnosis can be useful but is not mandatory to proceed with surgery. Other diagnostic modalities can be useful in select cases. For example, in IPMN cases with whole pancreas duct dilation, a preoperative pancreatoscopy can help define the extent of the disease in the main duct [15]. A full evaluation of operative risk is mandatory before pancreatic surgery. This is doubly important in cases where surgery is being offered for IPMNs and MCNs, given the absence of a clear diagnosis of cancer in many of these cases.

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Considering the complexity of these cases, a review at a dedicated pancreas multidisciplinary conference is, in our opinion, recommended [16].

Pancreaticoduodenectomy (Whipple procedure)

An open pancreaticoduodenectomy can be done with a midline incision (method preferred by the authors) or a subcostal incision. The first part of the operation is dedicated to excluding the presence of radiologically undetected metastatic disease. The liver, peritoneum, and mesentery are carefully examined for the presence of undetected metastasis. If suspicious lesions are detected, a frozen section histologic analysis is required.

Once the presence of visible metastatic tumor is excluded, a full Kocher maneuver (extending to the aorta) is performed. This maneuver enables the surgeon to better evaluate the mass in anatomic relation to the superior mesenteric vessels. In the case of suspected superior mesenteric artery (SMA) involvement, the aortic origin of the vessel can be identified and an artery first approach can be performed.

After completing the Kocher maneuver, the lesser sac can be assessed through dissection of the gastrocolic ligament. This gives the surgeon the ability to assess the body and neck of the pancreas. The superior mesenteric vein can be identified below the pancreatic neck and assessed for tumor involvement. In the event of vein involvement, control of the vein can be achieved below the mesocolon, in the mesenteric root using a mesenteric approach, to assess the possibility of vein reconstruction [17].

After this step, the hepatoduodenal ligament is dissected. The gallbladder is removed (*en bloc* with, or separate from, the main specimen). A hepatoduodenal ligament lymphadenectomy is then performed *en bloc* with visualization of the left and right hepatic arteries, common and proper hepatic arteries, gastroduodenal artery, hepatic portal vein, and distal bile duct. The dissection can be easily extended to expose the celiac trunk, depending on surgeon preference. The distal bile duct is divided. We recommend a frozen section histologic analysis of the margin. The right gastric artery is ligated and divided. To exclude the presence of critical celiac trunk stenosis, the gastroduodenal artery (GDA) is clamped and the flow in the hepatic artery is evaluated. The GDA is then ligated and divided.

At this point, the duodenum is divided 1.5 cm distal to the pylorus (for pylorus-preserving procedures) or an antrectomy is performed (for nonpylorus-preserving procedures). A tunnel below the pancreatic neck is then created and the pancreas neck is transected. In case of venous involvement at this level by the tumor, this tunnel is made distal in the pancreas body and the pancreas is divided at the left aspect of the superior mesenteric vein. The jejunum is then transected approximately 15 cm distal to the ligament of Treitz and the ligament is fully mobilized. At this point, the head of the pancreas is dissected out from the superior mesenteric portal vein with selective suture ligation of the venous branches. Finally, the SMA margin is taken following 180° full clearance of the right side of the artery and selective suture ligation of the pancreaticoduodenal arteries. The specimen is then removed with *en bloc* resection of, at a minimum, lymph node stations 5, 6, 8a, 12b, 12c, 13a, 13b, 14, 17a, and 17b. The aortocaval lymph nodes may also be removed as a staging measure.

The reconstruction after resection can be performed using different techniques. Normally, a trans-mesocolic pancreatojejunostomy (duct-to-mucosa is the authors' preference) is created on the proximal jejunal loop. Distally, an end-to-side hepaticojejunostomy (the authors prefer using 4-0 or 5-0 absorbable, interrupted suture) is performed. Finally, an antecolic duodeno- or gastrojejunostomy is performed.

Distal Pancreatectomy

An abdominal exploration, as described in the previous section, is performed at the beginning of the operation. The gastrocolic ligament is divided and the lesser sac is explored. The splenic flexure of the colon is fully mobilized. In cases where the lesion is in proximity to or contact with the superior mesenteric vein, a Kocher maneuver is performed to better control possible bleeding during the dissection. The origin of the splenic artery from the celiac trunk is identified. As part of this maneuver, a lymphadenectomy of stations 8a and 9 is performed. This is done both for oncologic reasons and to clarify anatomy [18]. The splenic artery is controlled, ligated, and divided.

If the lesion is not in contact with the superior mesenteric portal vein, a tunnel is created below the pancreatic neck and the pancreas is divided. Notably, this step is performed last in operations for lesions close to the superior mesenteric portal vein. The pancreatic neck is generally transected using a stapler device. Stapler reinforcement is not mandatory, given the lack of evidence for reinforcement reducing the incidence of pancreatic fistula [19]. In cases where the pancreatic parenchyma is very thick or when a resection should be extended towards the pancreatic head, the parenchyma is transected with scalpel or electrocautery. The main pancreatic duct is identified and closed with nonabsorbable suture. The transected parenchyma is then closed using interrupted non-absorbable suture. The short gastric vessels are then ligated and divided. The spleen is

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mobilized from the retroperitoneum *en bloc* with the body and tail of the pancreas.

At this point, the splenic vein is divided and the specimen removed *en bloc* with lymph nodes stations 10, 11, and 18 [18]. For lesions more distal in the pancreas, a portion of the pancreatic body can be preserved by moving the parenchymal line of resection distally, as long as there is adequate margin. A radical antegrade modular pancreatosplenectomy (RAMPS) approach can be performed as an alternative, especially in cases with clear signs of invasive cancer [20].

Total Pancreatectomy

Total pancreatectomy is not often performed for IPMNs and almost never used for MCNs (with the possible exception of locally advanced disease). A total pancreatectomy can be performed when there is extensive main duct involvement in IPMN or when it is not possible to achieve a margin free of cancer or high-grade dysplasia after partial pancreatectomy [6]. The technique used is a combination of the distal pancreatectomy and the Whipple procedure, as described above.

Treatment of Borderline Resectable or Locally Advanced Disease

For malignant MCNs, no definitive data are available regarding the use of neo-adjuvant treatment. For invasive IPMNs, we follow the same indications as for pancreas cancer. At our institution, a surgical exploration is indicated in every patient with radiologic response or stable disease after neo-adjuvant treatment, especially when there is a biomarker response, regardless of the vessels involved. The technical aspects of vessel management have been described previously [21,22].

Use of Intraoperative Pancreatoscopy

The role of frozen section analysis of the resection margin in the prevention of recurrence in the pancreas remnant in IPMNs patients is debated [23]. This is due to the possibility of skip lesions being present in the pancreatic remnant that cannot be detected by a margin analysis. Recently, intraoperative pancreatoscopy has been proposed as a tool to individualize the extent of resection in MD-IPMN patients [24]. However, the utility of this modality still needs to be validated in prospective studies.

Results of "Oncologic" Surgery for IPMNs and MCNs

Even if invasive IPMNs and pancreatic cancer share many biologic aspects, the long-term prognosis of patients with invasive IPMN who undergo resection seems to be better than that of patients with pancreas cancer (five-year overall survival 31.4% vs 12.4%) [25]. The use of adjuvant therapy for invasive IPMN has the same indications as in pancreas cancer. However, based on retrospective studies, the role of adjuvant treatment seems to be debatable for invasive IPMNs in the case of N0 disease [26].

Invasive MCNs are associated with an even better prognosis than invasive IPMNs. In a recent large single-institution experience, the disease-specific survival at 10 years of patients who underwent surgery for MCNs was significantly higher than for those who underwent surgery for invasive IPMNs (79.6% vs 27.2%). Despite the lack of clear supporting data for this practice in invasive MCNs, the same adjuvant approach as for pancreas cancer is generally used.

Conflict of interest

Dr. Del Chiaro has been awarded an industry grant (Haemonetics, Inc) to conduct a multi-center study to evaluate the prognostic implications of TEG in pancreas cancer.

Dr. Del Chiaro is a co-PI of a sponsored Boston Scientific study on the use of intra-operative pancreatoscopy in IPMN's patients.

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Surgical Treatment of Cystic Neoplasms: Laparoscopic and Robotic Approach—Results

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Introduction

Pancreatic cystic neoplasms (PCNs) are a diverse and genetically unrelated group of neoplastic pancreatic diseases which include the mucinous neoplasms—intraductal papillary mucinous neoplasia (IPMN) and mucinous cystic neoplasia (MCN)—as well as serous cystic neoplasia (SCN), solid pseudopapillary neoplasia (SPN), and cystic neuroendocrine tumors (cNET) [1]. Their shared tendency to macroscopically form cystic structures belies their distinct underlying molecular compositions. More importantly, these distinct clinical entities differ in their evolutionary propensity to progress from benign to malignant disease, which has enormous implications for management [2]. As PCNs are mainly diagnosed incidentally in a premalignant stage and commonly asymptomatic, the primary goal of therapy is the timely prevention of invasive cancer [3]. Thus the indications, extent, and approach of surgical treatment are guided by the attributes of each cyst's biology.

In this chapter, we stress the importance of oncologic surgical principles for lesions that suggest high-grade dysplasia or malignancy. The value of pancreas parenchyma-sparing techniques, particularly enucleation and central pancreatectomy, are highlighted for certain cyst configurations which indicate an early stage with potentially progressive dynamics. Focusing on laparoscopic and robotic approaches, we discuss the implications of cyst biologies on surgical strategy, reflect on the conceptual framework of minimally invasive surgery for pancreatic resections, and summarize the current evidence. Collectively, we deliberate on how these modern techniques for PCN surgery can address the quandary of balancing survival benefits with possible sequelae of overtreatment (Table 90.1).

Specific Implications of Cystic Neoplasms for Surgical Treatment

From the surgeon's perspective, resections of PCNs demand specific considerations. As a universal concept, the risk of malignant transformation needs to be balanced with potential complications along with long-term endocrine and exocrine pancreatic insufficiency. Here, a formal oncologic resection and parenchyma-sparing surgical techniques stand against surveillance. If high-grade dysplasia or a malignant disease stage are suspected, oncologic resections with a radical margin and lymphadenectomy (with splenectomy during distal or total pancreatectomy) should be performed independent of PCN etiology [1]. However, the preoperative determination of epithelial dysplasia grade (low-/intermediate-grade vs high-grade vs malignancy) and prediction of future cancer from, at diagnosis, benign neoplastic lesions are challenging and vary depending on the specific cyst biologies. For instance, the probability of IPMNs transforming into malignancy is substantially higher if the pancreatic main duct (MD) is affected (MD-IPMN and mixed-type [MT]-IPMN) compared to isolated branch duct (BD) involvement [4,5]. Furthermore, the risks of both focal-to-multifocal cyst evolution and concomitant pancreatic adenocarcinoma (PDAC) are increased which suggests the proposition that IPMN reflects vulnerability of the whole pancreatic gland through an underlying genetic field defect [6]. Consequently, experts have elaborated on a potential role of preventive total pancreatectomy for selected patients (no established indications currently) [7,8].

Details of the current PCN guidelines with integrated indications of surgical treatment are beyond the scope of this chapter (e.g., differentiation of IPMN characteristics into "high-risk stigmata" and "worrisome features" for risk stratification) [4,5]. Briefly, due to a considerable risk of

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Table 90.1 Considerations for modern surgery of pancreatic cystic neoplasia.

Keynotes

- Pancreatic cystic neoplasms are amenable to minimally invasive pancreatic surgery, if laparoscopic or robotic approaches *do not compromise* the indicated extent of resection and safety.
- Oncologic resections are critical for high-grade dysplasia and invasive cancer.
- Pancreas parenchyma-sparing techniques, such as enucleation and central pancreatectomy, are suitable for early-stage lesions and efficient in preventing pancreatic insufficiency (endocrine and exocrine).

high-grade dysplasia or malignancy, an oncologic resection is indicated generally for all MD- or MT-IPMNs (MD dilation ≥5 mm according to the 2018 European guidelines, MD dilation ≥10 mm according to the 2017 IAP/Fukuoka guidelines), BD-IPMNs with at least one high-risk stigma and MCNs ≥4 cm with suspicious radiologic features [4,5]. For BD-IPMNs with a suggested risk of benign-to-malignant progression without signs of high-grade dysplasia or malignancy (worrisome features but no high-risk stigmata), parenchyma-sparing techniques such as central pancreatectomy and enucleation are considered sufficient alternatives (Tables 90.2 and 90.3) [4].

However, the finite accuracy of IPMN grading is unknown before the completed histomorphologic investigation of the surgical specimen. For SPNs, as they rarely metastasize even given their malignant potential, parenchyma-sparing procedures are also proposed to be adequate [9]. In contrast, lymphadenectomy should be performed for resections of cNETs (surgical indication if ≥2 cm in diameter) [4]. Finally, SCNs are benign lesions which only require a nononcologic resection if crucial surrounding structures (e.g., mesoportal venous system) are mechanically compressed [4].

Table 90.3 Indications for pancreas parenchyma-sparing resections for pancreatic cystic neoplasms (PCNs).

Candidacy for pancreatic enucleation	Candidacy for central pancreatectomy
PCN without main duct involvement and low potential for high-grade dysplasia or malignancy	PCN with low potential for high-grade dysplasia or malignancy
BD-IPMN without high-risk stigmata	BD-IPMN without high-risk stigmata but close main duct proximity
SPN	SPN with close main duct proximity
SCN, if essential pancreas-surrounding structures are compressed	SCN with close main duct proximity, if essential pancreas-surrounding structures are compressed

BD-IPMN, branch-duct intraductal papillary mucinous neoplasia; SCN, serous cystic neoplasia; SPN, solid pseudopapillary neoplasia.

Conceptual Framework of Minimally Invasive Pancreatic Surgery

Laparoscopic surgery, the first technique developed for a minimally invasive operation, has revolutionized surgical care, especially for procedures such as appendectomies and cholecystectomies. The laparoscopic approach can effectively reduce the trauma of surgical access (smaller wounds with decreased systemic inflammation/stress response along with improved cosmetics compared to laparotomy) and consequently lead to a shorter length of hospital stay (enhanced recovery) [10]. Moreover, patients experience a decreased prevalence of postoperative incisional hernias and fewer intraabdominal adhesions [11]. Given the compelling data and successes, minimally invasive techniques have been applied

Table 90.2 Available trials with high-level evidence from randomized controlled data on minimally invasive pancreatic surgery.

Trial ID	Year of publication	Country	Centers	Approach	Patients analyzed
Distal pancreatectomy					
LEOPARD	2019	Netherlands	Multicenter	Laparoscopic/robotic vs open	42/5 vs 55
LAPOP	2020	Sweden	Single center	Laparoscopic vs open	29 vs 29
Pancreatoduodenectomy					
PLOT	2017	India	Single center	Laparoscopic vs open	32 vs 32
PADULAP	2018	Spain	Single center	Laparoscopic vs open	34 vs 32
LEOPARD-2	2019	Netherlands	Multicenter	Laparoscopic vs open	50 vs 49
MITG-P-CPAM	2021	China	Multicenter	Laparoscopic vs open	297 vs 297

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to procedures of higher technical complexity characterized by increased intraabdominal trauma.

During pancreatic surgeries, major veins and arteries are encountered, requiring delicate technical maneuvers. Furthermore, during a pancreatoduodenectomy (PD) and total pancreatectomy, intestinal reconstruction is performed with a series of anastomoses (gastrojejunostomy and hepaticojejunostomy; pancreaticojejunostomy during PD). In 1994, Gagner and Pomp reported the first case of laparoscopic PD (for pancreas divisum-related chronic pancreatitis) and Cuschieri published his initial laparoscopic pancreatic surgery experience including PD, distal pancreatectomy (DP), and insulinoma resection [12,13]. Robotic pancreatic resections, which are characterized by superior manual dexterity and optics, were pioneered by Giulianotti et al. in 2001 [14]. The benefit of the minimal access approach described above for laparoscopic surgery applies to robotic operations.

Intriguingly, prognostic and epidemiological evidence specific to PCNs may favor a minimally invasive approach for a set of patients with its proposed clinical benefits. The majority of PCNs are detected in a premalignant disease stage which suggests surgical treatment as an opportunity for prophylaxis. As opposed to patients with PDAC, patients with detected PCNs are frequently cured with resection and tend to be younger at time of diagnosis, making a long-term high quality of life particularly desirable. This translates into the premise to deliver surgery with the least possible morbidity. However, the underlying PCN biology specifically needs to be addressed and, if indicated, it is imperative that a minimally invasive resection is performed with the oncologic principles similar to the open approach. For technically complex and radical resections with intestinal reconstructions, the impact of reduced surgical access trauma on outcomes is beneficial [15].

Minimally Invasive Distal Pancreatectomy

Distal pancreatectomy comprises resection of the pancreatic body and tail with simultaneous splenectomy for oncologic resections. The laparoscopic approach has been widely applied for DP and various single- and multicenter case series have demonstrated similar perioperative outcomes with a shorter hospital stay when compared to open DP [16]. A metaanalysis of 29 observational studies confirmed superiority of laparoscopic DP for hospital stay (mean difference 4.6 days), time to first oral food intake (mean difference 1.3 days), and blood loss (mean difference 308 mL) while rates for overall morbidity (37%), postoperative pancreatic fistula (POPF) (22%), and 30-day mortality were similar (0.4% vs 1.1%) [17]. In this study with a pooled laparoscopic DP cohort of 880 patients, 49% underwent resection for PCNs. For robotic DP, several reports indicated equivalent perioperative mortality, morbidity, and length of hospital stay compared to laparoscopic DP, with similar advantages over the open approach for selected patients [18,19]. In one of the observational studies, robotic DP was associated with a lower rate of conversion and splenic preservation, but longer duration of surgery than laparoscopic DP [19].

Recently, data from two randomized controlled trials (RCTs) designed to compare minimally invasive vs open DP were presented [20,21]. In the multicenter LEOPARD trial, 47 patients underwent minimally invasive DP (42 laparoscopic, five robotic) and 55 open DP. With the primary outcome being postoperative time to functional recovery, the trial demonstrated a benefit of two days with the minimally invasive approach (4 vs 6 days) along with a median two-day shorter hospital stay (6 vs 8 days). No mortality and a similar major complication rate (23% vs 38%) were observed in the minimally invasive cohort (spleen preserved in a similar fraction of patients, 45% vs 50%) [20]. Improved time to functional recovery (4 vs 6 days), shorter hospital stay (5 vs 6 days) and comparable major morbidity rates (4% vs 8%) were confirmed in the single-center Swedish LAPOP trial which enrolled 29 patients in each group of laparoscopic and open DP (overall 55% of patients with PCN) [21]. Interestingly, the major complication rates were substantially lower in the LAPOP than in the LEOPARD trial (Clavien-Dindo grade ≥IIIA, overall 6% vs 31%) and a conversion to open rate of 3% compared to 9%.

Minimally Invasive Pancreatoduodenectomy

Pancreatoduodenectomy is characterized by a complex *en bloc* resection and intestinal reconstruction with three anastomoses, thereby enhancing technical complexity compared to DP. For laparoscopic PD, early data by Kendrick and Cusati demonstrated safety in their initial experience of 65 consecutively selected patients with only one 30-day/in-hospital mortality [22]. Case–control matched single-center series revealed postoperative mortalities between 0% and 7% [23].

Since 2017, results of four conducted RCTs have been published investigating laparoscopic vs open PD. The PLOT [24] (India, 32 vs 32 patients) and PADULAP [25] (Spain, 34 vs 32 patients) trials both had a monocentric design and laparoscopic PD was restricted to two and one highly experienced surgeons only, respectively. In the PLOT trial, median hospital stay almost halved in the laparoscopic group (7 vs 13 days) with equal rates of

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complications (overall 28%) and postoperative mortality (one out of 32 patients in each group). Although a shorter length of hospital stay was also observed in the PADULAP trial, patients were not discharged until a median of 13.5 days (vs 17 days). None of the 34 patients died within 90 days after laparoscopic pancreatoduodenectomy. Encouraging safety was also demonstrated in the large multicenter MITG-P-CPAM trial (China, 328 vs 328 patients) with a 90-day postoperative mortality of 2% [26]. Notably, all participating surgeons from 14 centers had performed at least 104 laparoscopic PDs. However, although significantly shorter, length of hospital stay had an arguably small effect size of just one day benefit in the laparoscopic PD group (15 vs 16 days).

In contrast, the multicenter LEOPARD-2 trial (Dutch Pancreatic Cancer Group, 50 vs 49 patients) was prematurely terminated due to a mortality rate of 10% in the laparoscopic PD group (vs 2% after open PD) [27]. The participating eight surgeons from four centers had completed a specifically designed laparoscopy training program and had experience of at least 20 cases (during training, 90-day mortality rate 3.5%) [28]. A side analysis of 38 patients from the LEOPARD-2 cohort aimed to compare the systemic inflammatory response within 96 hours postoperatively through serum IL-6, IL-8, and CRP levels and found no differences [29].

Finally, data from a metaanalysis further indicate that a profound learning curve and high operative volume are needed to achieve results with potentially modest benefits [30].

To perform minimally invasive PD with improved technical feasibility, robotic technologies are gaining traction internationally [31]. In four independent single-center series of robotic PD which included between 96 and 500 patients, perioperative safety was demonstrated with postoperative 90-day mortalities between 2.1% and 3.6% [32–35]. With regard to complications, case–control (open PD) matched studies resulted in noninferior rates of POPF and anastomotic insufficiencies. In contrast, data suggest a shorter length of hospital stay and fewer wound infections [34,35].

Recently, delicate surgical refinements for a radical dorsal margin (retropancreatic nerve plexus with TRIANGLE resections, periadventitial dissection of major arteries) have been demonstrated to be feasible, exploiting the 10× optical zoom and seven degrees of freedom of the robotic instruments, so that steps of robotic resections increasingly resemble the open procedure [36]. Nevertheless, importantly, it has been recognized that skill and favorable perioperative outcomes come at the cost of an extensive learning curve.

A recent systematic review compared robotic with laparoscopic learning curves and found similar case numbers were required to achieve a plateau in operative time for both PD (37 vs 34 cases) and DP (21 vs 25 cases) [37]. Although case volume and reported experiences in an increasing number of institutions are promising, quality evidence from RCTs that recruited patients with robotic pancreatic resections compared to open or laparoscopic resections is unavailable, but trials are ongoing (e.g., EUROPA trial).

Minimally Invasive Parenchyma-sparing Pancreatic Resection

Parenchyma-sparing pancreatic resections include enucleation, central pancreatectomy, and uncinate process resections (referred to as inferior pancreatic head resection). They are performed for presumed noninvasive PCNs to maximize preservation of functional endocrine and exocrine tissue (indications summarized in Table 90.3) [38]. Data from open resections emphasize its efficacy. A metaanalysis on enucleation for BD-IPMN resection from 16 retrospective studies with 293 patients determined postoperative endocrine dysfunction in 1% and exocrine insufficiency in 7% of the patients, both substantially lower than after formal resection (38% and 30%, respectively) [39].

Reflections on conversion to formal resection and surgical technique were reported in a large retrospective single-center series from Heidelberg [40]. In this study, 115 patients underwent laparotomy with the intent of enucleation for BD-IPMNs with less than 3 cm in cyst diameter. The intraoperative decision to convert to a formal resection was made in approximately one-third of the patients, while 87 enucleations (59% located in the pancreatic head or uncinate process, no enucleations for tail lesions) were performed in 74 patients with no perioperative mortalities. Common causes of conversion were a larger than expected cyst size and multifocal appearance. Subsequently, cystic main duct involvement was detected in 56% of the converted patients on final pathology, whereas all enucleated patients showed cyst-free margins at the BD-IPMN specimen (confirming an uninvolved main duct). Compared to the converted patients, enucleation resulted in a shorter hospital stay (10 vs 14 days), lower endocrine dysfunction (2% vs 57%), decreased exocrine insufficiency (11% vs 46%), and a similar POPF rate (27%). Technically, the dissection was performed primarily bluntly with ligation of adherent vascular or ductal structures. The authors relied on routine intraoperative fresh frozen histology to rule out high-grade dysplasia or malignancy, which would have led to conversion [40].

Assessing open central pancreatectomy, a large metaanalysis (56% of patients had PCNs) with pooled 1305 patients from 50 studies resulted in postoperative endocrine and exocrine dysfunction in 4% and 5% (both lower than after DP or PD), verifying its proposed

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efficacy. While perioperative mortality was only 0.5%, POPF developed in 35% of the patients (higher compared to DP and PD) and contributed to an overall postoperative morbidity of 51% (higher compared to DP, but no difference from PD) [41]. Further analyzing and elaborating on potential advantages and risks, Lee et al inferred from their case–control study that central pancreatectomy is vindicated as an alternative to DP when a considerable pancreatic tail volume can be preserved [42]. Patients should have a high performance status to enhance postoperative recovery.

The feasibility of minimally invasive parenchyma-sparing pancreatic resections has been suggested by small single-center case series. Dedieu et al. analyzed outcomes in 23 consecutive patients with laparoscopic enucleation indicated for pancreatic neoplasms (insulinoma or PCNs). Uncertainty in localizing the tumor without palpation led to conversion to open surgery in two patients [43]. While in this series one patient died within 30 days postoperatively, a study by Mabrut et al. demonstrated no mortality after 21 laparoscopic enucleations [44]. For laparoscopic central pancreatectomy, Senthilnathan et al. indicated feasibility in 14 selected patients and reported no mortalities, with a POPF grade B in 14% of the patients as the only major morbidity. For Roux-en-Y anastomosis of the distal gland to the jejunum, the authors adjusted their technique according to the gland texture and duct size; for a soft gland with an undilated duct, "dunking" was performed whereas for a firm gland with a dilated duct, a duct-to-mucosa technique was preferred [45].

In a case–control study comparing laparoscopic to open central pancreatectomy, Song et al. demonstrated no postoperative 30-day mortalities for both approaches, and a longer operation time (350 vs 270 min) but shorter length of hospital stay (14 vs 22 days) after laparoscopic resection (26 vs 14 patients) [46].

Surgeons are also utilizing the robotic platform with its improved flexibility through the EndoWrist- instruments for parenchyma-sparing pancreatic resections. In 2015, Shi et al. retrospectively compared perioperative outcomes in patients who underwent robotic vs open enucleation (26 vs 13 patients) for insulinoma or PCNs. In addition to no endocrine and exocrine insufficiency with the robotic approach, they reported less trauma, shorter operation time, less blood loss, faster wound recovery, and unchanged events of POPF (23% grade B, no grade C, all patients received somatostatin) [47]. Technically, enucleation was mainly performed with a robotic ultrasound scalpel (alternatively, electronic hook or monopolar curved scissors) and, for securely localized tumors, the surgeon placed a suture through the lesion as an anchor for refined traction. The authors described how the amplified vision at the robotic console enabled direct ligation of the proximal branch duct at the resection margin after enucleation of an BD-IPMN and proposed that the superior precision granted by the robotic system may therefore decrease rates of POPF [48].

In an independent series where propensity-score matching was applied (robotic vs open enucleation of pancreatic neuroendocrine tumors smaller than 2 cm), similar frequencies between the two cohorts of major complications and POPF validated feasibility and safety [49]. For robotic central pancreatectomy, a recent metaanalysis of 12 observational studies with 265 patients suggested a 0.5% postoperative mortality, a major morbidity rate of 9.4% and a clinically relevant POPF in 42.3% of the patients [50]. Endocrine insufficiency occurred in only 0.3% of the patients, confirming efficacy of the surgical technique.

In summary, parenchyma-sparing pancreatic resections are highly effective to prevent endocrine and exocrine pancreatic insufficiency. Experienced surgeons demonstrated comparable outcomes of laparoscopic and robotic compared to open resections. A considerable limitation is that palpation is not possible due to the lack of haptic feedback of minimally invasive tools, which complicates identification of tumors, making high-resolution preoperative imaging and anatomic landmarks critical. Potential advantages are improved precision through a magnified view, decreased surgical access trauma, and enhanced recovery.

Conclusion

Pancreatic cystic neoplasms are amenable to minimally invasive pancreatic resections, if the indicated extent of resection can be achieved without compromises. Guided by the specific cyst biology, surgical techniques include oncologic as well as nononcologic, parenchyma-sparing methods such as central pancreatectomy and enucleation particularly for certain BD-IPMNs. The laparoscopic platform is established for DP and has been proven in RCTs to accelerate functional recovery. Regarding PD, the robotic approach is promising to overcome the limited flexibility and dexterity of laparoscopic instruments to perform a safe and noninferior operation. Parenchyma-sparing methods are highly effective to preserve endocrine and exocrine pancreatic function. As such, enucleation should be considered as a suitable procedure for BD-IPMNs without high-risk stigmata, allowing risk elimination of lesion-specific malignancy. Although feasible as demonstrated by experienced surgeons, clinical trials are important to validate noninferiority compared to open parenchyma-sparing pancreatic resections and identify milestones of procedure-specific learning curves.

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Future innovations in robotics, computation, and imaging for improved precision, assistance, and intraoperative PCN localization may further accelerate the benefit of minimally invasive PCN surgery.

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Robotic-assisted Resection of Cystic Neoplasms

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Introduction

The evolution, adoption, and routine use of robotic platforms to advance the field of pancreatic surgery have evolved over the past 18 years since Melvin et al. [1] first published the case of a robotically resected pancreatic neuroendocrine tumor. Since then, several international case series have supported the safety and equivalency of surgical outcomes in highly selected patients operated on by surgeons experienced in both hepatobiliary and minimally invasive surgical techniques [2–13]. Review articles, metaanalyses, and international consensus guidelines have summarized multiinstitutional outcomes and arrived at similar conclusions [14–21]. Despite these meaningful advances and comparable outcomes, less than 10% of all pancreatic surgery is performed robotically, even at high-volume academic centers [7,16].

Robotic pancreatic surgery offers several key advantages when compared to open and laparoscopic surgery. Three-dimensional magnified optics enhance intraoperative visualization [14,15], the camera itself has increased stability compared to traditional laparoscopy and is controlled by the operating surgeon, and the use of indocyanine green fluorescence improves the visualization of biliary anatomy. EndoWrist® instruments allow increased degrees of operative freedom, making technically challenging dissections and anastomoses possible, and the lack of tactile feedback does not limit operative capability [15,22,23]. As with other minimally invasive approaches, wound complications, including wound infections and incisional hernias, are significantly minimized with use of the robotic platform. The robotic approach also makes the difficult laparoscopic pancreatectomy feasible and easier to teach.

In this chapter, we discuss indications and techniques for robotic-assisted resection of benign and malignant cystic lesions with a focus on parenchyma-preserving pancreatectomy. Given the benign nature of most cystic neoplasms, robotic resection is leading the way in technical advances that enable surgical resection of premalignant pancreatic lesions with reduced morbidity and improved patient outcomes (Table 91.1).

Indications for Robotic-assisted Resection of Cystic Neoplasms

The indications for robotic-assisted resection of cystic neoplasms (Table 91.2), including mucinous cystic neoplasms (MCN), serous cystic neoplasms, intraductal papillary mucinous neoplasm (IPMN), solid pseudopapillary neoplasm (SPN), and cystic pancreatic neuroendocrine tumors (C-PanNET), are identical to those for open and laparoscopic procedures with additional consideration given to prior history of abdominal surgery, body habitus, and tumor location. Indications for resection of asymptomatic branch-duct IPMN (BD-IPMN) include the presence of worrisome features such as the presence of mural nodules, given that nodules >5 mm have been shown to be highly predictive of invasive carcinoma and/or high-grade dysplasia. Indications for main-duct IPMN (MD-IPMN) resection include main pancreatic duct dilation >10 mm, jaundice, and mural nodules. Depending on which guidelines are followed, indications for resection of MCN include all surgically fit patients with cysts >4 cm and/or cysts causing symptoms [24–26]. Surgery for SCN is rarely indicated except when the patient has symptoms secondary to mass effect.

Overall performance status such as patient age and body mass index (BMI) should be considered when using a robotic platform. Recent data support the use of robotic pancreatic surgery for patients with BMI greater than 25 [27].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Table 91.1 Early postoperative outcome metrics of robotic-assisted pancreatectomy.

	Sanchez-Velazquez et al., 2019 [55]	Zureikat et al., 2021 [56]	Timmermann et al., 2021 [3]	Shi et al., 2020 [13]	Shi et al., 2016 [57]	Shi et al., 2020 [58]
Number of patients treated	N = 78 This is a benchmarking study for low-risk minimally invasive pancreatic surgery cases	N = 500 Not specific to cystic neoplasms	N = 101 20.4% of the resected tumors were IPMN/PanNETs	N = 187 33.7% were reported as low-grade malignancies or benign lesions	N = 26 This series included only patients who had undergone enucleation of pancreatic lesions, the majority of which were for cystic pathologies	N = 110 This series included only patients who had undergone middle pancreatectomy, the majority of which were for cystic pathologies
Estimated blood loss	–	250 cc	–	297 cc	76 cc	88 cc
Conversion to open	–	5.2%	2.9%	–	0%	–
Mean number of harvested LNs	32	28	15	17	–	–
Frequency of early postoperative complications	Clinically relevant POPF: 19.4% Biochemical leak: 7.6%	Clinically relevant POPF: 7.8% Biochemical leak: 12.4%	Clinically relevant POPF: 23.8% Biochemical leak: 7.9%	Clinically relevant POPF: 10.2% Biochemical leak: 4.8%	Clinically relevant POPF: 27.0% Biochemical leak: 19.2%	Clinically relevant POPF: 34.5% Biochemical leak: –
Major complications	16.7%	24.8%	48%	–	46.2%	21.9%
Need for reoperation	–	4.8%	16.7%	3.7%	–	4.5%
Length of stay (median)	14 days	8 days	15 days	22 days	22 days	25 days
In-hospital mortality/90-day mortality	2.4%	3%	2.9%	2.1%	–	0.9%

IPMN, intraductal papillary mucinous neoplasm; LN, lymph node; POPF, postoperative pancreatic fistula.

Table 91.2 Indications for robotic-assisted resection of cystic neoplasms.

Pancreatic cystic neoplasm	Malignant potential	Location	Cyst fluid analysis		
			CA 19-9	CEA	Amylase
IPMN	Variable [49]	61% head/uncinate, 39% neck/body/tail cysts [50]	Variable/high	High	High
MCN	12–39% [51]	11–22% head/neck, 78–89% body/tail [51]	Variable	High	Low
SCN	None	26.4% in pancreatic head, 10.1% in pancreatic neck and 63.5% in pancreatic body and tail [5]	Variable	Low	Low
SPN	Low [52–54]				
C-PanNET				Low	Low

C-PanNET, cystic pancreatic endocrine neoplasm; IPMN, intraductal papillary mucinous neoplasms; MCN, mucinous cystic neoplasms; SCN, serous cystic neoplasms; SPN, solid pseudopapillary neoplasm.

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Preoperative Preparation

Prior to taking a patient to the operating room for robotic-assisted resection, it is essential to review the preoperative imaging studies including cross-sectional imaging such as high-quality pancreatic-protocol computed tomography (CT) and/or magnetic resonance imaging (MRI). Review of cyst fluid analysis (amylase, lipase, CEA, cytology) obtained from endoscopic ultrasound (EUS) should be performed if available [28]. In general, the need to remove the spleen should be determined preoperatively.

Reusable robotic instruments should be available, including EndoWrist® monopolar hook cautery, scissors, Maryland bipolar forceps, fenestrated bipolar forceps, medium-large clip applier, large SutureCut™ needle driver, and Tip-Up fenestrated grasper (Intuitive Surgical, Sunnyvale, CA, USA) [29]. If the need for intraoperative ultrasound is anticipated, it should be ready and available.

For robotic pancreatic surgery, the patient can be positioned supine with split legs and both arms untucked. Five robotic ports are placed in a linear fashion (Fig. 91.1). The robot can be docked on either side of the patient depending on the set-up in the operating room. Diagnostic laparoscopy is performed first to rule out metastasis or carcinomatosis or severe intraabdominal adhesions that would prohibit the planned robotic surgery.

Specific Surgical Considerations and Procedures

Distal Pancreatectomy +/– Splenectomy for the Resection of Cystic Neoplasms

Many surgeons elevate the left side of the body with a kidney rest or similar support to facilitate intraoperative exposure of the distal pancreas and spleen hilum.

The dissection starts by dividing the gastrocolic ligament to enter the lesser sac either from the pylorus towards the gastroesophageal junction or in a clockwise approach [29,30]. The stomach is retracted anterocephalad and the splenic flexure is mobilized. The retroperitoneum is incised along the inferior aspect of the pancreas in a medial to lateral fashion to expose the superior mesenteric vein (SMV) and create a retropancreatic tunnel.

It is our routine practice to preserve the spleen for patients without malignancy whenever possible. We favor the "Kimura-first" approach to preserve the splenic vessels with conversion to the Warshaw procedure (segmental resection of the splenic vessels and preservation of the left gastroepiploic vessels and the short gastric vessels for splenic blood supply) if the splenic vessels cannot be preserved for anatomic reasons [31]. Some surgeons advocate splenic artery isolation and control prior to pancreatic division [29].

The pancreas is divided using a robotic harmonic or linear stapler, depending on the size and thickness of the gland. Dividing the pancreas first will help with dissection of the root of the splenic artery and the confluence of the splenic vein and portal vein. The splenic artery and vein can be divided with a linear vascular stapler or after suture ligation, depending on the location of the tumor. If a pancreatic duct can be identified on the cutting surface of pancreas, it should be sutured closed with a 5-0 prolene [29]. If there is high suspicion for cancer, oncologic resection should be performed to achieve negative margin and adequate lymphadenectomy.

Once the pancreas is fully mobilized off the retroperitoneum, the specimen is placed in a specimen removal bag, and removed from the body through a Pfannenstiel or enlarged assisting trocar incision. Drains are placed per surgeon preference.

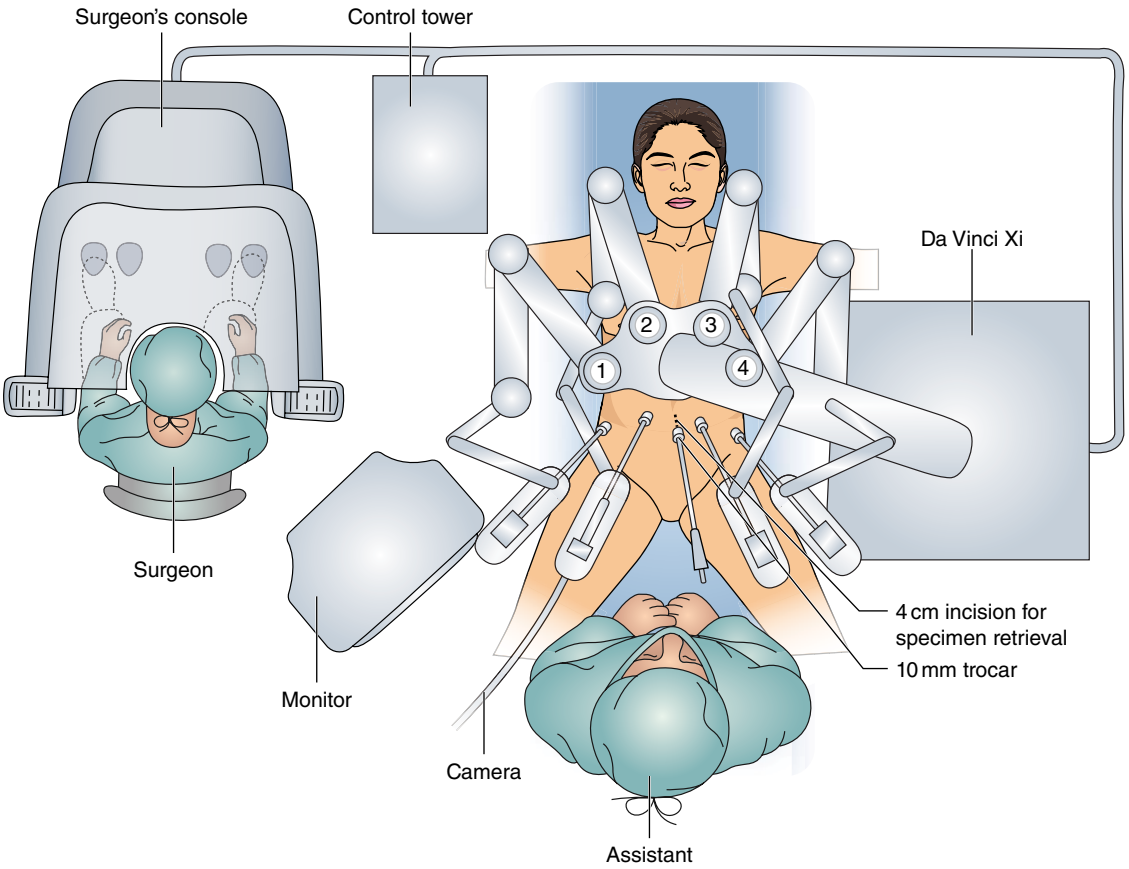
Pancreaticoduodenectomy for the Resection of Cystic Neoplasms

For robotic pancreaticoduodenectomy (RPD), the first step is entering the lesser sac by dividing the gastrocolic ligament as well as the right gastric and right gastroepiploic vascular bundles, followed by dissecting the posterior stomach off the anterior pancreas. At least two approaches for proceeding with the dissection have been published [4,32,33]. One starts with dissection of the porta hepatis by identifying and transecting the cystic duct, cystic artery, and common hepatic duct and exposing the portal vein and common bile duct (CBD). The other approach begins by mobilizing the duodenum, exposing the inferior vena cava (IVC) and transecting the proximal jejunum. Next steps include portal lymphadenectomy and identification and ligation of the gastroduodenal artery (GDA). The distal stomach is divided 5 cm proximal to the pylorus using the regular Endo GIA™ stapler from the assisting trocar.

Alternatively, the proximal duodenum can be divided just distal to the pylorus if a pylorus-preserving technique is favored. The portal (PV) and superior mesenteric veins (SMV) are identified.

The pancreas is divided with the robotic harmonic and the duct is cut with cold scissors. During dissection of the uncinate process away from the superior mesenteric artery (SMA) (Fig. 91.2), the inferior pancreaticoduodenal artery is identified and divided after being clipped with Hem-o-lok® clips (Teleflex Inc., Morrisville, NC, USA). The gallbladder is dissected to be included with the pancreaticoduodenectomy specimen.

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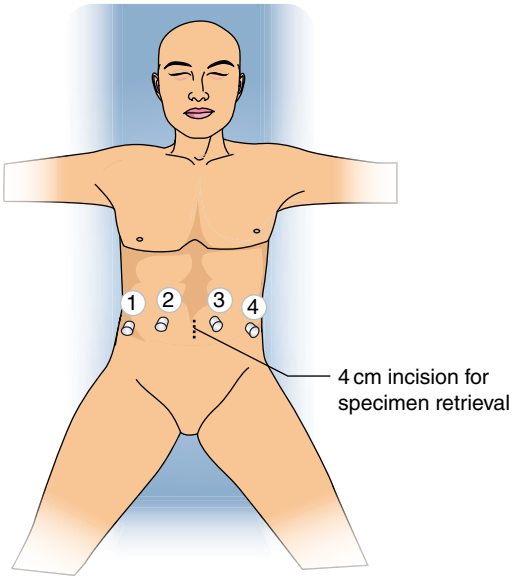


Figure 91.1 Linear placement of robotic ports for robotic-assisted pancreatectomy using the DaVinci Xi robotic surgery platform.

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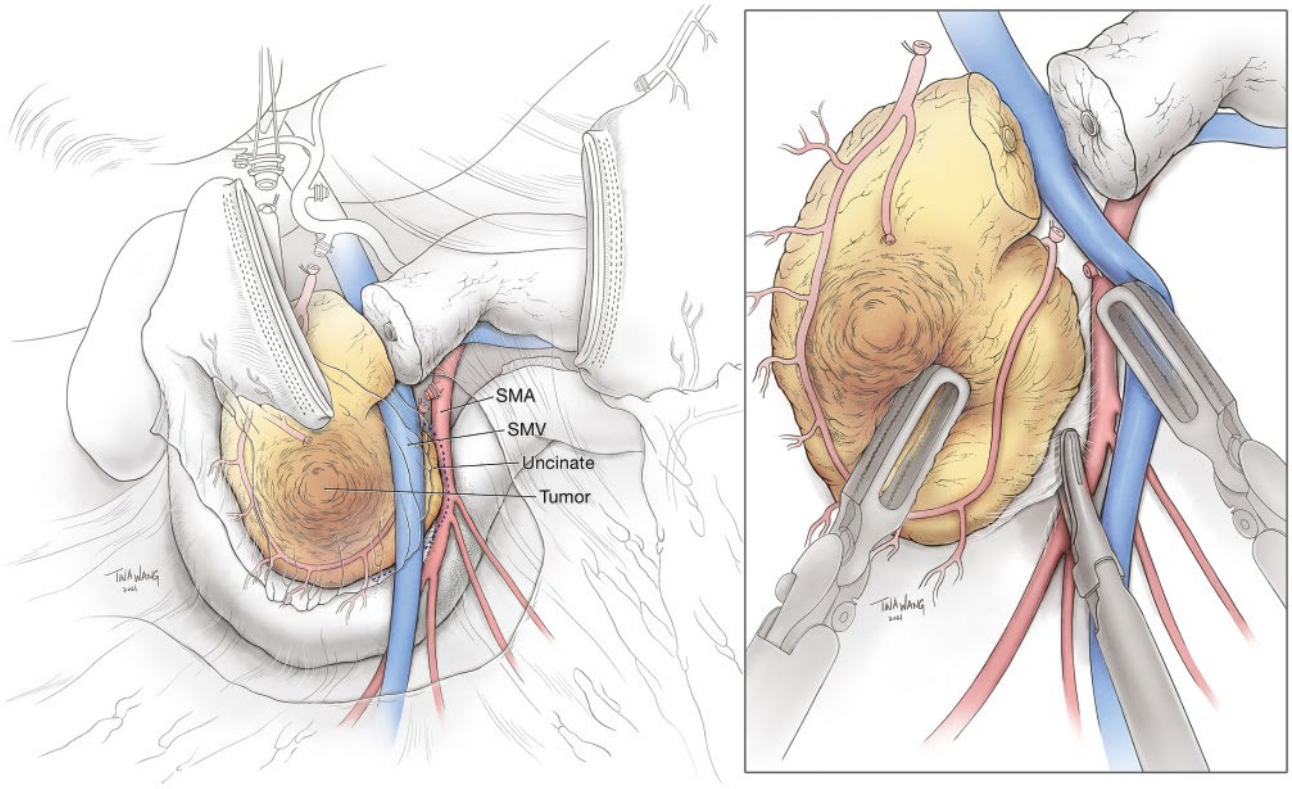


Figure 91.2 Graphic depiction of robotic separation of the uncinate from the SMA.

Robotic reconstruction proceeds conventionally in the same order as the open procedure: pancreaticojejunostomy (PJ), hepaticojejunostomy (HJ), and gastrojejunostomy (GJ). The robotic EndoWrist manipulation allows these technically challenging anastomoses to be performed with significant precision. Depending on the size and tissue quality of the pancreas, we typically perform a two-layer anastomosis for the PJ. The anterior and posterior layers are commonly sewn with either a 3-0 or 4-0 V-Loc™ running suture. The duct-to-mucosa technique is routinely performed with a 5-0 PDS interrupted suture with placement of a pediatric feeding tube as an internal PJ stent. Approximately 5–10 cm distal to the PJ, the HJ is created in an end-to-side fashion with two 4-0 V-Loc running sutures. An antecolic side-to-side anastomosis is commonly chosen for the GJ. This anastomosis can be created with a regular Endo GIA stapler from the assisting trocar.

We close the enterotomy with a 3-0 V-Loc running suture. The falciform ligament is routinely used to wrap the GDA stump so we can separate the GDA stump away from the surrounding PJ and HJ anastomoses. Drains are placed around anastomoses and the specimen is removed through the enlarged assisting trocar incision.

Cyst Resection/Enucleation

Parenchyma-preserving pancreatectomy including enucleation is not recommended for MD-IPMN, cyst <2 mm from the main pancreatic duct, multifocal cystic lesions, and lesions >4-6 cm in size given their higher rate of associated malignancy [34]. Briefly, indications for excision most commonly include isolated C-PanNET, BD-IPMN >2 mm distance from the main duct, and MCN lesions in the head and body that are less than 4 cm in diameter [34,35].

Exposure for lesions in the head [36] begins by opening the gastrocolic ligament to explore the head and neck of the pancreas whereas direct entry into the lesser sac is the preferred approach for lesions in the body/tail. Given the focused nature of enucleation, intraoperative ultrasound is highly recommended in order to confidently identify the lesion, rule out the presence of intramural nodules, assess its proximity to the main pancreatic duct, and minimize parenchymal dissection. It is our routine practice to check intraoperative frozen section pathology to confirm that the resected lesion is benign in nature. If there is cytologic concern for malignancy, we convert the parenchyma-preserving surgery to a formal oncologic resection [34].

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Once the tumor has been circumferentially dissected and removed, the resection bed is examined to achieve hemostasis. The use of indocyanine green fluorescence to visualize the biliary anatomy is critical to avoid unnecessary injury to the bile duct. If the main pancreatic duct is injured, it can be repaired with 6-0 PDS sutures with the placement of an internal stent. Some studies support the practice of closing the pancreatic parenchyma with absorbable suture after the enucleation has been completed, citing evidence that doing so may reduce the incidence of postoperative pancreatic fistula [34]. Many surgeons routinely leave drains to assess for postoperative pancreatic fistula. Recovery time is shorter, with similar morbidity and mortality for cysts that are enucleated with robotic assistance compared to open enucleation.

Central Pancreatectomy with Pancreaticogastrostomy or Pancreaticojejunostomy

Central pancreatectomy is a conservative approach for surgical resection of benign, premalignant and low malignant potential tumors of the pancreatic neck and proximal pancreatic body. First reported in the literature by Dr Oskar Ehrhardt of Prussia in 1907 and Dr Finney in the United States in 1910, the technique of central pancreatectomy and stump ligation/reconstruction has continued to evolve over the last century [37]. Pancreatic fistula was a frequent early complication as surgeons navigated the best way to reconstruct both the proximal and distal pancreatic stumps. Currently, lesions recommended for central pancreatectomy are <3 cm in size and located >5 cm from the tip of the pancreatic tail.

Exposure of the pancreas proceeds as previously described. Once the location of transection is identified, the pancreatic neck is transected proximally using a robotic harmonic or a linear stapler, depending on the size and thickness of the gland, followed by the distal transection encompassing the lesion. Use of intraoperative ultrasound is essential to confirm that the lesion of interest is bounded by the two transection planes. Once the specimen is resected, intraoperative frozen margin evaluation is used to evaluate the margins and ensure lack of tumor tissue.

Reconstruction options depend on surgeon's preference and how difficult it is to mobilize the distal pancreas. Pancreaticogastrostomy is possible and avoids the need for Roux limb creation whereas pancreaticojejunostomy is fashioned in the routine Roux-en-Y manner. Comparative studies of PG versus PJ after central pancreatectomy found that patients undergoing PG had fewer postoperative intraabdominal fluid collections, less delayed gastric emptying, fewer pancreatic fistulae, fewer readmissions and postoperative complications compared to those undergoing PJ [38,39]. However, a Cochrane review of 10 randomized studies found no difference between PG and PJ although the quality of available evidence was low [40].

Robotic-assisted central pancreatectomy has been reported since 2010 [41,42], along with a recent description of an end-to-end pancreatic anastomosis technique for benign and low malignant potential neoplasms [43].

Total Pancreatectomy

Total pancreatectomy is an option for patients with diffuse IPMN and multifocal PanNET [44]. Despite its technical and postoperative challenges such as brittle diabetes and absent exocrine function, total pancreatectomy can be considered in selected patients. Using the current Xi robotic platform, the entire gland can be dissected and mobilized for excision.

Surgical Outcomes

Estimated blood loss (EBL), conversion to open, operative time, postoperative mortality, postoperative pancreatic fistula (POPF), and Clavien-Dindo grade 3–5 complications (such as sepsis, anastomotic leak, delayed gastric emptying [DGE], fascial dehiscence, myocardial infarction, pleural effusion, pulmonary embolism, respiratory failure and small bowel obstruction) as well as length of stay (LOS) are the most commonly tracked general outcomes when comparing open pancreatic resection to robotic surgical resection [7,11]. For robotic pancreatic surgery specifically, EBL, LOS, splenic preservation in distal pancreatectomy, and conversion to an open procedure have been shown to be statistically lower for robotic versus laparoscopic pancreatic resection [7,21]. Other outcomes such as wound infection, DGE, sepsis, POPF, and 30- and 90-day mortality were all statistically equivalent while financial cost and operative time were increased using the robotic platform compared to traditional laparoscopy [7,21].

Though less relevant to cystic tumor resection, oncologic-specific outcomes have been found to be equivalent in both laparoscopic and robotic pancreatic tumor resection when compared to open resection [45,46].

Widespread Adoption

In a recently published worldwide survey on the opinions and use of minimally invasive pancreatic resection, 435 surgeons from 50 countries shared their perspectives on the utility of minimally invasive and robotic pancreatic procedures [47]. Ninety percent of respondents

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felt that minimally invasive pancreatic surgery was beneficial for patients, with 81% of respondents stating that they felt that robotic pancreatic resection was equivalent or superior to laparoscopic resection. Of the surgeons who felt that robot-assisted surgery was superior, the improved dexterity, superior ergonomics, and improved visibility were the top three reasons cited. Among surgeons surveyed, lack of training in minimally invasive and robotic techniques was cited most frequently as the reason for not routinely performing these procedures.

To address the need to train the next generation of surgical oncologists and hepatobiliary surgeons in robotic techniques, surgeon researchers from the University of Pittsburgh Medical Center studied and implemented a robotic surgery pilot curriculum. Results showed that time spent on the curriculum was associated with increased percent mastery as measured by virtual reality performance. However, lack of protected time and limited access to the robotic simulator were two of the primary reasons cited by trainees who were unable to fully participate in the curriculum as envisaged [48].

Conclusion

Robotic-assisted minimally invasive pancreatic surgery has been shown to be safe and effective with equivalent or improved outcomes compared to laparoscopic and open pancreatic surgery. Specific to resection of pancreatic cystic neoplasms, which are most commonly benign, a robotics approach is now favored at some institutions given its increased degrees of rotational freedom, improved ergonomics, and better visualization. Global use, proficiency, and safety of robotic-assisted pancreatic surgery have significantly evolved over the last decade and will continue to advance. Improved patient outcomes and the technical advantages of robotic-assisted surgery over more traditional approaches set it apart as the future of pancreatic surgery for selected indications.

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Duodenum-preserving Pancreatic Head Resection for Cystic Neoplasms of the Pancreatic Head: Indications and Limitations

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Introduction

Standard surgical treatments for benign cystic neoplasm of the pancreas are currently pancreatoduodenectomy (PD) for tumors of the pancreatic head and a left-sided pancreatic resection, either spleen-preserving or with splenectomy, for tumors in the body and tail. Many of the cystic neoplasms are benign and small (tumor size <3 cm) at the time of diagnosis. The question arises as to why a surgical treatment with radical resection of the tumor-bearing pancreas, associated with tissue loss of the duodenum, pancreatic head, extrahepatic biliary ducts and gastric antrum, is applied for a benign lesion. Parenchyma-sparing, local resection procedures for pancreatic tumors are recommended. They have the potential of low procedure-related postoperative morbidity and preservation of exocrine and endocrine pancreatic functions [1,2].

Classic Pancreatoduodenectomy or Local Extirpation for Cystic Neoplasms of the Pancreatic Head?

Currently, the standard treatment for a benign cystic neoplasm in the pancreatic head is the Kausch–Whipple resection or pylorus-preserving PD. PD is a multiorgan resection associated with considerable loss of functional pancreatic and extrapancreatic tissue. It is associated with the risk for severe postoperative complications, including pancreatic fistula, disruption of anastomosis, surgical side abscess, intraabdominal hemorrhage and delayed gastric emptying, requiring reoperation and/or reintervention in 5–12% of cases [3,4]. Hospital mortality after PD in high-volume institutions ranges betweeen 3% and 5%. However, 90-day mortality rates as high as 4–8% have been reported [4–6]. Postoperatively, new diabetes mellitus develops in 12–20% of patients after surgical resection of a benign or premalignant pancreatic tumor [7–11]. In total, 30–40% of preoperative diabetic patients display postoperatively an escalation to insulin-dependent diabetes [11]. Following PD, exocrine pancreatic functions are significantly reduced in 30–50% of patients [12]. The PD-inherent duodenectomy effects long-lasting dysfunction of secretion of gastrointestinal hormones and gastrointestinal motility disorders [13–16] (Table 92.1).

Duodenum-preserving total pancreatic head resection for benign pancreatic head tumors is associated with low postoperative surgery-related morbidity and a very low hospital mortality [18]. A metaanalysis published in 2015 on functional changes before and after DPPHR and PD revealed that exocrine and endocrine pancreatic functions following DPPHR were almost unchanged, in contrast to PD [8]. Despite the resection of pancreatic head tissue, total duodenum-preserving pancreatic head resection maintains endocrine functions, as reflected by HBA1c levels, glucose tolerance testing and the frequency of postoperative new-onset diabetes mellitus [8]. DPPHR preserves exocrine functions, whereas after PD there is often a significant decrease, requiring enzyme supplementation. The probability of developing endocrine and exocrine pancreatic insufficiency one year and five years following PD was found to be 32% and 85%, respectively [19].

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Table 92.1 Short- and long-term metabolic and functional sequelae after pancreatoduodenectomy (Whipple OP/PPPD).

	Results			
	Percentage	**Number**	**Period of follow-up**	**Reference**
New-onset diabetes mellitus	12.2% 16.4% 18% 16% 17%	4/32 pts[a] 28/171 pts[b] 24/135 pts[a] 28/178 pts[a] 17/76 pts[a]	2.8 years, median 3–6 months 25 months –3 months 1 year	J Gastrointest Surg 2012 [7] Pancreatology 2015 [8] J Gastrointest Surg 2015 [9] HBP 2016 [10] Br J Surg 2013 [11]
Impaired glucose tolerance	47.4%	36/76 pts[a]	1 year	Br J Surg 2013 [11]
Postoperative escalation of diabetes mellitus	48% 44.4%	21/44 pts[a] 19/42 pts[a]	25 months, median 2.8 years	J Gastrointest Surg 2015 [9] J Gastrointest Surg 2012 [7]
Exocrine pancreatic insufficiency	44% 43%	42 pts[b] 94/214 pts[a]	3–6 months –3 months	Pancreatology [8] HBP 2016 [10]
Failure of biliary anastomosis	14% cholangitis, jaundice,leak, stricture	49/352 pts[a]	Early, –3 months	HBP 2016 [17]
Reduced level of gastrointestinal hormones	Cholecystokinin Motilin Secretin	51 pts[a] 9 pts[a] 14 pts[a]	3–6 months 6 months 6 months	J Hep Bil Pancreat Sci 2000 [16] Surgery 1996 [14] Jpn J Gastroenterol Surg 1997 [13]

[a] Of the 1008 patients who had pancreatoduodenectomy, 44% suffered a benign tumor and 56% a cancerous lesion.
[b] PD for benign tumors only.

Rationale for Parenchyma-sparing Pancreatic Head Resection

The rationale for local resection of benign tumor in the pancreatic head includes: (i) preserving the duodenum, distal biliary ducts, and gallbladder as well as gastric antrum and pylorus; (ii) maintenance of the functional integrity of the duodenum regarding coordination of digestive, metabolic, and motility functions of the pancreas, liver, and stomach respectively; (iii) conserving a maximum of the pancreatic tissue; (iiii) protecting the patient against metabolic and nutritional, long-term GI tract disorders of glucose metabolism and disturbances of carbohydrate, fat, and protein digestion.

The goals of limited, local pancreatic head resection are: (i) application of a procedure with low risk for surgery-related severe complications and hospital mortality, superior to the standard surgical procedure; (ii) maintenance of patient quality of life; (iii) prevention of fear of tumor growth and of suffering from pancreatic cancer.

Duodenum-preserving Total Pancreatic Head Resection with or without Segmental Resection of the Peripapillary Duodenum and the Intrapancreatic Common Bile Duct

Tumor size and location, radiomorphologic type, and histopathology of the neoplasm determine whether a total or partial pancreatic head resection should be undertaken (Table 92.2).The surgical technique of DPPHR is almost identical to the standard PD procedure except for dissection of the pancreatic head along the duodenal wall and conservation of the intrapancreatic common bile duct (CBD), and in some instances resection of a 4 cm segment of the peripapillary duodenum. To preserve the duodenum and intrapancreatic CBD, a total pancreatic head resection (DPPHR-T) entails complete resection of the pancreatic head, including the uncinate process (Fig. 92.1).

Duodenum-preserving total pancreatic head resection with segment resection of the peripapillary duodenum comprises total pancreatic head extirpation and resection of the segment of the peripapillary duodenum and the intrapancreatic CBD, while preserving the pancreatic neck (Fig. 92.2). Three anastomoses need to be performed to ensure postoperative GI integrity. An excluded jejunal loop or the stomach is used for anastomosis of the left pancreas. Partial pancreatic head resection is performed by extirpating the tumor-bearing tissue from the pancreatic head or resecting of the uncinate process (Fig. 92.3). A duodenum-preserving total pancreatic head resection with preservation of the peripapillary duodenum and intrapancreatic CBD is associated with a higher frequency of local complications in the area of the peripapillary duodenum and intrapancreatic CBD [18].

Duodenum-preserving total or subtotal pancreatic head resection has been applied in two-thirds of patients with a monocentric cystic neoplasm of the head of pancreas (Table 92.3). Most total head resections have been

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Table 92.2 Indication for duodenum-preserving partial or total pancreatic head resection with or without resection of peripapillary segment of the duodenum for benign tumors of the pancreatic head and cystic and neuroendocrine neoplasms.

1. IPMN	**Symptomatic** MD or BD benign, monofocal tumors (histologically mild, moderate or severe dysplasia)
	Asymptomatic benign MD or BD neoplasm with pancreatic MD stenosis or tumor growth (worrisome feature)
	MT-IPMN alike MD-IPMN
	Asymptomatic, **monofocal** BD-IMPN, presence of mural nodule >5 mm or TM size >30 mm
2. MCN	**Symptomatic** neoplasm (histologically mild, moderate or severe dysplasia)
	Asymptomatic, benign neoplasm (size >3 cm) with pancreatic MD compression/stenosis or mural nodule or tumor growth (worrisome feature)
3. SPN	**Symptomatic** neoplasm, surgery at any age
	Asymptomatic neoplasm (size ≥2 cm) (children)
	Neoplasm + local lymph node enlargement
4. SCA	**Symptomatic** neoplasm with pancreatic MD compression
	Asymptomatic neoplasm (size >4 cm)
5. Neuroendocrine tumor	**Symptomatic** nonfunctional, benign neoplasm
	(G_1/G_2/Mitosis <2–20/Ki-67 <3%/3–20%)
	Functional, benign insulinoma
	Asymptomatic, nonfunctional tumors, size 1.5–2 cm, growing during observation period
	Asymptomatic, nonfunctional tumor size >2 cm

BD, branch duct; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MD, main duct; MT, mixed type; SCA, serous cystadenoma; SPN, solid pseudopapillary neoplasm.

performed for an intraductal papillary mucinous neoplasm (IPMN), followed by serous cystadenoma (SCA); in one-third of cases a partial, subtotal head resection was performed, whereas in two-thirds of cases a total, parenchyma-sparing head resection was executed. Approximately 10% of the cystic neoplasms resected by local head resection have been reported to contain high-grade dysplasia. The procedure-related morbidity included severe complications (Clavien–Dindo >3); POPF B+C; reoperation; rehospitalization; 90-day mortality. After a mean follow-up time of 62 months, recurrence was observed in 2.9% of cases (Table 92.4).

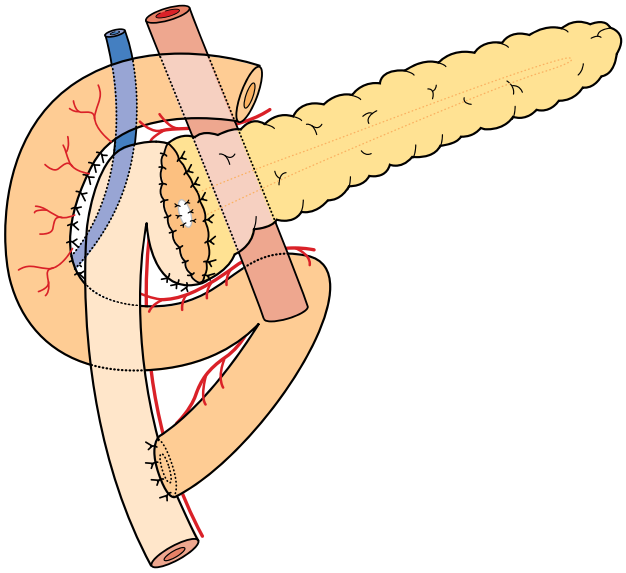


Figure 92.1 Duodenum-preserving total pancreatic head resection conserving the duodenum and the CBD.

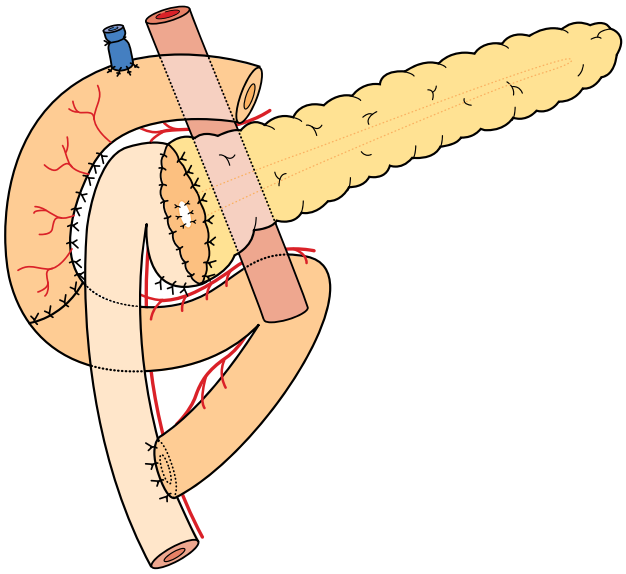
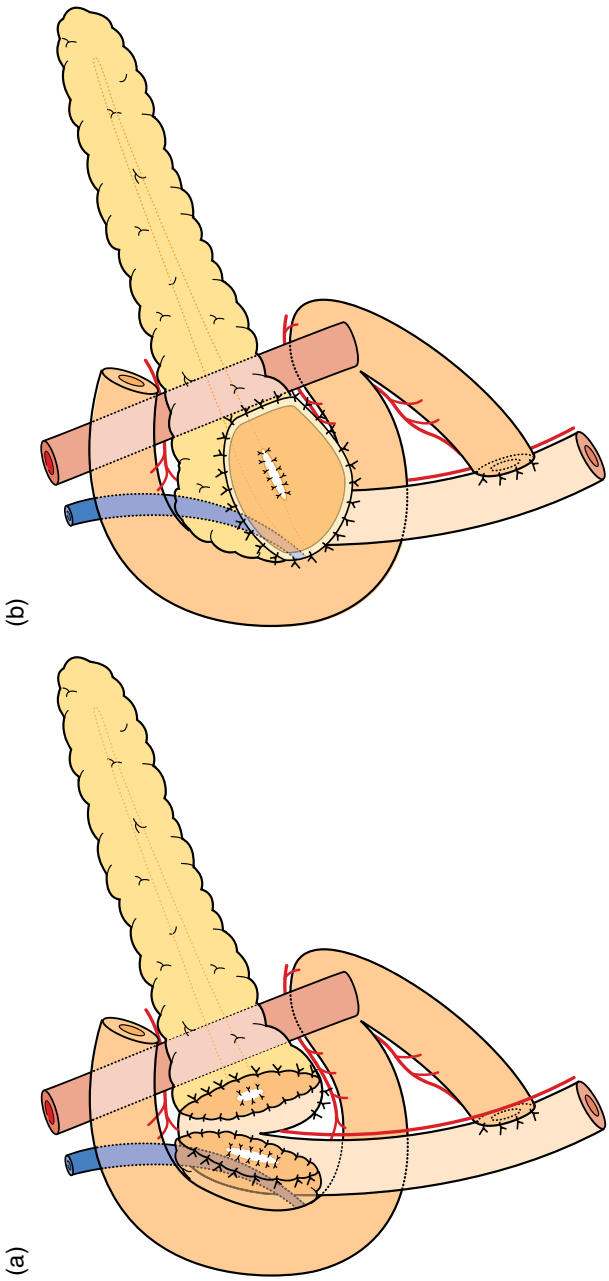


Figure 92.2 Duodenum-preserving total pancreatic head resection including resection of peripapillary duodenum and CBD.

Conclusion

For surgical treatment of benign and low-risk cystic neoplasms of the pancreatic head, a local, parenchyma-sparing head resection offers major benefits to the patient by maintaining quality of life. The advantages of duodenum-preserving total or partial pancreatic head resection compared to PD are a low surgery-related early postoperative morbidity and a very low hospital mortality. Local pancreatic head resections are

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associated with almost complete conservation of endocrine and exocrine pancreatic functions. The risk of recurrence after local head resection of cystic neoplasms, including high-grade dysplasia, is very low provided frozen section investigation is used to exclude an advanced cancer.

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Table 92.4 Early postoperative morbidity of 702 patients following DPPHR for benign neoplasms (review data).

Type of DPPHR	Patients N	Tumor size cm	DGE[a] n/N %	PPH n/N %	SSI/Abscess[a] n/N %	POPF B+C[a] n/N %	Reoperation[a]	Hospital mortality	Length of hospital stay days, mean	Rehospitalization[a]
DPPHR partial head resection	214	2.97±0.1[b]	10/149[c] 6.7%	8/183 4.1%	6/154 3.9%	10/149 6.7%	7/172 4.1%	0/214[d] 0%	17.2	6/89[a] 6.7%
DPPHR total/near-total head resection	488	3.7±0.62[b]	53/453[c] 11.7%	23/396 5.8%	19/376 5.8%	20/197 10.4%	13/360 3.6%	5/488[d] 1.02%	25.7	9/145[a] 6.2%

[a] Not all cohort studies reported postoperative outcome data.
[b] Tumor size p <0.001.
[c] DGE p <0.012.
[d] Hospital mortality p = 0.330.
DGE, delayed gastric emptying (definition 2007 [20]); POPF, postoperative pancreatic fistula (definition 2005 [22]); PPH, postpancreatectomy hemorrhage (definition 2010 [21]); SSI, surgical site infection/intraabdominal abscess.
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Pancreatic Middle Segment Resection of Cystic Neoplasms: Indications and Limitations

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Introduction

Pancreatic middle segment resection (PMSR), also known as the Dagradi–Serio–Iacono operation, central pancreatectomy, middle pancreatectomy, medial pancreatectomy, intermediate pancreatectomy, and limited conservative pancreatectomy, is a parenchyma-sparing operation that is indicated for the removal of benign or low-grade malignant tumor of the isthmus and proximal part of the pancreas body (Fig. 93.1) [1]. Compared to pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), PMSR is associated with a lower risk of postoperative pancreatic exocrine and endocrine insufficiency. In addition, this type of pancreatic resection spares the spleen, preventing infective and thromboembolic complications, and also spares the upper digestive and biliary tract, which is not possible in PD, avoiding digestive disorders.

The first PMSR was performed in 1982 by Dagradi and Serio resecting a neuroendocrine tumor (insulinoma) located in the neck of the pancreas and was reported few years later in the Enciclopedia Medica Italiana [2]. Subsequently, Iacono validated PMSR using functional endocrine and exocrine tests and popularized it all over the world [3]. These findings were included in several international reports demonstrating that there is almost no postoperative impairment of endocrine and exocrine functions when appropriate indications and technique are respected [2–4]. In recent decades, several authors have reported clinical series on patients who underwent PMSR, demonstrating that this operation has become a standardized technique commonly applied in the surgical treatment of pancreatic diseases [3,4]. Currently, PMSR is performed worldwide either by traditional open surgery [2–9] or by minimally invasive approaches [2,4,10–12].

Indications

Pancreatic middle segment resection can be performed for low-grade malignant or benign lesions between 2 and 5 cm in size, where the close relationship between the lesion and the main pancreatic duct (MPD) prevents a simple enucleation because of the risk of duct injury and consequently high-output and prolonged pancreatic fistula (PF). The main indication concerns cystic neoplasms, but PMSR can also be performed for neuroendocrine tumors or other nonneoplastic lesions.

The indications are summarized as follows:

- neoplastic cystic lesions as symptomatic serous cystadenoma (see Fig. 93.1), mucinous cystadenoma, solid cystic pseudopapillary tumors, selected cases of intraductal papillary mucinous neoplasm (IPMN)
- nonneoplastic cysts such as simple lymphoepithelial or hydatid cysts
- small neuroendocrine tumors (especially functioning)
- focal chronic pancreatitis with isolated short stenosis of the MPD
- solitary metastases located at the pancreatic neck (i.e., from kidney cancer).

Contraindications

The contraindications are as follows.

- A short distal remnant pancreas stump (less than 5 cm in length).
- Atrophy of the body–tail of the pancreas.
- Diagnosis of malignant tumors (i.e., pancreatic ductal adenocarcinoma).

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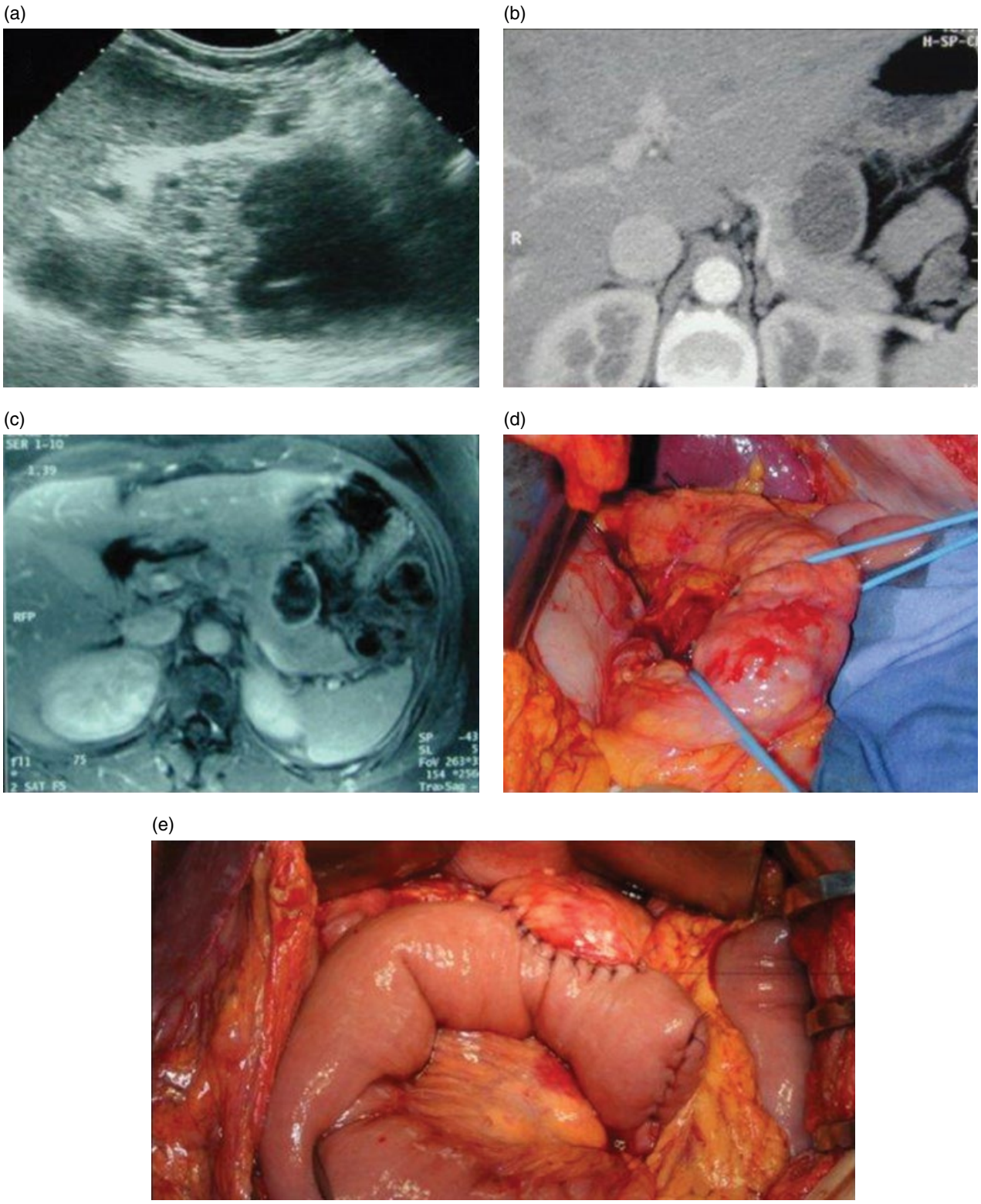


Figure 93.1 The case of a young patient with a symptomatic pancreatic serous cystadenoma. (a) Ultrasonography, (b) computed tomography, and (c) magnetic resonance imaging showing a cystic mass at the neck of the pancreas. (d) Intraoperative evidence of lesion localized to the pancreatic neck. (e) End of the reconstructive phase of PMSR. The cephalic stump was sutured and the distal stump was anastomosed by duct-to-mucosa pancreaticojejunostomy with a Roux-and-Y jejunal loop.

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- Evidence of tumors originating from nearby organs and infiltrating the pancreas.
- Diffuse or focal chronic pancreatitis not involving the central part of the gland.
- The presence of vascular variant type III according to Mellière and Moullé, where the arterial supply for the body–tail of the pancreas is maintained exclusively from the transverse pancreatic artery (left branch of the dorsal pancreatic artery).

Technique

The PMSR consists of a resection phase that ends with the resection of the central pancreatic segment (isthmus and/or proximal body) (Fig. 93.1d) and a subsequent reconstructive phase which involves suturing the MPD of the cephalic stump and performing the digestive anastomosis with the distal stump (Fig. 93.1e) [1,3,13,14].

Resection phase

Open PMSR requires a midline incision. Access to the lesser sac is achieved by dividing the plane of fusion between the omentum and the transverse colon (the authors' preferred procedure) or through the section of the gastrocolic ligament. When the pancreatic gland is widely exposed, the surgeon can proceed with the pancreatic ultrasonography to better identify the extent and anatomic relationships of the lesion and/or to guide fine needle biopsy in cases of uncertain preoperative diagnosis.

After the proximal section of the pancreatic isthmus, the splenomesenteric axis, and the splenic vein and artery are dissected free from the posterior surface of the gland. The surgeon should be aware that the presence of a large dorsal pancreatic artery raises a high index of suspicion that the left pancreatic blood supply is exclusively maintained by the transverse pancreatic artery. This vascular variation is, as previously mentioned, a clear contraindication to PMSR. In fact, section of the artery would lead to necrosis of the pancreatic body–tail. Occasionally, it is necessary to isolate and mobilize the common hepatic artery to divide those branches originating from it (i.e., dorsal pancreatic artery) that supply the central pancreas. The extent of PMSR is limited on the right by the gastroduodenal artery and on the left by at least 5 cm of normal pancreatic remnant.

After stay sutures are placed in the superior and inferior pancreatic margins to indicate the proximal and distal limits of division, the pancreatic cephalic end is transected using either a scalpel or a stapler. For the distal side, the resection should be performed with a scalpel in order to avoid damage to the splenic artery or vein. The resected specimen is then sent to the pathologist to verify that the resection margins are adequate and to confirm the diagnosis by frozen sections. In case of intraoperative diagnosis of malignant tumor, the operation has to switch to PD or DP (splenopancreatectomy) with lymphadenectomy. Hemostasis of the two raw surfaces is achieved with interrupted nonabsorbable stiches, and the integrity of the main pancreatic duct on the distal stump is preserved by the insertion of a small catheter. In the presence of IPMN, a pancreatoscopy can be performed, just after resection, through the MPD in both stumps to rule out other ductal lesions.

Reconstructive phase

The MPD of the cephalic stump, when not stapled, is sutured selectively with figure-of-eight nonabsorbable stitches; the pancreatic stump is sutured along the entire length with a row of interrupted and overlapping mattress-type stitches.

The digestive anastomosis of the distal stump can be performed using several techniques commonly applied in PD. Roux-en-Y pancreaticojejunostomy can be conducted in different ways: end to end (simple or telescopic invagination), end to side, duct to mucosa, and side to side (Puestow procedure or Partington–Rochelle technique if the duct of Wirsung is dilated as in chronic pancreatitis). Some authors also perform an anastomosis of the cephalic stump using the same jejunal loop (double pancreaticojejunostomy). Pancreaticogastrostomy is usually performed by implantation of the open end of the pancreas directly into the gastric pouch through a 2–3 cm opening in the posterior surface.

Another type of reconstruction is the end-to-end anastomosis of the MPD and parenchyma, with or without stent placement for internal or external pancreatic juice drainage [15]. In the past, this reconstruction was used to repair traumatic pancreatic neck transections with minimal loss of parenchyma. Notably, the MPD of most patients who undergo PMSR is too thin (not dilatated) to confidently perform duct-to-duct anastomosis. The posterior and anterior parts of the anastomosis were closed with stitches that were tied one after another. To avoid any damage to the duct of Wirsung, a small catheter was introduced before the stitches were inserted and was removed just prior to the stitches being tied. Currently, we prefer to perform a duct-to-mucosa leaving a plastic transanastomotic catheter (Fig. 93.1e).

The operation concludes with the end-to-side jejunojejunostomy with a double layer of absorbable stitches, approximately 50 cm distal to the pancreatic anastomosis. Lastly, two soft drains are placed; one close to the proximal pancreatic stump and the other close to the digestive anastomosis.

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Minimally invasive approach

In the laparoscopic procedure, the patient is placed in supine or reverse Trendelenburg position, with the surgeon standing between the patient's legs. Four trocars are placed under direct scope vision [12]. In the robotic-assisted technique, patient position is similar but the surgeon operates from the console. Four ports are placed for the robotic arms and an additional port is inserted in the left lower quadrant and used for assistant-surgeon and Endo GIA^{TM} application [16]. The minimally invasive approach follows the same steps as the open technique. After completing the dissection phase, the resected specimen is placed in an entrapment bag and delivered through the extension of the umbilical incision.

Results

Recent advances in diagnostic imaging have resulted in an increased incidence of incidental benign, low-grade, small-sized tumors of the pancreas, some of which require surgical resection. Especially in young and middle-aged patients with long life expectancy, PMSR is an excellent alternative to conventional pancreatectomies as it preserves healthy functional pancreatic parenchyma and accordingly pancreatic endocrine and exocrine function, improving quality of life after surgery. Nevertheless, PMSR is still performed less frequently than PD or DP, probably because the operation is technically demanding and requires specific surgical experience. Nowadays PMSR is mainly performed in specialized centers by either open or minimally invasive approach.

In the last decade, minimally invasive pancreatic surgery has undergone fast development even if most of the cases are still performed by an open approach. In series reporting at least 50 patients who underwent PMSR by the open approach [9,17–22], the severe complication and clinically relevant pancreatic fistula (PF) rates were 12–36% and 8–44% respectively, while the incidences of endocrine and exocrine insufficiencies were 0–15% and 0–10%, respectively (Table 93.1). The

Table 93.1 Outcomes of pancreatic middle segment resection performed by open surgery in series that report at least 50 cases.

	Cases (N)	Operative time (min)	EBL (mL)	Complication (Dindo ≥3)	PF (grade B-C)	Reoperation	Readmission	Mortality (90-day)	Endocrine insufficiency	Exocrine insufficiency
Crippa et al. 2007	100	248 (± 60)	311 (± 335)	10%[a]	17%	0%	16%	0%	4%	5%
Adham et al. 2008	50	201 (110–360)	–	26%	8%	12%	–	0%	0%	–
DiNorcia et al. 2010	73	254 (213–351)	400 (225–675)	12%	16%	3%	12%	0%	14%	10%
Iacono et al. 2013	656[b]	–	–	–	19%	4%	–	1%	5%	10%
Goudard et al. 2014	100	245 (212–288)	250 (100–300)	18%	44%	6%	6%	3%	7%	6%
Chen et al. 2017	50	193 (160–230)	200 (95–300)	18%	36%	4%	2%	0%	–	–
Paiella et al. 2018	116	265 (± 62)	293 (± 120)	36%	27%	8%	7%	0%	8%	0%
Lee et al. 2020	55	215 (± 5 6)	–	24%	24%	–	4%	0%	15%	–

[a] Only complication requiring interventional radiology procedure.
[b] Review.
Categorical variables are expressed in numbers or percentages. Continuous data are expressed as median values and range or as mean value and standard deviation.
EBL, estimated blood loss; PF, pancreatic fistula.

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type of surgery does not influence morbidity and mortality, nor the long-term outcomes. However, compared to open PMSR, laparoscopic PMSR is associated with lower estimated blood loss, reduced postoperative pain, faster recovery, and better quality of life [23] while robotic PMSR seems to be associated also with reduced operative time and clinical PF rates, according to the largest randomized controlled trial published so far [20]. An international consensus on robotic pancreatic surgery states that robotic PMSR is feasible and safe, but there is still little evidence to support the better short-term outcomes of robotic PMSR versus open resection [24]. PMSR outcomes by laparoscopic [25–28] and robotic [20,29,30] approach are summarized in Table 93.2. Studies comparing outcomes of laparoscopic versus robotic approach are lacking.

Robotic technology allows wristed articulation of the surgical instruments, three-dimensional high-definition visualization with variable magnification, and computer-aided dexterity to enhance the precision of placing fine sutures in the pancreatic duct. These benefits may help the surgeon to perform more complex laparoscopic procedures, especially for pancreatic anastomosis.

There are three types of reconstruction for distal pancreatic stump: pancreatogastrostomy (PG), pancreaticojejunostomy (PJ), and end-to-end pancreatic anastomosis. PJ is the most commonly performed reconstruction despite involving a Roux-en-Y jejunal anastomosis [4]. In contrast, PG does not require bowel mobilization and division and thereby avoids any increase in operative time, the interruption of intestinal continuity and potential leaks. PG is easier and faster for just one anastomosis (slightly preferred in minimally invasive approaches [31]) but is associated with delayed oral feeding, prolonged hospital stay, and long-term impairment of exocrine pancreatic function [23]. Lastly, end-to-end pancreatic anastomosis has the advantage of maintaining the integrity of the gastrointestinal tract and reducing operative time, but involves complex suturing of the Wirsung duct stumps, which can be very small or of different caliber, and extensive mobilization of the pancreatic stumps which need to be moved closer [15].

The best type of pancreatic anastomosis is still debated; the authors recommend using the procedure with which the surgeon is most confident. Thorough patient selection is essential for the benefits of PMSR to outweigh the possible complications [4].

Although PF is the most frequent complication in PMSR, only a minority of patients show a clinically relevant PF according to the International Study Group on PF (ISGPF) classification. This is due to the fact that there are two pancreatic stumps, and the anastomosis is usually performed on a soft pancreas with a nondilated main pancreatic duct. Interestingly, according to the published reviews [4,31], less than 5% of patients undergo reoperation for severe complications (PF, bleeding, intraabdominal collections, pancreatitis of the distal stump, bowel obstruction) and the mortality rate is below 1%. These results suggest that PMSR is a safe and feasible procedure. PMSR compared to DP showed no significant differences in reexploration, mortality, and clinically relevant PF, whereas PMSR was associated with lower intraoperative blood loss, higher morbidity, longer operating times, and longer hospital stay.

Regarding long-term outcomes, PMSR is an excellent alternative to DP as it preserves pancreatic endocrine and exocrine function to avoid new onset of diabetes mellitus and pancreatic exocrine dysfunctions in almost all patients in the long term. In fact, following left-sided pancreatic resection, exocrine dysfunction was observed in 12–18% of patients while new-onset diabetes or worsening preexisting diabetes was observed in 14–39% of patients [32,33]. PMSR, instead, shows significantly lower rates of overall endocrine and exocrine insufficiency, at 0–15% and 0–10%, respectively (see Table 93.1).

By following the right indications and careful selection of patients, PMSR can be considered the treatment of choice and not just an alternative to DP.

Conclusion

Pancreatic middle segment resection is a parenchyma-sparing surgery that preserves the functional tissue of the pancreatic body–tail where there are numerous islet cells releasing hormones and acinar cells producing digestive enzymes. Therefore, pancreatic exocrine and endocrine functions are usually maintained. Furthermore, PMSR avoids the infective and thrombotic complications commonly associated with splenectomy and could achieve a better quality of life after surgery, especially in young patients with long life expectancy. Despite the high risk of PF, probably due to the two pancreatic stumps, PMSR has demonstrated low rates of clinically relevant PF and reoperation. In addition, the mortality rate is almost nil. Hence, PMSR is a feasible and safe technique (either open or minimally invasive) that should be included in the armamentarium of the modern pancreatic surgeon. The laparoscopic approach appears to reduce hospital stay by promoting early recovery while a robotic-assisted technique may stimulate the surgeon to perform complex procedures more easily, effectively, and precisely. Nevertheless, careful case selection, accurate pre- and intraoperative evaluation of the lesion, and experience in pancreatic surgery are recommended to achieve optimal results.

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Table 93.2 Outcomes of pancreatic middle segment resection performed by minimally invasive approaches in series that report at least 20 cases by laparoscopic or 10 cases by robotic approach.

	Cases (N)	Operative time (min)	EBL (mL)	Complication (Dindo ≥3)	PF (grade B-C)	Reoperation	Readmission	Mortality (90-day)	Endocrine insufficiency	Exocrine insufficiency
Laparoscopy										
Song et al. 2015	26	350 (± 63)	477 (± 388)	15%	19%	2%	0%	0%	8%	–
Dokmak et al. 2017	35	191 (± 45)	111 (± 146)	–	23%	11%	3%	0%	–	–
Chen et al. 2019	30	266 (± 48)	98 (± 78)	30%	23%	20%	–	0%	–	–
Cai et al. 2021	20	198 (± 31)	50 (20–200)	20%	40%	5%	–	0%	0%	15%
Robot										
Zhang et al. 2015	10	175 (± 45)	113 (± 107)	10%	30%	0%	0%	0%	10%	0%
Chen et al. 2017	50	160 (120–210)	50 (50–100)	14%	18%	2%	2%	0%	–	–
Shi et al. 2021	123	158 (± 61)	86 (± 91)	9%	34%	4%	–	1%	4%	1%

Categorical variables are expressed in numbers or percentages. Continuous data are expressed as median values and range or as mean value and standard deviation.
EBL, estimated blood loss; PF, pancreatic fistula

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Tumor Enucleation for Cystic Neoplasms of the Pancreas: Indications and Limitations

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Introduction

Cystic neoplasms of the pancreas are increasingly diagnosed due to improvements in modern imaging modalities. Nearly 3% of all patients undergoing abdominal computed tomography (CT) and up to 50% of those undergoing abdominal magnetic resonance imaging (MRI) will have an incidentally detected pancreatic cystic lesion [1,2]. This number varies significantly according to the size of the cyst and the threshold of radiologists to report them. A recent prospective study found the prevalence of incidental pancreatic cysts >1 cm in size to be 6% in the studied population, and cysts >5 mm in size to be 37% [3]. While many cysts are benign, most carry some risk of malignancy, and all have the potential to cause symptoms.

Diagnosis is often unclear despite multiple strategies including CT, endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and fine needle aspiration (FNA) with cytology and cyst fluid biochemical and DNA analysis. A definitive diagnosis may be difficult without surgical resection. Treatment of these lesions must therefore balance the diagnostic and therapeutic benefit against the significant morbidity and potential mortality of surgical resection. If patients require surgical treatment, techniques associated with lower morbidity must be considered. In select cases, cyst enucleation is an effective option with lower morbidity and mortality than pancreatic resection [4–6].

Indications

A major challenge of pancreatic cyst enucleation is appropriate patient selection. Careful characterization of the cyst is necessary to determine if an indication exists for enucleation. Selection can be done with a thorough preoperative evaluation. The first step is cross-sectional imaging (CT or MRI-MRCP with thin slices). Additional diagnostic tests may help in diagnosis and oncologic risk stratification, including EUS with FNA for cyst fluid cytology and biochemical/DNA analysis, as well as ^{68}Ga-DOTA-PET/CT for pancreatic neuroendocrine tumors (PNETs). Figure 94.1 demonstrates MRCP of a branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) eligible for cyst enucleation. Radiographic and biologic work-up must take place in order to rule out malignancy, vascular involvement, and metastases, as these are all contraindications to enucleation [7].

Many lesions amenable to resection also may be eligible for enucleation. Patients who are symptomatic or have signs of malignant/premalignant pancreatic lesions generally should undergo surgical resection. Symptomatic pancreatic cysts should be resected, not only to alleviate symptoms but also due to the increased risk of malignancy associated with symptomatic lesions [8]. If evidence strongly suggests the lesion is malignant, an oncologic resection should be performed without consideration of enucleation. Findings consistent with malignancy include lymphadenopathy, mural nodules, and solid components [7]. Lesions with uncertain diagnosis or lesions that are premalignant may be appropriate

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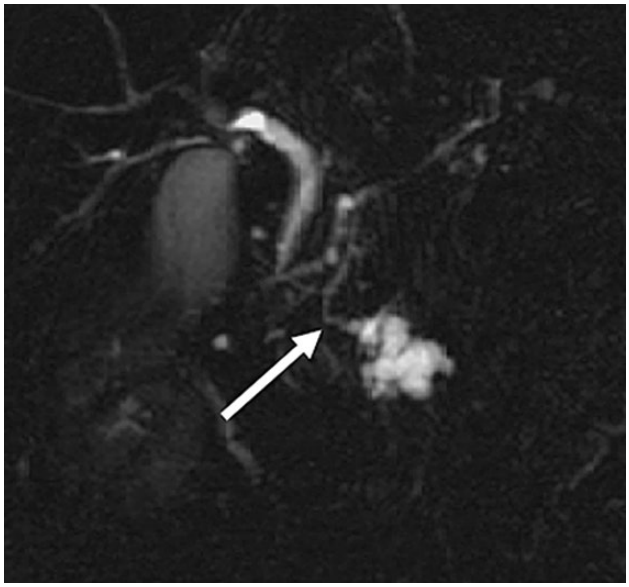


Figure 94.1 MRCP of a BD-IPMN of the uncinate process eligible for cyst enucleation. The arrow identifies the communicating duct. *Source:* Turrini O et.al (2011) / Reproduced with permission from Elsevier.

for cyst enucleation. When no oncologic need exists for traditional pancreatic resection, enucleation can avoid unnecessary sacrifice of pancreatic parenchyma, minimizing the risk of pancreatic exocrine and endocrine insufficiency [5,6].

Although pancreatic neuroendocrine tumors (PNET) are the most common lesion removed via cyst enucleation, many other cyst types are suitable for this method of resection [9]. These include, but are not limited to, mucinous cystic neoplasms (MCN), BD-IPMN [10], serous cystic neoplasms (SCN), and solid pseudopapillary neoplasms (SPN) [6,11]. Table 94.1 lists criteria for enucleation based on specific pathology. Cyst enucleation is considered the procedure of choice for most functional PNETs with a low risk for malignancy as long as technically feasible [7,9]. Nonfunctional PNETs should be enucleated if less than 2 cm and N0M0.

Table 94.1 Indications for pancreatic cyst enucleation.

Pathology	Criteria
Nonfunctional PNET	<2 cm, N0M0
Functional PNET	If technically feasible with low risk for malignancy
MCN	If likely benign; <4 cm; no mural nodules
BD-IPMN	Rapidly increasing size; symptomatic
SCN	Only if symptomatic
SPN	If technically feasible and no evidence of malignancy

BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PNET, pancreatice neuroendocrine tumor; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm.

The Sendai and Fukuoka guidelines address indications for surgical resection of MCN and BD-IPMN [8]. MCN should be removed and may be enucleated if they appear benign on imaging, are less than 4 cm, and do not contain mural nodules. The indications for resection of BD-IPMN are more controversial. These lesions are often observed, but may require resection if symptomatic or high-risk features exist such as rapidly increasing size, high-grade atypia, associated main duct dilation (early main duct involved IPMN), and mural nodules [8]. Symptomatic BD-IPMNs or those that are increasing in size but without other high-risk features may be considered for enucleation if technically feasible. If features suspicious for malignancy are present, a formal resection should be performed.

Because SCNs carry a very low risk of malignancy, they are generally only resected if the diagnosis is in doubt or if symptomatic. However, if they are allowed to grow, enucleation may no longer be technically possible. Thus, the decision for surgical management should be made on an individual basis.

If surgical resection is indicated, assessment of patient fitness must be undertaken. This assessment includes evaluation of comorbid conditions, nutritional status, and psychosocial health. Patients should be assessed for fitness for both enucleation and formal resection since the operation may convert to resection based on intraoperative findings. Fitness is not only an important factor in determining patient tolerance of the procedure, but also in determining life expectancy. Patients with limited life expectancy may be more likely to die of alternate diagnoses than cyst-related causes. In this case, a surgical procedure would not extend their life and would put them at undue risk of surgical complications.

Contraindications

Table 94.2 lists the major contraindications to pancreatic cyst enucleation. Patients with known or suspected malignancy should not undergo enucleation and instead should have an oncologic resection with negative margins and lymph node dissection [9,12]. Diagnosis of malignancy is based on symptoms, radiographic images, cytopathology, and DNA profile. Despite these multiple diagnostic tools, a definitive diagnosis of malignancy is often difficult to achieve preoperatively. In those cases, consultation with experts and the patient is necessary to determine the best course of action.

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Table 94.2 Contraindications to pancreatic cyst enucleation.

Suspected malignancy
Pancreatic duct involvement/close proximity
Location in tail
Large size
Multifocality
Poor patient fitness

The surgeon may elect to begin the operation as a parenchyma-sparing enucleation until they encounter evidence of malignancy intraoperatively. Malignant cysts can be difficult to dissect due to adherence to surrounding parenchyma.

Whether or not the surgeon suspects malignancy, intraoperative frozen section pathology confirmation of invasive cancer necessitates conversion to formal pancreatic resection.

The lesion's proximity to the main pancreatic duct is an important technical consideration for enucleation. If the cyst involves the main duct, enucleation cannot be achieved without transection of the duct and therefore is contraindicated [12]. Additionally, cysts involving the main duct, specifically main duct IPMN (MD-IPMN), are at a greater risk of conversion to invasive cancer and thus require formal resection [8]. Enucleation also may be contraindicated based on the cyst's close proximity to the main duct. Risk of injury and subsequent pancreatic fistula is greatly increased (70%) when the cyst is within 2 mm of the duct [13,14]. Distance of 2–3 mm between the cyst and the main pancreatic duct is safe for cyst enucleation and can be determined with preoperative imaging such as MRCP and EUS [15,16]. During surgery, this safe distance is confirmed with intraoperative ultrasound (IOU).

Location of the cyst within the pancreas is also important when considering enucleation. If located in the tail of the pancreas, enucleation does not save much parenchyma compared to distal pancreatectomy and thus would offer no benefit.

The mean size of enucleated pancreatic cysts is 2.4 cm [9]. This relatively small size is due to the relationship between larger size and higher likelihood of malignancy [8]. The size at which enucleation may be safely performed is controversial and differs based on pathology. Four centimeters is arguably the cut-off at which enucleation should be performed due to increased risk of recurrence of lesions greater than 4 cm [9,12,15]. Data suggest that this size limit may be increased to 6 cm in SCN and MCN without increasing recurrence, morbidity, or mortality [17]. Multifocality is a relative contraindication due to an incremental risk of pancreatic fistula with each enucleation. Depth of the cyst is also a relative contraindication for enucleation. More extensive dissection is required for deeper lesions. making their dissection more tedious and, at times, making formal resection the more appropriate choice [11,16,18].

Surgical Technique

Pancreatic cyst enucleation can be performed minimally invasively (laparoscopically/robotically) or open, based on surgeon preference. Minimally invasive enucleation has been more commonly performed in recent years and is associated with shorter operative and recovery times, less blood loss, and similar morbidity and mortality as open enucleations [14,19,20]. The steps of the procedure remain the same regardless of whether minimally invasive or open techniques are used.

After entrance into the abdomen, the liver, hemidiaphragms, and all peritoneal surfaces are surveyed for occult metastatic disease. Intraoperative ultrasound is used to identify intraparenchymal metastases, thus completing the survey of the liver. The pancreatic cyst is then exposed using the Kocher maneuver for head lesions, and entrance into the lesser sac for body and tail lesions. Ultrasound can again aid in both locating the cyst and careful characterization of the cyst. The distance between the cyst and the main pancreatic duct can be calculated to determine the safety of performing enucleation. Concerning features such as mural nodules and solid components can be identified with intraoperative ultrasound. After ultrasound evaluation, enucleation may be aborted due to suspicion for malignancy or duct proximity.

Superficial lesions with extrapancreatic components are the most amenable to cyst enucleation, as significantly less dissection is required to free them from surrounding parenchyma. Ultrasound guidance can assist in locating deeper lesions. Overlying parenchyma is dissected away until the lesion is identified. Frozen section pathology is always performed and if invasive disease is discovered, lymph nodes must be retrieved and negative margins achieved for maximal survival benefit. Parenchyma sparing must be balanced against, but never compromise, oncologic principles. The role of sentinel lymph node biopsy in treatment of biliary and pancreatic disease has recently been discussed in the literature, and may be useful for patients with unclear diagnoses or those benign lesions at higher risk for recurrence, particularly in young patients [21–23]. BD-IPMN have communicating ducts that must be identified and ligated to prevent leaks (Figure 94.2).

After removal of the cyst, the cavity is searched for small vessels and ducts which are ligated with clips, ties, or tissue coagulation devices. Thermal injury can result from cautery and should be avoided when the main duct

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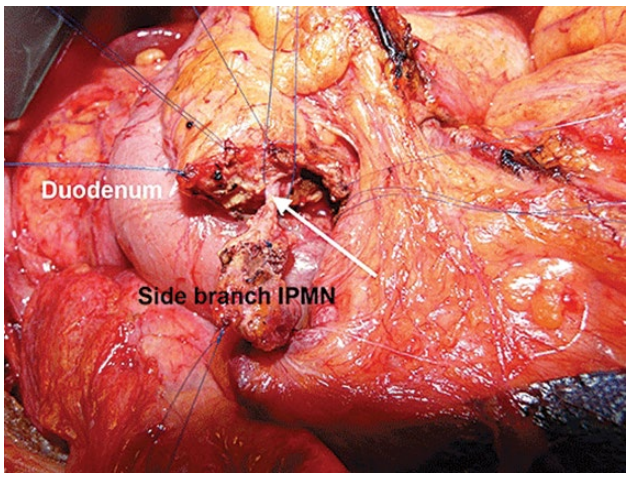


Figure 94.2 Intraoperative photograph of a BD-IPMN. The arrow identifies the communicating duct. *Source:* Turrini O et.al (2011) / Reproduced with permission Elsevier Inc.

is near. Main pancreatic duct integrity can then be evaluated with ultrasound and secretin stimulation. Some surgeons close the pancreatic parenchyma with absorbable suture on a large but fine needle, taking care to avoid any prominent vessels [24], and many routinely leave surgical drains. When the resected pancreatic bed measures >3 cm in diameter or when a main pancreatic duct injury is suspected, a Roux-Y loop to drain the wounded area may be considered [6,25].

Postoperative Management

Postoperative management of patients following cyst enucleation is the same as for any pancreatic resection. If surgical drains are placed intraoperatively, drain amylase should be followed. Drain amylase should be measured on postoperative day (POD) #1 [7]. Drain amylase elevated greater than three times the serum level indicates a pancreatic fistula [26]. Growing evidence suggests that in patients with low POD #1 drain amylase levels, drain removal by POD #3 dramatically reduces the incidence of a pancreatic fistula [27,28].

Management of pancreatic fistulas depends on grade and surgeon preference. No standardized management plan exists due to lack of strong evidence. Treatment of diet ranges from continued normal diet to nothing by mouth with total parenteral nutrition [7]. Other management options include endoscopic pancreatic sphincterotomy. This method has been practiced in patients with prolonged pancreatic fistula and may lead to improved healing time due to the decreased duct pressure [29].

Parenteral octreotide has been used by some surgeons in the immediate postoperative period to decrease the rate of pancreatic fistula [7,10]. A Cochrane review revealed a decreased rate of overall fistulas but no decrease in mortality, hospital stay, or rate of reoperation, and whether this difference holds for clinically relevant (grade B or C) pancreatic fistulas is unclear [30]. Those prescribing prophylactic octreotide endorse seven days of use. The authors of the Cochrane review recommend routine use in patients undergoing pancreatic resection because the potential benefit outweighs the low risk and low cost of the medication. However, a recent review by Vollmer et al. demonstrated that octreotide may increase the rate of pancreatic fistula [31]. Thus, the clinical role of octreotide in the prevention of pancreatic fistula remains controversial.

Postoperative Complications

Clinically relevant postoperative pancreatic fistula (CR-POPF) is the major morbidity following enucleation and occurs in 20% (range 9–41%) of cases (see Table 94.4). CR-POPF can be difficult to treat due to its many associated problems. Intraabdominal infection and/or hemorrhage, delayed gastric emptying, increased hospital stay, increased readmission, and the need for reintervention have all been associated with pancreatic fistula [18].

Specific risk factors for development of pancreatic fistula include soft pancreatic texture with absence of fibrosis, main pancreatic duct (MPD) diameter of less than 3 mm, cyst distance less than 2 mm from the duct, and cyst depth of greater than 3 mm (Table 94.3) [13–16]. Recently, Duconseil et al. found that tumor location in the inferior portion of the pancreatic head and uncinate process was an independent predictor of pancreatic fistula development, including clinically relevant (grade B or C) fistulas [32]. Other independent risk factors for fistula formation following enuclation include advanced age, New York Heart Association (NYHA) class II or III, recent episode of acute pancreatitis, and procedure time greater than 180 minutes [18,25].

Table 94.3 Risk factors for pancreatic fistula following cyst enucleation.

Soft texture
Pancreatic duct diameter <3 mm
Distance of cyst from pancreatic duct <2 mm
Cyst depth >3 mm
Recent episode of acute pancreatitis
NYHA class II or III
Operating room time >180 min
Lesion located in inferior pancreas or uncinate process

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Multiple studies have attempted to identify methods for decreasing the risk of fistula. In addition to the previously described prophylactic octreotide, a study by Kiely et al. demonstrated a decreased fistula rate (50% to 27%) by adding intraoperative ultrasound and closure of the space after cyst removal [24]. Preoperative nasopancreatic stenting is another approach that allows surgeons to palpate and directly visualize the duct, therefore avoiding MPD injury and fistula formation [18]. In addition, measurement of drain fluid amylase on POD #1 with drain removal by POD #3 will reduce the rate of CR-POPF [27].

Outcomes

Table 94.4 displays contemporary pancreatic cyst enucleation outcomes from major studies conducted since 2011. Overall morbidity and mortality of cyst enucleation have been reported to be 12–67% and 0–1% (with one exception), respectively, over the last decade. Many studies have demonstrated no statistical difference in morbidity or mortality when compared to formal resection [5,6,33–36]. However, a recent study by Beane et al., employing the American College of Surgeons National Quality Improvement Program (ACS-NSQIP), showed that cyst enucleation led to decreased morbidity and mortality when compared specifically to pancreatoduodenectomy, particularly with regard to delayed gastric emptying, surgical site infection, and sepsis [4]. Additionally, enucleation has consistently been shown to be associated with shorter operative time, less surgical blood loss, shorter ICU stay, and decreased postoperative endocrine and exocrine insufficiency when compared to formal resection. Patients undergoing enucleation also utilize fewer healthcare resources. Tumor recurrence and long-term survival also appear to be similar between the two groups [5,6,33–35].

Giuliani et al. recently compared quality of life metrics in patients after enucleation to healthy controls from the general population, and saw similar quality of life responses in almost all functional and symptom scales, except for those regarding "worries for the future" and "body image" [37].

The majority of recent studies have not demonstrated a difference in rate of postoperative pancreatic fistulas after enucleation compared to formal resection, when considering both all fistulas and clinically relevant (grade B or C) fistulas. The incidence of postoperative fistula after enucleation has ranged from 20% to 63% for all grades and 9–41% for grades B and C only. Jilesen et al. in particular reported a higher rate of clinically relevant pancreatic fistulas after enucleation of small PNETs when compared to pancreatoduodenectomy. The authors posited that this finding may have been due to a higher proportion of unfavorable pancreatic texture or due to proximity to the main pancreatic duct, both of which are known risk factors for fistula development (see Table 94.3) [35]. However, patients with higher grade fistulas after enucleation may need fewer invasive interventions, as Beane et al. reported fewer percutaneous drainage procedures following enucleation when compared to pancreatoduodenectomy (13.4% vs 22.4%) [4].

Cyst Ablation

Pancreatic cyst ablation is an alternate treatment option in which cysts are lavaged with ethanol or a chemotherapy solution, or ablated with radiofrequency alone. Potential candidates for cyst ablation are high-risk surgical candidates, those with a life expectancy of 3–5 years, or those who refuse surgery [8,38]. Ablation also may be used as a bridge to surgery when patients are already receiving EUS with FNA for indeterminate lesions [39]. Patients with coagulopathies should not undergo ablation as passage of the needle into the cyst may cause bleeding. Most endoscopists use the cut-off of international normalized ratio (INR) less than 1.5 and platelets greater than 50 000 [39,40]. Lesions that are consistent with a benign cyst by clinical, radiologic, cytologic, and chemical evaluation should not undergo ablation [38].

The procedure begins with a complete endoscopic ultrasound exam. The cystic lesion is located and characterized. Cysts must be greater than 2 cm in order to safely target. Multiple septations are another barrier to ablation. If the cyst contains multiple septations in which not all compartments communicate, complete drainage will not be possible. Unilocular or oligolocular cysts with 2–6 compartments are therefore preferred [38,39,41]. The main pancreatic duct should be carefully evaluated to confirm absence of communication with the cyst. The ablative agent will be lost through the communicating duct if the cyst is connected to the main duct [40]. Some authors advocate preoperative ERCP to determine the cyst's ductal relationship [39]. Intraoperative ultrasound also can serve as a final opportunity to diagnose overt cancers with peripancreatic invasion. Ablation may then be aborted.

Following a complete intraoperative ultrasound examination, a needle (22 gauge for cysts 2–3 cm, 19 gauge for cysts >3 cm) is passed transduodenal or transgastric into the cyst [38]. This passage is done under direct ultrasound guidance. The cyst is then aspirated until collapse. If the cyst fluid is thick and mucinous, the clinician may be unable to complete cyst aspiration [39]. Cyst fluid is used for cytology analysis and measurement of carcinoembryonic antigen (CEA) and amylase concentrations.

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Table 94.4 Major pancreatic cyst enucleation case control/case series studies from 2011 to the present.

Author	Year	Cyst type	Morbidity	Mortality	Fistula, all grades	Grade B or C fistula	Endo. insuf.	Exo. insuf.	OR time/ blood loss	Recurrence
Cauley	2011	21 NET, 10 MCN/IPMN, 10 SCN, 4 other benign	56% ↔	0% ↔	33% ↔	15% ↔	4% ↓	2% ↓	↓	
Brient	2012	35 NET, 6 MCN, 2 SCN, 10 other	37%	0%	27%	13%	0%	0%		2%
Crippa	2012	106 insulinoma	47% ↔	0% ↔	42% ↔	21% ↔	1% ↓	↔	↓	2% ↔
Zhang	2013	90 NET, 2 MCN	67%	0%	61%	28%	3%	0%		1%
Sauvanet	2014	44 BD-IPMN	55%	0%	47%	17%				
Song	2015	24 NET, 9 MCN, 7 IPMN, 3 SPN	12%	0%	20%	9%	2%			0%
Faitot	2015	47 NET, 38 BD-IPMN, 26 MCN, 16 other	63%	1%	57%	41%	8%			7%
Jilesen	2016	60 NET	55% ↔	0% ↔		40% ↑	7% ↓	5% ↓	↓	19% ↓
Zhang	2016	17 NET, 5 MCN, 4 SCN, 11 other	43%	0%	38%	16%	3%	8%		0%
Kaiser	2017	74 BD-IPMN	↔	0% ↔	46% ↔	27% ↔	2% ↓	11% ↓	↓	3% ↔
Sahakyan	2017	26 NET, 8 SPN, 4 SCN. 3 MCN, 1 BD-IPMN, 3 other	40% ↔	4% ↔	63% ↔	27% ↔	0%		↓	
Duconseil	2018	20 NET, 17 BD-IMPN, 10 others	62%	0%	50%	33%				
Wang	2018	31 SPNs	26% ↔	0% ↔	45% ↔	19% ↔	0% ↔	3% ↓	↓	0%
Wang	2018	74 NET, 16 SCN, 20 BD-IPMN, 6 MCN, 26 others	66%	1%	54%	15%				
Beane	2021	127 NET	36% ↓	0% ↓		14% ↔				
Giuliani	2021	68 NET, 6 MCN, 7 others	51%	0%	41%	21%	7%	10%		

BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; Endo. insuf., pancreatic endocrine insufficiency; Exo. insuf., pancreatic exocrine insufficiency; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumor; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm.

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If this analysis or ultrasound characterization is consistent with invasive cancer, formal pancreatic resection should be considered. With the cyst collapsed, 80% or 99% ethanol is injected into and aspirated from the cyst for 3–5 minutes with a volume equal to the volume of cyst fluid initially removed [38,40]. If the cyst is in communication with the main pancreatic duct as previously described, the ablative solution will not remain in the cyst during this time. Following ethanol lavage, a chemotherapeutic agent, most commonly paclitaxel, may also be infused into the cyst, again with a volume equal to the original cyst fluid aspirated [38,41].

Existing literature is heterogeneous with varying rates of cyst resolution, 33–85% [39–42]. Higher rates of resolution have been reported with the combined use of ethanol and chemotherapy agents [39, 41]. Recently, the CHARM trial, a randomized, double-blinded pilot study, demonstrated that an alcohol-free approach may be similarly effective with an improved side-effect profile [43]. A larger, NIH-funded, multicenter randomized control trial is currently ongoing to further investigate this finding [44]. Additional studies have shown greater decrease in size and higher rates of cyst resolution with multiple ablation sessions [41]. Resolution is most often based on radiographic evidence as shown in Figure 94.3 [40]. Resolution may be dependent upon cyst type, with mucinous cysts having much lower rates of resolution [42]. Other potential predictive factors of complete response include locularity, presence of mural nodules, and cyst size <35 mm [45].

Cysts which achieve complete resolution appear to have a low risk of recurrence. Limited longitudinal data so far have demonstrated 0–2% recurrence, although further studies are still needed [45,46]. While uncommon, multiple complications have been reported. Fever, abdominal pain or acute pancreatitis occurs in 2–10%. Intracystic hemorrhage, bowel perforation, and severe acute pancreatitis are even less commonly reported [39,40,42].

Radiofrequency ablation is another recently described technique for managing select pancreatic lesions [41]. A recent prospective trial of 30 patients demonstrated a 10% complication rate; however, the most serious adverse

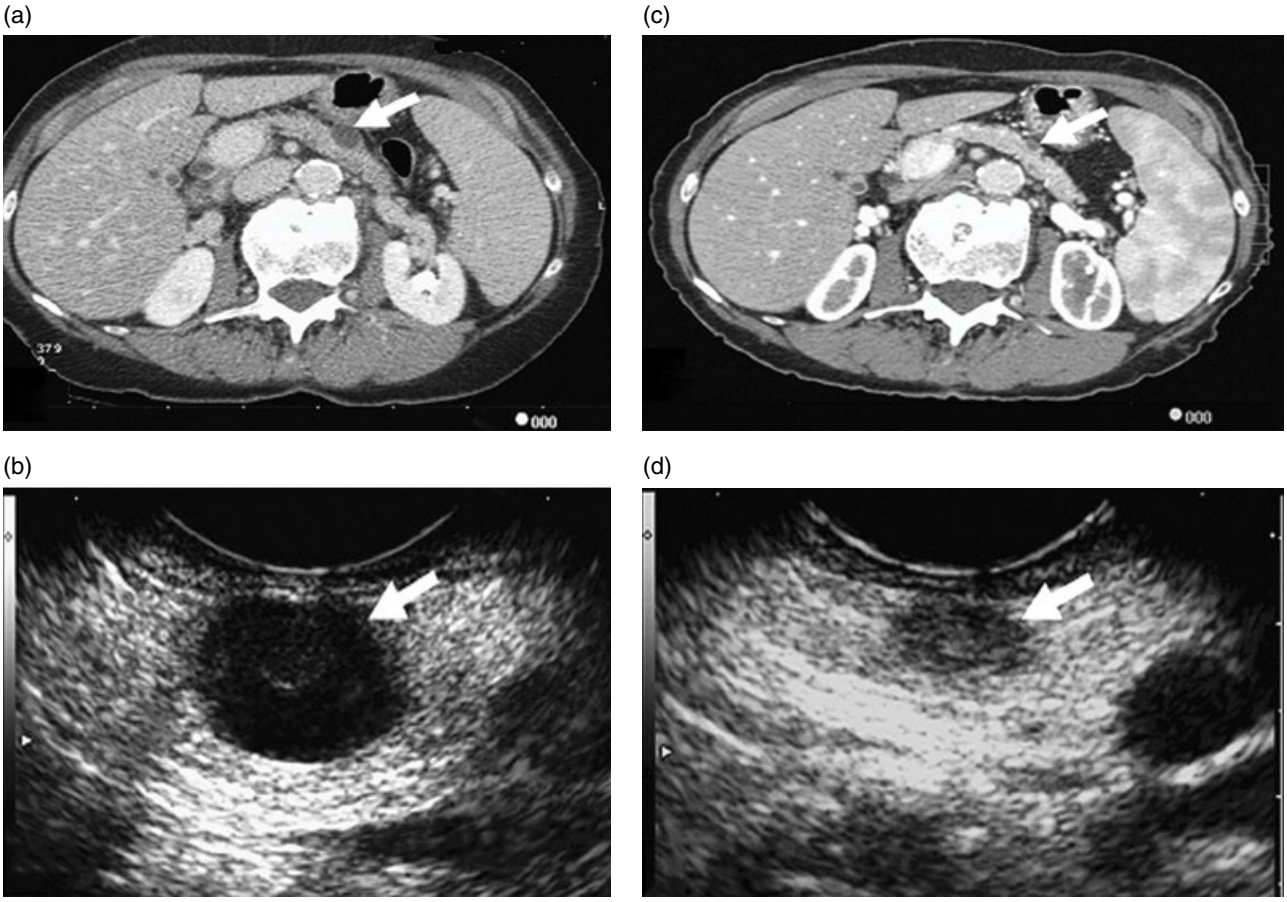


Figure 94.3 Radiographic evidence of cyst ablation after ethanol lavage. (a) CT scan of the abdomen showing a 13 mm cyst in the body of the pancreas (white arrow). (b) Ultrasound of the same pancreatic cyst. (c,d) CT scan and ultrasound of the same patient three months after ablation. The cyst measures 8 mm. *Source:* DeWitt J et.al (2009) / Reproduced with permission from Elsevier Inc.

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events of severe acute pancreatitis and jejunal perforation only occurred in the first two patients. The protocol was then modified to include prophylactic measures and cyst fluid aspiration prior to radiofrequency application, and no further adverse events were reported in the remaining 28 patients [47]. Since then, several studies have investigated the effectiveness of this modality in various pancreatic lesions, and reported response rates have ranged from 65% to 86% [47–49]. However, data on the long-term outcomes of this approach are still evolving.

Conclusion

Pancreatic cyst enucleation is an alternate surgical option for small, low-risk cystic lesions. Several factors make each pancreatic cyst more or less optimal for enucleation. Main duct involvement or close proximity increases the rate of postoperative fistula development. Enucleation of large, multifocal, or tail cysts does not yield significant parenchymal preservation and therefore is not beneficial. Patients considered for enucleation must receive appropriate preoperative evaluation and must be adequately fit. Postoperative pancreatic fistula is the major morbidity of enucleation but occurs at the same rate as in formal resection. Enucleation is associated with less utilization of healthcare resources and similar or lower morbidity and mortality without compromising local recurrence rates or long-term survival.

Lastly, cyst ablation is an alternate technique that may be employed in patients unwilling or unable to tolerate enucleation or resection.

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Duodenum-preserving Pancreatic Head Resection and Local Extirpation of SPTP in Children and Adolescents: Indications and long-term results

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Introduction

Solid pseudopapillary tumor of the pancreas (SPTP) was first described by Frantz in 1959 [1,2]. Since then, various names have been used to describe this unusual lesion, such as solid and cystic tumor of the pancreas, papillary-cystic and solid tumor of the pancreas, solid and papillary epithelial neoplasm.

Solid pseudopapillary tumor of the pancreas is a rare tumor and typically shows a benign clinical course with a low malignant potential. Although some cases may be locally aggressive and infiltrative, metastases to liver, lung, and skin occur very rarely. Little is known about the origin and histogenesis of this tumor. The fact that SPTP tumors may express epithelial as well as mesenchymal markers and occasionally show both exocrine and endocrine features suggests a stem cell origin [3]. Calcifications or internal septations are detected in some cases. The neoplasm is generally encapsulated and is well demarcated from the remaining pancreas. The most useful biochemical markers in the diagnosis are α1-antitrypsin, α1-antichymotrypsin, neuron-specific enolase, and vimentin.

The tumor occurs predominantly in girls and young women in their second or third decade of life.

Symptoms, when they occur, are often vague and nonspecific and include abdominal pain and palpable mass. About 50% of SPTPs are larger than 5 cm at the time of diagnosis. Some children with SPTP can manifest after abdominal blunt trauma [4]. In the series published by Snajdauf et al., four out of 28 patients with SPTP presented after blunt abdominal trauma (14%) [5,6].

Imaging methods used to diagnose SPTP include abdominal ultrasound, spiral computed tomography (CT), and magnetic resonance imaging (MRI). Characteristic images show a large, round, well-encapsulated, combined cystic and solid mass. The differential diagnosis of SPTP includes any cystic and/or solid pancreatic process, e. g., congenital pancreatic cysts, hemorrhagic pseudocyst, and other common cystic neoplasms of the pancreas, such as serous cystadenoma, mucinous cystic neoplasms or pancreatoblastoma.

Solid pseudopapillary tumor of the pancreas is a surgically curable tumor with an almost uniformly good prognosis. Pancreatic resection including pancreaticoduodenectomy and distal pancreatectomy is the standard of care for SPTP in children [7–16]. Tumor enucleation alone is not recommended as it will not provide a radical surgical management and does not prevent recurrence [17]. Distal pancreatectomy is performed for tumors in the body or tail of the pancreas, and pancreaticoduodenectomy for tumors of the pancreatic head. In cases of a tumor of the head of the pancreas, most pediatric surgeons would perform a modified Whipple duodenopancreatectomy [7–16] or Frey procedure [18–22]. However, the preferred surgical option for pediatric patients is Beger's operation – the duodenum-preserving head resection [23].

Duodenum-preserving Technique of Head Resection of the Pancreas in Children

The duodenum-preserving head resection of the pancreas (DPHRP) described in 1980 by Beger and colleagues and the extended pancreaticojejunostomy with conization of the pancreatic head described in 1987 by Frey represent new approaches to proximal inflammatory lesions and benign tumors [19,23]. These operations are recommended for adult patients with severe chronic pancreatitis and inflammatory enlargement of the head of the pancreas in cases of medically intractable pain,

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stenosis of the common bile duct, severe obstruction of the duodenum, or compression of the portal vein causing portal hypertension.

The surgical technique of DPHRP includes two major steps: first, total or subtotal resection of the head of the pancreas, preserving the duodenum; second, restitution of the exocrine pancreatic secretory flow from the body and tail of the pancreas using the first jejunal loop as an interposition. After an abdominal exploration through a transverse oblique muscle cutting incision in the right hypochondrium, the lesser sac is entered via the gastrocolic omentum and the anterior aspect of the pancreatic head is fully exposed. The Kocher maneuver is generally not necessary and is not performed in order to preserve mesoduodenal vessels. After the identification, ligation, and division of the anterior superior and anterior inferior pancreaticoduodenal artery and vein (ASPDA, AIPDV) (Fig. 95.1), resection of the head is performed mostly using an ultrasonic aspirator and dissector (Cavitron System 2000, Valley Lab) (Fig. 95.2). When the tumor spares the part of the gland adjacent to the first, second, and third parts of the duodenum, a 3–5 mm thick rim of pancreatic tissue is left *in situ* together with the capsule. During resection of the uncinate lobe, the superior mesenteric artery and vein are carefully and meticulously mobilized. The intrapancreatic portion of the distal common bile duct and the origin of the posterior superior pancreaticoduodenal artery (PSPDA) are identified and preserved. These vessels together with other posterior pancreatoduodenal vessels lie on a connective tissue membrane.

Preserving the membrane and thus the blood supply to the duodenum is one of the most important aspects of this procedure. Kimura examined the topography of the duodenum, pancreas, bile duct, and supplying vessels using

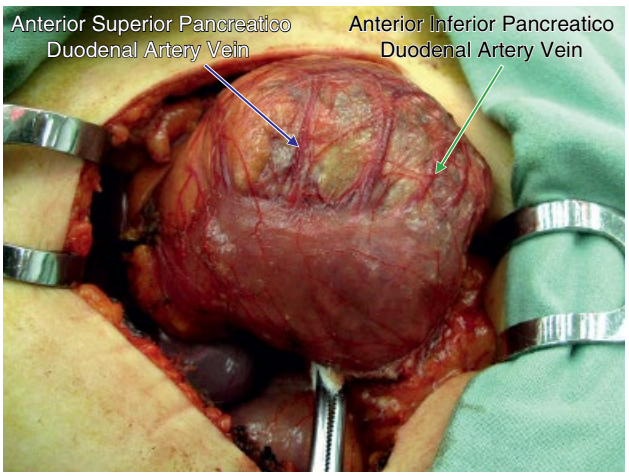


Figure 95.1 Ligation and division of the anterior superior and anterior inferior pancreaticoduodenal artery and vein (ASPDA, ASPDV, AIPDA, AIPDV).

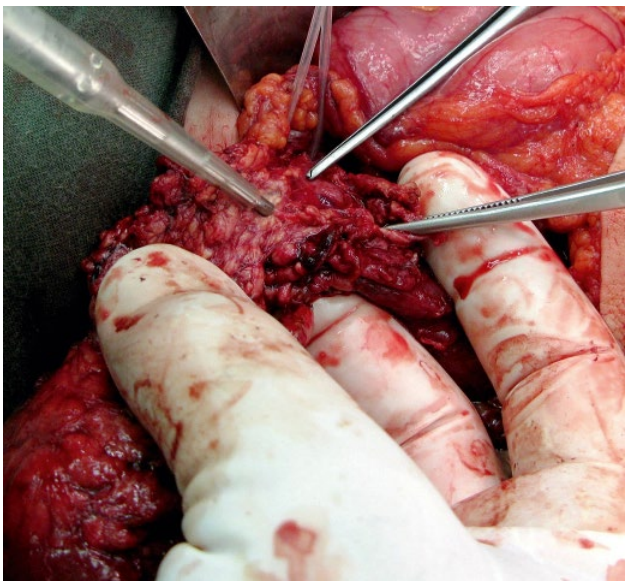


Figure 95.2 Resection of the head is performed using an ultrasonic aspirator and dissector (Cavitron System, Valley Lab, USA).

autopsy materials in 40 cases and also concluded that it is important to preserve the posterior superior and posterior inferior pancreaticoduodenal artery and vein [24].

During ultrasonic excavation of the head of the pancreas, meticulous care has to be taken to properly identify and not injure the bile duct (Fig. 95.3). The pancreatic duct is transected near the ampulla. The resection itself is performed at the level of the mesenteric vein, or more laterally if the tumor involves part of the body as well. The rest of the gland is drained into the jejunum by means of a retrocolic single end-to-end, Roux en-Y pancreaticojejunostomy (Fig. 95.4). A single-layer anastomosis is performed between the pancreas and the jejunal loops with absorbable sutures [5,6].

In summary, the principle of the Beger operation is a subtotal resection of the head of the pancreas leaving a small part of the head of the pancreas close to the duodenal wall, while preserving the duodenum and distal common bile duct [21]. In comparison to the Whipple procedure, the DPHRP spares the patient a gastric resection, a duodenectomy, and a common bile duct resection. The procedure represents one of the new approaches to treating proximal inflammatory lesions and tumors [25–27].

Complications

Complications after DPHRP and distal pancreatectomy for SPTP are relatively rare and similar in children and adults. Possible complications are bile duct stricture and fluid collection which can be managed conservatively by balloon dilation and percutaneous drainage, respectively.

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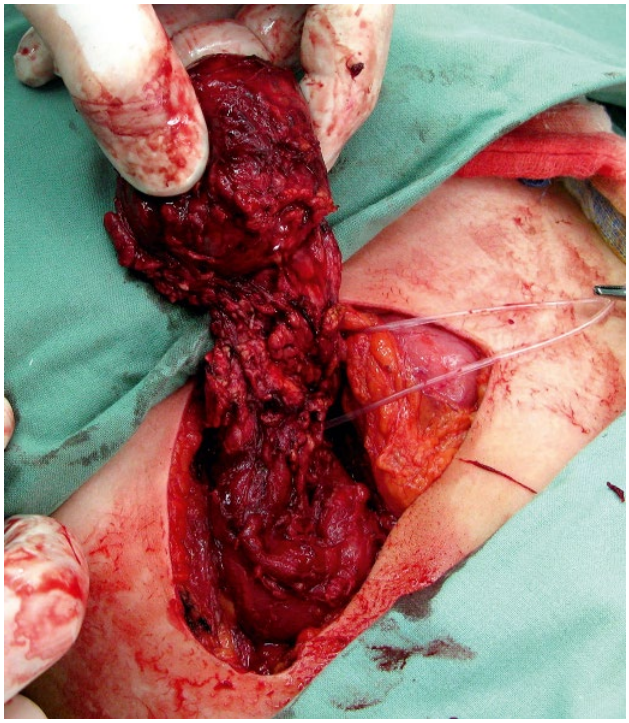


Figure 95.3 The head of the pancreas with the tumor.

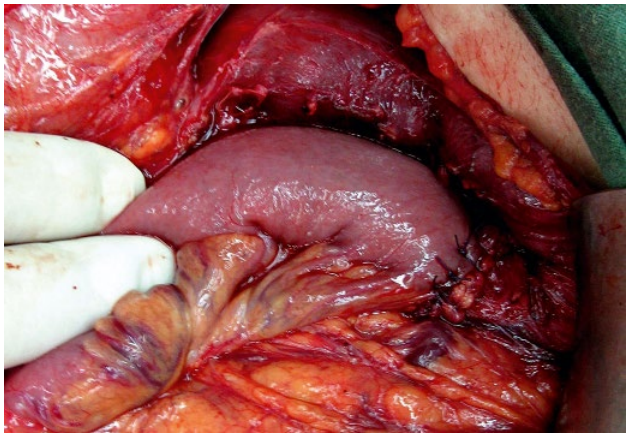


Figure 95.4 The rest of the pancreas is drained into the jejunum by means of a retrocolic single end-to-end Roux en-Y pancreaticojejunostomy.

Other reported complications include pancreatic fistula, wound infection, pancreatic duct stenosis, delayed gastric emptying, abdominal pain, pancreatiti,s and exocrine pancreatic insufficiency [28,29].

Recurrence

Larger tumors (diameter >5 cm), lymphovascular invasion, lymph node metastasis, synchronous metastasis, and positive margin increase the risk of postoperative recurrence of pancreatic SPN. Due to the low but actual malignant potential, all SPTPs should be excised, which could provide positive prognoses [30–32].

Metastases

Approximately 6% of all SPTPs are reported to invade surrounding organs and about 10–15% develop distant metastases. Occasionally, the tumor may spread to the liver, lung, or lymph nodes. The most common metastatic organ is the liver, into which tumor cells metastasize through either the superior mesenteric vein or the portal vein. The treatment of liver metastasis most commonly involves liver resection. Pulmonary metastases are extremely rare [33–36].

Long-term Follow-up in Children

The survival rate in children after DPHRP and distal pancreatectomy for SPTP is higher than 95%, but pancreatic surgery may result in impaired exocrine and endocrine pancreatic function. Currently, only limited data are available on long-term pediatric pancreatic function following surgical resection. Careful and long-term monitoring should follow any pancreatic surgery in order to recognize and promptly treat exocrine and endocrine pancreatic insufficiency, which can occur in 12–25% of patients after surgery [37]. According to a large population-based database, the rates of postpancreatectomy endocrine (diabetes) and exocrine insufficiency in adults were 40% and 35%, respectively. Exocrine insufficiency is defined by the use of pancreatic enzyme replacement [38]. New onset of diabetes in children after pancreatic resection of SPTP was reported in 5–10% of cases [39]. The authors' experience is summarized in Table 95.1.

The duodenum-preserving technique discussed above has an important role for the developing child with a life expectancy of at least 7–8 decades. A procedure resulting in minimal interference with normal gastrointestinal function and causing no or minimal long-term discomfort should be proposed for these patients. The duodenum and common bile duct sparing resection of the head of the pancreas is a highly effective surgical procedure with low early and late morbidity and no mortality as published in the series by Snajdauf et al. It ensures total removal of pathologic tissue of the SPTP of the head of the gland, as shown by the fact that there was no local recurrence in their study [5,6]. The duodenum-preserving resection of the head of the pancreas should be the procedure of choice in pediatric SPTP.

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Table 95.1 An overview of the authors' experience with management of SPTP in pediatric patients.

Type of surgery	Number of patients	Mean age at surgery	Gender	Tumor size (cm)	Re-surgery	Complications	Pancreatic enzyme supplements	Survival
DPHRP	11	14.5 years	F	7.5 (4–15)		1 POPF, 1 intraoperative lesion of CBD, 4 mild PP	5 patients	All
Distal pancreatectomy	13	13.7 years	11F, 2M	9.5 (5–16)	1 resection of pancreatic cyst, 1 liver resection for metastasis	1 hemoperitoneum	2 patients	All, 1 insulin-dependent DM
Resection of the pancreatic body	2	15.7 years	F	5		1 pseudocyst (conservative management)	1 patient	All
Modified Whipple	1	10.8 years	F	12		1 biliary fistula (ERCP stent)	0	All

CBD, common bile duct; DM, diabetes mellitus; DPHRP, duodenum-preserving head resection of the pancreas; ERCP, endoscopic retrograde cholangiopancreatography; POPF, postoperative pancreatic fistula; PP, postoperative pancreatitis.

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Management of Recurrence of Cystic Neoplasms

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Introduction

With the increased routine usage of high-resolution cross-sectional imaging and thus increasing identification of cystic neoplasms (CN) of the pancreas, often as incidental findings, surgical resection of CN has become part of the daily routine in specialized centers.

Cystic lesions of the pancreas represent a very heterogeneous group of tumors. Intraductal papillary mucinous neoplasms (IPMN) represent about 35% of all CN of the pancreas and about half of the resected ones [1], with different potential for malignant transformation depending on a number of variables, including patterns of duct involvement (main duct [MD], branch duct [BD], mixed type) and epithelial subtypes, amongst others [2,3]. Further CN with potential for malignant transformation include mucinous cystic neoplasms (MCN) and solid-pseudopapillary neoplasms (SPN). SPN are very rare tumors with a reported five-year overall survival rate of 94–97% and a rate of recurrence of 4% [4]. MCN are mostly solitary and thus complete resection is often curative [5,6].

The follow-up and surveillance strategy for patients after resection of an IPMN in contrast to other CN, however, remains a matter of debate, which is mainly due to the fact that their natural history varies widely. The possibility of progression to an invasive carcinoma for some IPMN, as well as the risk of a synchronous or metachronous pancreatic ductal adenocarcinoma (PDAC) in patients with known IPMN, is well known. The publication of the 2015 American Gastroenterological Association (AGA) Institute Guideline explicitly suggesting against routine surveillance of resected CN without high-grade dysplasia (HGD) or malignancy has thus sparked a controversial discussion on the appropriate postoperative management of these lesions [7]. Consequently, the International Association of Pancreatology (IAP) established an updated consensus guideline in 2017 [6,8] and the European evidence-based guidelines [9] and the American College of Gastroenterology (ACG) clinical guideline [10] were published, all three explicitly addressing the postoperative management of resected IPMN.

In terms of recurrence of an IPMN, there are different scenarios to be considered. Traditionally, recurrence has been used in the context of malignancy and in the case of IPMN would therefore describe the recurrence of an IPMN-associated invasive cancer after curative resection. However, in most cases, patients with IPMN present with multifocal disease and thus residual or metachronous developed lesions in the pancreatic remnant initially not meeting the criteria for resection may either stay stable, progress into IPMN meeting those criteria or even develop into PDAC. Especially with the establishment of parenchyma-sparing techniques for IPMN [11], it is extremely important to bear those different settings in mind when releasing patients into postoperative care.

This chapter will focus on the risk of recurrence for IPMN of the pancreas as well as appropriate surveillance strategies.

The Pancreatic Remnant

IPMN are believed to represent a part of the so-called "field defect," meaning that the entire ductal system of the pancreas is at risk of developing dysplasia and not only the radiographically detectable lesion [6,12]. Thus, the remnant gland is predisposed to developing significant neoplasia even after resection of the primary lesion.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Recurrence rates for resected IPMN are between 9% and 14% [13–15]. For invasive IPMN, Kim et al. reported a recurrence rate as high as 34% in their cohort of 117 invasive IPMN out of 548 resected IPMN [14], which is in accordance with their previously published analysis of 366 resected IPMN [13]. For their 431 patients with noninvasive IPMN resected between 2000 and 2018, the reported recurrence rate after resection was 1.7% (6/353) and 5.1% (4/78) for low-grade (LGD) and HGD, respectively [14]. For resected patients between 1995 and 2014, Kang et al. reported a recurrence rate of 5.4% for 298 resected non-invasive IPMN [13]. Importantly, in both analyses, distant recurrences or pancreatic cancer occurred after resection of noninvasive IPMN in two and seven cases, respectively. However, it is important to note that distant metastases from other organ malignancies were not excluded in either analysis.

Marchegiani et al. analyzed 299 patients with noninvasive IPMN and reported a recurrence rate of 9% after surgical resection. Importantly, they found that 2% of these recurrences presented as invasive cancer. Further, MD-IPMN recurred more often as invasive cancer (5/6) than BD-IPMN (1/22) did [16]. This is in line with other literature reporting recurrence rates of resected noninvasive IPMN ranging from 1% to 20% and a recurrence rate of secondary invasive lesions between 2% and 7% [17–23].

However, the five-year recurrence-free survival rate (RFS) has been reported to be favorable, ranging from 77% to 100% (Table 96.1). The median time to recurrence has been described to range from 15 months to 4.5 years, stressing the necessity for long-term surveillance as has recently been recommended by several authors.

Two comprehensive analyses evaluating the natural history of the pancreatic remnant after resection of a noninvasive IPMN were published by the Johns Hopkins group. In 2013, an analysis of 130 patients undergoing resection of noninvasive IPMN was reported by He et al. with a one-, five-, and 10-year risk of developing a new IPMN of 4%, 25%, and 62%, respectively, with the chance of requiring surgery being 1.6%, 14%, and 18%, respectively [24]. Importantly, the risk of developing invasive cancer at one, five, and 10 years was found to be 0%, 7%, and 38%, respectively (Fig. 96.1) [24]. At a median follow-up of 60 months, all patients who were found to have invasive carcinoma on completion pancreatectomy remained alive with no evidence of recurrent disease.

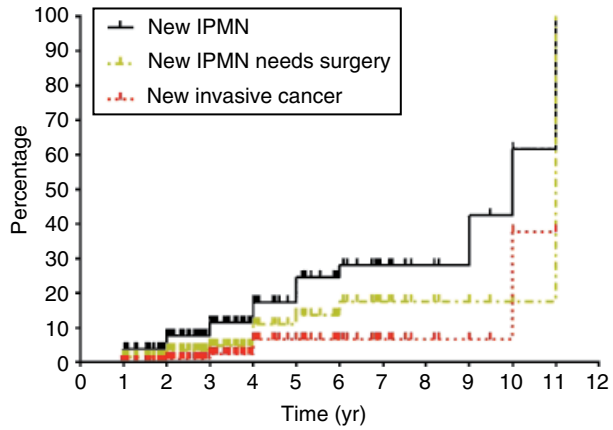
In 2020, the same cohort was reevaluated with a prolonged follow-up time and focus on the identification of risk factors for recurrence [12]. At a median follow-up of 9.5 years, clinically relevant recurrence was now observed in 15% of patients with a three- and five-year RFS rate of 95% and 86%, respectively. Importantly, 14 of 19

Table 96.1 Studies reporting recurrence rates after resection of benign IPMN.

Study, year	N	Single (s)-/multi (m)- center study	Median follow-up, months	Recurrence rate, %	Recurrence rate with invasion, %	Time to recurrence, months	Five-year RFS, %
Chari, 2002 [18]	60	s	37	8.3	3.3	40	85
Sohn, 2004 [35]	84	s	–	8.3	5.9	–	77
Wada, 2005 [36]	75	s	–	1.3	0	–	100
Raut, 2006 [37]	28	s	34	0	0	–	100
White, 2007 [21]	78	s	40	7.7	5.1	22	87
Fujii, 2010 [19]	103	s	–	9.7	7.8	–	–
Miller, 2011 [17]	191	s	–	20	2	35	83
He, 2013 [24]	130	s	38	17	4	46	81
Kang, 2014 [13]	298	s	44	5.4	2.3	47	–
Marchegiani, 2015 [16]	316	s	58	9	5	48	–
Blackham, 2017 [23]	100	s	35	9	3	15	–
Dhar, 2018 [20]	502	m	36	10	3.6	31	89
Hirono, 2020 [15]	827	m	54.2	5.8	–	–	–
Kim, 2020 [14]	431	s	56	2.3	0.2	–	82–89[a]
Pflüger, 2020 [12]	126	s	9.5y	15	4.8	4.5y	86

IPMN, intraductal papillary mucinous neoplasm; RFS, recurrence-free survival rate; y, years.
[a] High-grade dysplasia versus low-grade dysplasia.

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	1yr	5yr	10yr
New IPMN	4%	25%	62%
New IPMN requiring completion pancreatectomy	2%	14%	18%
New invasive cancer	0%	7%	38%

Figure 96.1 Cumulative recurrence curve for patients undergoing resection of noninvasive intraductal papillary mucinous neoplasm (IPMN). *Source:* Adapted from [24]/with permission of Elsevier.

recurrences were detected after three years and six recurrences after five years. Further, 13 of those 19 patients recurred as a PDAC. These two studies thus underline the importance of indefinite surveillance after resection of noninvasive IPMN, because of these long-term risks.

It is important to mention the possibility that the invasive cancer recurrences could represent concurrent PDAC that were undetected at the time of surgery instead of the metachronous development of a new invasive adenocarcinoma. However, the fact remains that these patients still require long-term surveillance.

Predictors of Recurrence

Identification of predictors for postsurgical recurrence for noninvasive IPMN is essential to guide postoperative surveillance strategies. Three main factors have been subject to discussion as predictors of postsurgical recurrence in recent years.

In the Johns Hopkins series, He et al. identified family history as an independent predictor for postsurgical recurrence in their initial analysis [24], which was later confirmed in the same cohort with long-term data by Pflüger et al., who reported family history of pancreatic cancer as an independent risk factor for recurrence in uni- and multivariate analysis (adjusted hazard ratio [aHR] 3.05, 95% confidence interval [CI] 1.17–7.94, P = 0.023) [12]. Further, the group from the Massachusetts General Hospital reported that a higher number of patients with family history of pancreatic cancer died of metastatic or recurrent disease than those without family history (72.7% versus 45.1%). However, they also found an increased incidence of concomitant PDAC (11.1% vs 2.9%, P = 0.02) as well as of extrapancreatic malignancies (35.6% vs 20.1%, P = 0.03) in patients with a positive family history of pancreatic cancer [25]. Thus, it remains unresolved in this analysis whether the observed difference in survival is due to the recurrence of the IPMN or the concurring PDAC [25].

Interestingly, an analysis of 315 surgically resected IPMN showed that 7.3% of patients had an underlying germline mutation associated with cancer risk and 2.9% had a germline mutation in a known pancreatic cancer susceptibility gene [26], which is similar to the rate of germline mutations found in sporadic PDAC patients [27]. Also, IPMN patients with a germline mutation in a susceptibility gene were observed to have a significantly higher likelihood of concurrent PDAC than those without a germline mutation.

In summary, patients with a family history of pancreatic cancer represent a high-risk cohort that should be closely monitored after surgical resection of the index lesion. Also, given the association with extrapancreatic malignancies in patients with family history of pancreatic cancer, these patients should be encouraged to participate in established age-appropriate cancer screening programs. Further, germline testing in selected IPMN patients may have value in postsurgical risk stratification.

For HGD as a postsurgical risk factor, the literature is quite consistent. The Johns Hopkins group reported a recurrence rate of 21% in patients with HGD in the resected lesion, which was, however, not significantly different to those with LGD (22%) nor those with intermediate-grade dysplasia (IGD) (14%) [24]. Importantly, though, three patients in their cohort with a recurrence of PDAC had HGD in their primary specimen.

In an analysis of 100 patients with HGD IPMN, the postsurgical recurrence rate was found to be 9%, median time to recurrence was 15 months and 3% patients developed invasive recurrences [23]. Similarly, the Seoul National University group found a significant association between pathological dysplasia and rate of recurrence (P = 0.021) and confirmed HGD as well as invasive IPMN as independent predictors of recurrence [13]. In their updated analysis of the same cohort, Kim et al. reported the five-year disease-free survival according to pathology as 88.7%, 83%, and 45.5% for LGD versus HGD versus invasive pathology, respectively [14]. Also, upon reevaluation of their 2013 cohort, the Johns Hopkins group identified high-grade IPMN as an independent risk factor for postsurgical recurrence on uni- and multivariate analysis (aHR 1.88, 95% CI 1.17–3, P = 0.008) [12]. In a separate analysis of 140 patients, the group reported

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that patients with HGD in their primary resected IPMN were more than eight times more likely to subsequently develop invasive cancer (odds ratio [OR] 8.82, 95% CI 2.56–30.43, P = 0.001) [28]. Consequently, there is no question that patients with HGD in their resected specimen are prone to recurrences and also at risk of invasive recurrences. Thus, this cohort, as a high-risk group, needs to be kept under close surveillance.

The factor that has initiated the most controversy in terms of impact on postsurgical recurrences is that of the surgical margin as conflicting outcomes continue to be reported by different centers. The Johns Hopkins Group [12,24] as well as Kang et al. [13] reported no differences in recurrence rates in margin-positive patients compared to margin-negative patients (16.7% vs 10.2%, P = 0.421). Similarly, in a multicenter analysis of 502 noninvasive IPMN, Dhar et al. found margin positivity not to be associated with recurrence of the remnant pancreas. In their analysis, margin positivity was mainly due to LGD [20].

In contrast, a report from the Memorial Sloan Kettering group reported that dysplasia of any degree at the resection margin was a risk factor for recurrent disease in the remnant gland (OR 2.9, P = 0.02), but not for recurrent disease at the resection margin itself [22]. Further, Marchegiani et al. reported a significantly higher rate of recurrence in patients with positive margins (25% vs 14%, P = 0.008). In their analysis, margin status was identified as a strong independent predictor of recurrence on multivariate analysis (HR 2.6, P = 0.0046) [29]. Also, the updated analysis of the Seoul National University group by Kim et al. identified HGD and invasive pathology at the resection margin to be significantly associated with recurrences (P = 0.036) [14]. HGD margins had a five-year cumulative recurrence rate of 4.3% compared to 0.7% for LGD. Taken together, HGD and invasive pathology at the resection margin had a significantly worse cumulative five-year recurrence rate of 50.6% compared to 5.9% for LGD and 8.3% for R0 resection.

The discrepant findings are likely to be a result of the retrospective nature of underpowered studies in trying to analyze a small, specific subcohort of patients. However, even though reports are still diverse, in the case that invasive cancer and also HGD are found at the resection margin, additional resection to achieve negative resection margins is recommended by the current IAP guideline [8].

Concomitant Low-Risk Lesions

Only very few studies have examined the progression of lesions left in the pancreatic remnant after removal of the index lesion separately from newly developing lesions due to the inconsistent use of the terms "progression" and "recurrence" for synchronous or *de novo* developing lesions, respectively.

Miller et al. reported on 38 of 243 (20%) patients undergoing surgical resection for noninvasive IPMN with concomitant residual IPMN in the pancreatic remnant [17]. One of those patients developed invasive disease. The authors report a five-year progression-free survival of 88% for those patients compared to 83% in patients without a known remnant lesion (P >0.05). Moriya et al. reported on 14 of 203 (7%) patients with residual lesions in the pancreatic remnant after resection of an IPMN [30]. After a median follow-up time of 40 months, none of these lesions required surgical intervention. Similarly, in a study by Marchesini et al., 33 of 412 (9%) resected IPMN patients had residual BD-IPMN in their pancreatic remnant, none of which met criteria for resection after a median follow-up of 58 months.

Further, in an analysis from the Memorial Sloan Kettering Cancer Center 49 of 319 (16.2%) patients resected for non- or microinvasive IPMN were identified as having residual lesions in the remnant pancreas not meeting surgical resection criteria at the time of the index operation [31]. Importantly, residual lesions in the pancreatic remnant were not significantly associated with an increased risk of progression on univariate analysis.

Furthermore, Lee et al. analysed 103 patients with BD-IPMN under surveillance not meeting the criteria for resection. During a median follow-up of 51.5 months, 43 (40.2%) patients had progressive disease, 21 of which presented with cancerous changes [32], and 32 (29.9%) patients required surgery. Similarly, Del Chiaro et al. surveyed 395 patients with BD-IPMN without features indicating surgery [33]. In this cohort, the cumulative one-, four-, and 10-year risk of disease progression and the need for surgery were 11.2%, 70.6%, and 97.5% and 2.9%, 26.2%, and 72.1%, respectively. Median follow-up time was 932 days. IPMN-specific one-, five-,-, and 10-year survival rates were 100%, 100%, and 94.2%, respectively. Four patients died of pancreatic cancer. In 49 patients with BD-IPMN in whom indications for surgery existed but who could not be operated on for other reasons, one-, five-,- and 10-year IPMN-specific survival rates were 90.7%, 74.8%, and 74.8%, respectively, suggesting a fairly indolent nature of disease.

Both studies, however, confirm a significant risk for progression and the need for surgery over time even in cases of BD-IPMN that initially do not meet the criteria for surgical resection.

From the few available data, it seems that patients with synchronous lesions in the pancreatic remnant are not at any higher risk for recurrence or progression, justifying current practices of only operating on IPMN that meet criteria for resection. However, long-term surveillance is necessary due to the possibility of long-term progression (Fig. 96.2).

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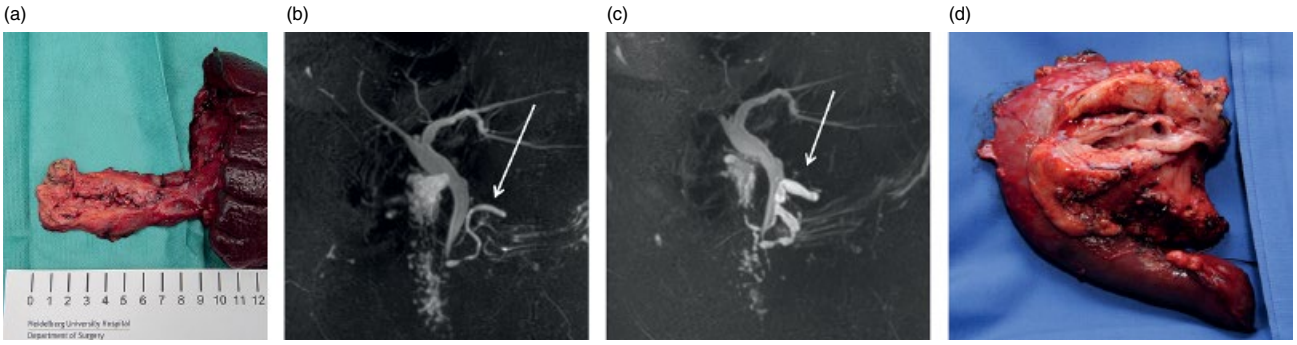


Figure 96.2 Malignant recurrence of disease in pancreatic remnant.

Postoperative Surveillance Strategy

Postoperative surveillance strategies aim at early detection of recurrent or progressive IPMN meeting criteria for surgical resection before invasive cancer occurs and thus improve long-term survival. Several guidelines with different strategies for postoperative surveillance of noninvasive IPMN exist.

As discussed above, there are at least three groups of "high-risk" patients in whom correlation with recurrence is likely to be higher than in other patients, namely those with a positive family history for pancreatic cancer, positive resection margin and HGD in the primary lesion. These patients should be monitored closely as the risk of development of high-risk lesions or invasive pathology is high. Further, as described above, time to recurrence can be up to five years after the index operation and all patients are at risk of developing invasive disease in the pancreatic remnant or extrapancreatic lesions requiring long-term surveillance. Furthermore, after partial pancreatoduodenectomy, an increase in diameter of the main pancreatic duct of the pancreatic remnant poses a radiographical challenge in differentiating between chronic obstructive pancreatitis and recurrent IPMN.

The 2017 IAP guideline [8], the European evidence-based guidelines on pancreatic cystic neoplasms [9], and the ACG guideline [10] recommend lifelong surveillance of all patients undergoing surgical resection of any IPMN as long as the patient remains fit for surgery.

The IAP guidelines recommend cross-sectional imaging at least twice a year for patients with positive family history, margin positivity for HGD and a nonintestinal subtype of resected IPMN, and every 6–12 months for all other patients. The modality of imaging is not specified.

The European evidence-based guidelines recommend surveillance of resected HGD or MD-IPMN every six months for the first two years, followed by yearly surveillance, whilst patients with LGD-IPMN should be followed in the same manner as nonresected IPMN patients (every six months for the first year, then yearly thereafter) and those with IPMN in the pancreatic remnant not meeting criteria for resection should be evaluated as nonresected BD-IPMN. The guidelines recommend MRI or EUS as the imaging modality of choice.

The ACG guidelines recommend a follow-up every six months with MRI or EUS for patients with resection of an HGD-IPMN and an MRI every two years for patients who had LGD or IGD in their IPMN. For patients with an IPMN in the remnant pancreas, recommendations for surveillance strategies are based on the size of the lesion.

In contrast, the AGA guidelines recommends an MRI scan every two years after resection of invasive disease or HGD. Further, they suggest against the routine surveillance of pancreatic cysts without HGD or malignancy at surgical resection [7]. In the light of the above discussion, both ACG and AGA recommendations do not seem to be sufficient as late long-term progression of IPMN is observed in both scenarios – under mere surveillance as well as postoperatively following partial pancreatectomy.

However, more research on the identification of both postoperative and preoperative predictors of recurrences, such as serum signatures [34], is needed in order to optimize modern treatment strategies for noninvasive IPMN. For selected elderly or frail patients with significant comorbidities in whom life expectancy is short or who would not be fit to tolerate pancreatectomy, follow-up after resection of a BD-IPMN may not be necessary.

Conclusion

The recurrence rate after resection of a noninvasive IPMN ranges between 1% and 20% with about 2–7% of invasive recurrences with a cumulative 10-year risk of

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developing indications for resection or invasive cancer of 18% and 38%, respectively. Early detection of progressive or recurrent IPMN before invasive cancer occurs improves long-term survival. The median time to recurrence can range up to five years after initial resection. Especially for patients with family history of pancreatic cancer, HGD in the resected specimen and positive resection margins present a high risk of recurrence also of invasive disease and should be monitored closely. All patients undergoing surgery for noninvasive IPMN should have lifelong surveillance, preferably with MRI or EUS. Age-appropriate cancer screening programs should be recommended due to the risk of extrapancreatic lesion development.

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Long-term Outcome after Observation and Surgical Treatment of Cystic Neoplasms: What is the Evidence?

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Introduction

Incidentally discovered pancreatic cyst neoplasms (PCNs) represent a modern pancreatic "pandemic" as their prevalence among the general population is constantly rising due to the extensive use of cross-sectional imaging such as computed tomography (CT) scan and magnetic resonance imaging (MRI) [1,2].

Originally, their treatment consisted of an aggressive surgical approach, based on the role of intraductal papillary mucinous neoplasms (IPMNs) as precursors of pancreatic cancer [3,4] with high presumed risk of malignancy resulting from retrospective and uncontrolled historical data.

Only recently, new evidence from large observational studies has highlighted that most cases can be safely watched over time due to a low risk of malignant progression [5–9]. Therefore, the management of PCNs has evolved towards fewer patients undergoing operative resection and fewer benign lesions being resected.

Three main guidelines are available to help determine the management of PCNs, namely the International Association of Pancreatology, the European evidence-based guidelines, and the American Gastroenterological Association [10–12]. All of them tend to be consistent regarding the main indications for surgery, as selective resection of PCNs seems to be appropriate, balancing the risk of malignancy with the risks of an operation. However, current recommendations are still based on expert opinions and scientific evidence provided mostly by surgical series, explaining why available guidelines remain characterized by high sensitivity and low specificity, and consequently burdened by a high rate of surgical overtreatment. In patients undergoing resection, either at the time of diagnosis or after observation, the chance of cure, the incidence of tumor recurrence, and disease-specific or overall survival depend on the cyst type and the presence of an invasive component.

Guidelines tend to significantly diverge regarding indications for surveillance and surveillance discontinuation. Patients managed nonoperatively are enrolled in radiologic surveillance protocols, with the aim of finding signs of possible malignant degeneration. Surveillance protocols require periodic cross-sectional imaging and/or endoscopic ultrasound, at a high economic cost for the community. Furthermore, there is no ideal test to diagnose transformed PCNs, and there is not general agreement on the optimum method and timeframe for follow-up for these lesions. Long-term results of surveillance protocols are starting to be reported in the literature, especially for lesions amenable to initial observation, such as serous cystic neoplasms and branch-duct IPMNs (BD-IPMNs) [13,14]. The cost of observing thousands of patients is a relevant burden for healthcare systems, and an ideal target for safe surveillance discontinuation also represents an urgent issue [9]. This chapter describes the long-term outcomes after observation or surgical resection of PCNs.

Serous Cystic Neoplasms

The invariably benign nature of serous cystic neoplasms, combined with the morbidity and potential mortality of pancreatic resections, led to a conservative management strategy. The safety of nonoperative management and the generally slow growth rate of these lesions have been extensively demonstrated [15,16]. A critical review of their pathologic features revealed the misinterpretation of the few cases reported as malignant in literature [17]. The optimal interval between follow-up imaging tests in pancreatic serous cystic must be tailored based on cyst

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morphology (i.e., unclear discrimination between serous and mucinous lesions) and growth rate, patient's age, sex, and tumor location. As a matter of fact, most of the patients currently undergoing resections for a serous cystic neoplasm are misdiagnosed with another pancreatic neoplasm, especially in younger individuals with body/tail lesions [13]. In case of a correct diagnosis, surgical resections only play a role for large cysts and with mass effect symptoms. In patients managed operatively, surgical resection ensures cure as serous cystic neoplasms do not recur. Therefore, a postoperative regular radiologic follow-up program is not necessary, thereby saving cost. Follow-up outpatient visits should be therefore focused on quality of life.

Mucinous Cystic Neoplasms

The rate of malignant MCNs found in surgical series is significantly variable, ranging from 0% to >30% and reaching the higher extreme in older studies. Different diagnostic criteria were used over the years, probably causing the inadvertent incorporation of several IPMNs (with a more aggressive behavior) in series which were also including only surgically resected tumors, with a consequent significant selection bias. Conversely, recent data have suggested a lower risk of malignant transformation, especially for smaller tumors [18–20]. In the absence of mural nodules, enhancing walls or cysts <50 mm, the incidence of malignancy may be negligible (and probably not higher than BD-IPMN), favoring surveillance in selected cases given the low risk of malignancy and the high rate of misdiagnosis [21]. As most patients with mucinous cystic neoplasms are middle-aged women with a long-life expectancy, nonoperative management of low-risk lesions based on periodic imaging may require years of radiologic follow-up at high cost. However, the surgical costs are probably higher, the complication rates and mortality are not negligible, and postoperative follow-up is required as well.

Radical resection of noninvasive neoplasms ensures cure. These neoplasms do not recur and, as already pointed out for serous cystic neoplasms, outpatient follow-up should be focused on quality of life. A regular radiologic postresection surveillance can probably be discontinued after five years, depending on final pathology.

Minimally invasive mucinous cystic neoplasms (invasion limited to the ovarian stroma), but without tissue invasion, have an excellent prognosis. On occasion, undocumented foci of invasive carcinoma may exist within a presumably noninvasive proliferative MCN and this emphasizes the importance of a careful histopathologic analysis of the entire lesion. In such cases, recurrence and metastases can be observed. In general, these patients should undergo a radiologic follow-up protocol, despite minimally invasive adenocarcinomas arising in mucinous cystic neoplasms being virtually cured by surgery, particularly if the neoplasms are completely examined histologically [22].

Five-year survival of patients with invasive mucinous cystic neoplasms (true cystadenocarcinoma) appears quite poor, ranging from 15% to 35%, albeit still somewhat better than those for typical ductal adenocarcinoma of the pancreas. The extent of invasion is the most significant prognostic factor in malignant mucinous cystic neoplasms. Some authors have suggested that patients with resected mucinous cystadenocarcinoma should be carefully followed on a six-month basis with cross-sectional imaging, matching the follow-up interval of ductal adenocarcinoma [23]. However, proof that surveillance imaging improves the prognosis compared with a strategy based on symptom recurrence is lacking.

Intraductal Papillary Mucinous Neoplasms

Outcome of IPMN Managed Nonoperatively

Initial follow-up is generally proposed only for patients with BD-IPMN devoid of malignant features (worrisome features and high-risk stigmata according to international guidelines), in which the risk of invasive cancer appears to be low. The majority of evidence confirmed this policy to be safe, with long-term data eventually becoming available.

The decision to follow up a presumed IPMN is based on multiple factors, namely the neoplasm type (main duct/mixed versus branch duct), patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference [10,11].

A recent observational study focused on IPMNs "crossing over" from observation to surgery, aiming to identify further dynamic predictors of malignant degeneration. In BD-IPMNs under surveillance, the development of additional worrisome features or high-risk stigmata was associated with the presence of high-grade dysplasia, while harboring a stable worrisome feature carried the lowest risk of malignant disease [24].

Subgroups of patients affected by BD-IPMNs with a low risk of malignant degeneration were identified by large observational studies. BD-IPMNs smaller than 1.5 cm without worrisome features were found by Pergolini et al. to have a significantly lower risk of malignant degeneration compared to larger cysts [5]. Marchegiani et al. found that patients older than 65 years of age with a BD-IPMN not developing worrisome

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features or high-risk stigmata in the first five years of diagnosis have the same risk of malignancy as the age-matched general population [9]. These findings are consistent with data from Lee and colleagues, estimating an invasive cancer incidence of around 1% in patients with BD-IPMNs without significant changes within the first five years of surveillance [25].

However, recently the largest surgical series on IPMNs ever published by a single referral center was presented by the Heidelberg group [26]. In this study comprising around 1439 patients, the "timing" of surgical resection was categorized according to final pathology: too early in case of low-grade dysplasia, too late in case of invasive cancer, and timely in case of intermediate- and high-grade dysplasia. Conversely, radiographic criteria of suspicion were present only in 34% and 88% of the "timely" and "too late" groups, respectively. Therefore, a cautious application of watch-and-wait policies was advocated by the authors.

In general, there is little evidence in the literature to guide the frequency and type of surveillance for IPMN managed nonoperatively. Some authors propose that surveillance can be safely spaced to every two years or even discontinued after long-term stability in low-risk lesions. However, concern over the development of pancreatic ductal adenocarcinoma in the pancreas harboring IPMN prompts continuation of active life-long surveillance at short intervals. Despite a decrease in the presumed overall malignancy risk, it is still too early to recommend discontinuation of surveillance in general based on current evidence, which is still germinal. Undoubtedly, surveillance results in significant utilization of cross-sectional imaging, endoscopic ultrasound, and economic investment. Research is focusing on fluid cyst biomarkers able to discriminate cystic malignant potential.

Outcome after Resection of IPMN

The outcome after resection of IPMN depends on different factors.

- Presence of an invasive component
- Epithelial histologic subtype
- Type of invasive component
- Duct involvement (BD vs MD)
- Resection margin
- Lymph node status (in invasive IPMN)

The prognosis of patients with noninvasive IPMN is excellent, and the five-year survival rate is reported to be >70% in most series. Some series have even suggested a five-year disease-specific survival close to 100% after resection. Conversely, the five-year survival rate for invasive IPMN (carcinoma arising in the background of IPMN) ranges from 34% to 62%. The outcome of invasive IPMN is therefore poor in comparison with noninvasive IPMN, but appears to be better than pancreatic ductal adenocarcinoma, which exhibits a five-year survival ranging from 9% to 21%. Whether this is due to a stage-shift with earlier diagnosis of IPMN, or to a true less aggressive behavior of invasive IPMN remains controversial [27]. Moreover, it has recently emerged that a genetically independent invasive cancer (namely, concomitant) could also arise in the context of an IPMN, making it indistinguishable from an IPMN-derived invasive cancer by classic clinical and pathologic features alone [28]. Disease recurrence may arise either in the pancreatic remnant or in peripancreatic or extrapancreatic sites.

There are data indicating that invasive IPMN is a heterogeneous disease, as it can exhibit different histologic patterns, namely colloid (colloid carcinoma), tubular (tubular adenocarcinoma) or oncocytic (oncocytic carcinoma). According to reports by Furukawa et al. and Mino-Kenudson et al., colloid carcinoma derives from intestinal-type IPMN, and is associated with a particularly indolent behavior [29]. Tubular adenocarcinoma correlates with the gastric and pancreatobiliary epithelial subtypes, and is associated with a dismal prognosis, like that of pancreatic ductal adenocarcinoma. Oncocytic carcinoma derives from the uncommon oncocytic subtype, and has a significantly better outcome than ductal adenocarcinoma, even though it can present with very late tumor recurrence (up to seven years after surgical resection) [27,29,30].

It is well established that the type of duct involvement, branch versus main duct (MD), is associated with the risk of harboring invasive cancer. Because the type of duct involvement correlates with epithelial subtypes of IPMN, it may also identify the likely histologic subtype of cancer. In particular, MD type is mainly intestinal and oncocytic, whereas BD type were often associated with the gastric epithelial type. The association of BD-IPMN/gastric subtype/tubular adenocarcinoma seems paradoxical, because gastric-type BD-IPMNs most often harbor low-grade dysplasia and absence of invasion. In the series by Mino-Kenudson et al., 15.6% of surgically resected gastric-type IPMNs gave rise to tubular adenocarcinoma [27]. According to these findings, the final pathologic report of resected invasive IPMN should indicate the histologic pattern of the invasive component and the background histologic subtype. This is of essential prognostic significance.

The clinical implications of surgical resection margin (frozen section of the pancreatic cut surface) are controversial, and results in the literature are mixed on this topic [31]. In general, not all studies found a strong correlation between margin status and risk of recurrence. There have been reports of invasive carcinomas in association with only mild or moderate dysplasia (adenomas or borderline lesions) within the IPMN in the remnant pancreas. A metaanalysis showed that the recurrence

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rate in patients with noninvasive IPMN was 3.72% with negative margins and 9.56% with positive margins. The same metaanalysis showed that recurrence after surgical resection of invasive IPMN occurred in 33.8% of patients with negative margins and 53.6% of patients with positive margins [32]. These data are reinforced by a large series from the Massachusetts General Hospital, stating that resection margin is indeed an independent predictor of tumor recurrence for invasive IPMNs [33].

Because recurrence in the remnant may be due to the presence of multifocal disease or to the development of a metachronous IPMN rather than the progression of margin-positive disease, the margin should be used as a marker of residual disease throughout the remnant.

Lymph node status is another factor affecting long-term outcome in invasive IPMN. The five-year survival of patients with positive lymph nodes ranged from 20% to 30%, while N0 patients lived much longer, ranging from 80% to 85%. Lymph node ratio >0.2 has been shown to be associated with worse prognosis [34]. Data from a metaanalysis demonstrated that nearly 77% of lymph node-positive patients recurred, while disease recurrence occurred in only 30.8% of patients with negative lymph nodes [32].

Very little is known about adjuvant chemotherapy for IPMNs, which seemed to improve survival only in invasive IPMNs with nodal disease or tubular differentiation in a recent retrospective series [35]. Evidence is even poorer with respect to neoadjuvant therapies, especially with modern chemotherapy regimens. One of the reasons for this may be the difficulty of achieving a cytologic differential diagnosis between invasive IPMN and pancreatic ductal adenocarcinoma, before the start of chemotherapy. Future trials are urgently needed to improve the level of evidence in this field.

Solid Pseudopapillary Neoplasms

More than 95% of patients with solid pseudopapillary neoplasms limited to the pancreas are cured by complete surgical excision. Local invasion or resectable liver and lymph node metastases are not contraindications for resection, and some patients with advanced tumors can survive for more than 10 years after the operation. During the follow-up period, recurrence of the disease in the liver or lymph nodes is uncommon, at 6.6%. Prognosis for solid pseudopapillary neoplasms with treated liver metastases usually surpasses five years. Conversely, other factors such as the presence of capsular invasion and pancreatic parenchyma invasion seem to correlate with the likelihood of tumor recurrence after complete surgical excision [36]. Overall, two-year survival rate (with or without metastases) was 97%, and five-year survival was around 95%.

Conclusion

The actual natural history of PCNs represents an enigma, which is slowly becoming clearer due to a new era of observational studies with long-term follow-up availability. Because it seems that survival is clearly favorable in comparison with pancreatic ductal adenocarcinoma, it will be of great importance to precisely predict how these neoplasms behave, with respect to the time to degeneration, the risk of developing a new IPMN or additional malignancy, and the risk of disease-specific mortality. The overall major postoperative morbidity and mortality of patients undergoing pancreatic resection for PCNs remain relatively high, similar to those for other indications. For this reason, a tailored and patient-centered decision is mandatory. Accurate surveillance, either pre- and postoperatively, seems necessary in most cystic neoplasms, since most have the potential to become malignant or to recur. On the other hand, the cost of observing thousands of patients is a relevant burden for healthcare systems and being able to select patients amenable for surveillance discontinuation according to different PCNs biology represents an urgent issue.

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Section 7

Neoplastic Tumors of the Endocrine Pancreas: Neuroendocrine Tumors of the Pancreas

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Epidemiology and Classification of Neuroendocrine Tumors of the Pancreas

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Introduction

Neuroendocrine tumors (NETs) of the pancreas are a heterogeneous group of epithelial neoplasms with a highly variable clinical presentation, malignant potential, and prognosis. Pancreatic NETs (pNETs) range from small, slow-growing, incidentally detected nonfunctional and/or functional tumors to frank aggressive malignancies. These lesions were earlier described as "islet cell tumors" based on the belief that they originate from cells in the islets of Langerhans. They were later considered to be "pancreatic endocrine tumors" when evidence suggested that they might be originating from pluripotent cells in the ductal epithelium [1,2]. The 2010 World Health Organization (WHO) classification system [3] recommended the use of the term "neuroendocrine" to describe these tumors as they are now considered to arise from cells that are part of the diffuse neuroendocrine cell system of the gastrointestinal tract and pancreas. These cells share certain unique biochemical (ability to synthesize, store, and secrete a number of amines and peptides) and immunohistochemical properties (documentation of markers of neuroendocrine differentiation, mainly expression of antigens commonly expressed by neuronal elements such as chromogranin A and synaptophysin, together with neuron-specific enolase) [4].

Epidemiology of Pancreatic Neuroendocrine Tumors (Table 98.1)

Data on epidemiology of pNETs are limited. Variations in coding and classification over time, and between different countries, have resulted in difficulties in precisely understanding the true epidemiology of these tumors. Moreover, various national, regional, and institutional cancer or NET registries, with their inherent deficiencies in data collection, are the major sources of epidemiology of pNETs.

The pNETs are rare tumors that possibly constitute <3% of all pancreatic tumors [5], and approximately 4–8% of all neuroendocrine tumors [6]. The annual incidence rate of pNETs is reportedly less than 1 per 100 000 person-years in population studies [5]. The absolute annual incidence rate of pNETs varies among registries in various countries, with pNETs ranging from the most common to the second most common site among gastroenteropancreatic NETs. The pNETs are most common between 60 and 80 years of age, with an earlier age of onset in patients with multiple endocrine neoplasia type 1 (MEN 1).

The incidence of pNETs is higher in autopsy studies, ranging from 0.1% to 10% [5]. Grimelius et al. from Sweden reported 13 pancreatic "islet cell adenomas" at autopsy among 1366 adults (0.95%) [7]. Kimura et al. from Japan found 20 "endocrine tumors of the pancreas" among 800 autopsy cases (mean age 78.7 years); the incidence of tumor was higher among the 60 randomly selected cases that had 5 mm thick sections of the pancreas; six (10%) of them were found to have an endocrine tumor as opposed to only 12 out of 738 cases (1.6%) that had histologic studies of three random sections of the pancreas [8]. However, Lam et al. from Hong Kong found only 13 cases (0.1%) of "pancreatic endocrine tumors" among 11472 autopsies performed from 1972 to 1995 [9].

There has been a rise in the incidence and prevalence of pNETs over the past few decades; this could either reflect a true increase in incidence or be the result of increased awareness of these tumors among physicians

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Table 98.1 Incidence of pancreatic neuroendocrine tumors in selected autopsy series after 1970s.

First author	Year published	Country	Number of autopsies	Number of "islet cell tumors"	Percentage
Grimelius L	1975	Sweden	1366	13	0.95
Kimura W	1991	Japan	800	20	2.5
Kimura W	1991	Japan	60 (5 mm sections)	6	10
Lam KY	1997	Hong Kong	11472	13	0.1

because of increased recognition and widespread adoption of nomenclature, grading, and staging of these tumors. Moreover, the availability of more sensitive imaging techniques has led to increased detection [10,11]. Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, Dasari et al. in 2017 reported that the age-adjusted annual incidence of all NETs in the USA had increased from 1.09 per 100 000 persons in 1973 to 6.98 per 100 000 persons in 2012, which includes a steep rise in the incidence of pNETs from 0.4 to 0.8 per 100 000 persons from 2000 to 2012 [12]. Another study, which specifically analyzed the annual age-adjusted incidence of pNETs in the USA using the SEER 18 database, reported a sharp increase in incidence of pNETs from 0.2647 to 1.0618 per 100000 persons over the time period 2000-2016 [13]. Similarly, an updated analysis of the epidemiologic trends of NETs in Taiwan reported an increase in incidence from 0.017 in 1996 to 0.446 per 100 000 persons in 2015, an annual percentage change of 28%; the overall percentage of pNETs among 7760 people with NETs increased from 3.65% (1996-2003) to 7.27% (2004-2009) to 13.09% (2010-2015) [14]. Studies based on national databases from China [15], India [16], Japan [17], and Norway [18] have all reported a similar increase in the incidence of pNETs.

Classification of Pancreatic Neuroendocrine Tumors

The classification of pNETs has changed periodically since the first attempts at classification of these tumors were made in the early 60s. They can be classified based upon:

- functionality as "functional or nonfunctional"
- association with inherited syndromes as "sporadic or syndromic"
- tumor biology and morphologic features
- evaluation of spread based on the Tumor-Node-Metastasis (TNM) staging system.

Functional vs Nonfunctional pNETs (Table 98.2)

"Functional" pNETs are associated with a hormone-secreted clinical syndrome. The clinical presentation of these tumors is dominated by the metabolic effects of the excess hormone(s) secreted by the tumor, and they are classified based upon the predominant clinical syndrome produced by the hormone secreted by the tumor. There is a poor correlation between peptide expression on immunohistochemical staining of the tumor and the circulating levels of respective secretory products; thus, the mere presence of positive immunohistochemical staining is not a defining criterion for a "functional" pNET. The updated 2016 European Neuroendocrine Tumor Society (ENETS) consensus guidelines for the management of functional and nonfunctional pNETs divides functional pNETs into "most common functional pNET syndromes," "established rare functional pNET syndromes," and "very rare functional pNET syndromes" [19]. Of the many established and possible functional pNETs, the two that are more commonly seen in clinical practice are insulinomas and gastrinomas.

"Nonfunctional" pNETs do not produce any specific hormone-secreted clinical syndromes. They are either detected incidentally during imaging or present with symptoms attributable to mass effect due to tumor bulk or distant metastases. Although some of them do not produce any amines or peptides, most do secrete substances such as chromogranin, pancreatic polypeptide, neurophysin, neuron-specific enolase, α subunit of human chorionic gonadotropin, and other peptides that do not result in any specific clinical syndrome.

Earlier reports suggested a preponderance of functional pNETs as they presented with recognizable clinical syndromes and were thus easier to identify. However, over the past two decades, nonfunctional pNETs have become the more common pNET as a result of improvement in imaging techniques and increased detection rate [10,11].

The differentiation of pNETs based on functionality does not shed light on their biological behavior or help predict their long-term prognosis in the majority of situations; the one exception is insulinoma, which in the majority of cases runs an indolent course. As such,

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Table 98.2 Functional pancreatic neuroendocrine tumors.

	Endocrine hormone secreted	Approximate incidence Patients per million per yr	Likelihood of malignancy (%)
More common			
Insulinoma	Insulin	2	<10
Gastrinoma	Gastrin	1	>50
Less common			
Glucagonoma	Glucagon	0.05 or more	>50
VIPoma	Vasoactive intestinal peptide	0.05	>50
Somatostatinoma	Somatostatin	Rare	>50
ACTHoma	Adrenocorticotrophic hormone	Rare	>50
GRFoma	Growth hormone-releasing hormone	Rare	>50
"Classic" carcinoid syndrome	Serotonin	Rare	>50
PTHrp-oma	Parathyroid hormone-related peptide	Rare	>50
Rare			
Calcitonin-omas	Calcitonin	Very rare	>50
Others (may be mixed)			
Hormones	"Big IGF-II", erythropoietin, luteinizing hormone, renin, CCK, GLP-1	Very rare	Unknown

the biological behavior of functional pNETs should also be classified as one would classify a nonfunctional pNET, including the grade and stage of the tumor. However, it is essential to identify functional pNETs because they produce classic hormone-secreted clinical syndromes that require dedicated investigations, therapeutic interventions, and structured long-term follow-up.

Sporadic vs Syndromic pNETs (Table 98.3)

Less than 10% of pNETs are associated with inherited disorders. The four common inherited disorders that manifest a pNET are multiple endocrine neoplasia type 1 (MEN 1), von Hippel–Lindau disease (VHL), neurofibromatosis type 1 (von Recklinghausen disease) (NF 1), and tuberous sclerosis complex (TSC) [20].

Approximately 80–100% of patients with MEN 1, 10–17% of patients with VHL, up to 10% of patients with NF 1, and 1% of patients with TSC will develop a pNET within their lifetime [20]. The pNETs associated with inherited disorders are frequently multifocal. As with functional pNETs, the association of these tumors with a specific inherited syndrome does not help predict their biological behavior or long-term prognosis. However, it is important to recognize a syndromic pNET not only to prompt a diligent search in the index patient to identify the multifocal pancreatic and extrapancreatic tumors but also to allow early and periodic surveillance of family members.

Table 98.3 Pancreatic neuroendocrine tumors associated with hereditary syndromes.

Syndrome	Gene location	Incidence %	Tumor type	Location
MEN 1	11q13	80–100	Nonfunctional, gastrinoma, insulinoma	Pancreas Duodenum
VHL disease	3p25	10-17	Nonfunctional	Pancreas
NF 1	17q11	Up to 10	Somatostatinoma	Pancreas
TSC	9q34 (TSC 1) 16p13.3 (TSC 2)	<5	–	Pancreas

MEN, multiple endocrine neoplasia; NF, neurofibromatosis; TSC, tuberous sclerosis complex; VHL, von Hippel–Lindau.

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Based on Tumor Biology and Morphologic Features (Tables 98.4–98.6)

Over the years, the classification of this rare group of tumors has evolved, and a number of earlier classification systems exist. Most classification systems do make a clear and sharp distinction between well-differentiated pNETs and poorly differentiated pancreatic neuroendocrine carcinomas (pNECs) that have an aggressive course with poor prognosis. Morphologic features of the tumor, extent of local/distant spread, and aggressiveness of the tumor are common to most classification systems. It should be emphasized that almost all pNETs are potentially malignant, and can metastasize, even after many years.

The salient classification systems proposed over the years for pNETs include the following.

- Capella classification system 1995 [21]
- Armed Forces Institute of Pathology (AFIP) classification system 1997 [22]
- Memorial Sloan Kettering classification system 2002 [23]
- 2004 WHO classification system [24]
- 2006 ENETS TNM staging and grading system [25]
- 2010 WHO classification system [3]
- International Union for Cancer Control/American Joint Committee on Cancer/WHO TNM staging system 2010 [26,27]
- 2017 WHO classification system [28]
- Eighth edition of the AJCC/UICC TNM staging system (2018) [29]

Table 98.4 2006 European Neuroendocrine Tumor Society grading proposal for pancreatic neuroendocrine tumors.

Grade	Mitotic count per 10 high-power fields[a]	Ki-67 labeling index (%)[b]
Grade 1 (G1)	<2	≤2
Grade 2 (G2)	2–20	3–20
Grade 3 (G3)	>20	>20

[a] 10 high-power fields = 2 mm^2, at least 40 fields (at 40× magnification; evaluated in areas of highest mitotic density).
[b] MIB1 antibody; percentage of 2000 tumor cells in areas of highest nuclear labeling.

Table 98.5 2017 World Health Organization classification and grading of pancreatic neuroendocrine tumors.

Classification/grade	Mitotic count (per 10 high-power fields)	Ki-67 labeling index (%)
Well-differentiated pNETs		
Neuroendocrine tumour – Grade 1	<2	<3
Neuroendocrine tumour – Grade 2	2–20	3–20
Neuroendocrine tumour – Grade 3	>20	>20
Poorly differentiated pNETs		
Neuroendocrine carcinoma – Grade 3 (Small cell type) (Large cell type)	>20	>20
MiNEN (Mixed endocrine nonendocrine neoplasm)		

Table 98.6 Comparison of the 2010 and 2017 World Health Organization classification and grading of pancreatic neuroendocrine tumors.

WHO 2010 classification/grade	WHO 2017 classification/grade	Mitotic count (per 10 high-power fields)	Ki-67 labeling index (%)
Well-differentiated pNETs			
Neuroendocrine tumour – Grade 1	Neuroendocrine tumour – Grade 1	<2	<3
Neuroendocrine tumour – Grade 2	Neuroendocrine tumour – Grade 2	2–20	3–20
–	Neuroendocrine tumour – Grade 3	>20	>20
Poorly differentiated pNETs			
Neuroendocrine carcinoma – Grade 3 (Small cell type) (Large cell type)	Neuroendocrine carcinoma – Grade 3 (Small cell type) (Large cell type)	>20	>20
MANEC (Mixed adenoneuroendocrine carcinoma)	MiNEN (Mixed endocrine nonendocrine neoplasm)	–	–

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We will restrict ourselves in this chapter to describing in detail the 2004, 2010, and 2017 WHO pNETs classification systems [3,24,28], the ENETS TNM staging and grading system proposed in 2006 [25], and the seventh (2009/2010) and eighth editions (2018) of the AJCC/UICC TNM staging systems [26,27,29].

2004 WHO Classification of pNETs

The 2004 WHO classification system divided pNETs into well-differentiated endocrine tumors with benign behavior, well-differentiated endocrine tumors with uncertain behavior, well-differentiated endocrine carcinomas (WDEC), poorly differentiated endocrine carcinomas (PDEC), and mixed exocrine and endocrine tumors [24]. Unlike the earlier 1995 Capella classification system [21], apart from staging parameters (such as tumor size, invasion of adjacent structures, and metastases), grading parameters (such as the aggressiveness of the tumors, as assessed by the mitotic activity and/or Ki-67 labeling index) were introduced to refine prognostication. Unlike the earlier 2002 Memorial Sloan Kettering classification system [23], which included presence of necrosis for grading, the 2004 WHO classification was based solely on the proliferative rate of the tumor as reflected by the mitotic activity and/or Ki-67 labeling index for grading. This classification was tested clinically and found to have prognostic relevance [30].

The 2004 WHO classification system was a hybrid of staging and grading; an attempt at classification of pNETs was made based not only on staging parameters but also on the grade of tumor. However, tumor stage and grade have independent prognostic significance. Moreover, the 2004 WHO classification system did not allow for the application of the system to advanced stages of the disease; an advanced pNET need not necessarily be very aggressive; this is evident especially in metastatic pNETs wherein, depending upon tumor grade, some metastatic disease remains indolent for prolonged periods of time whereas others progress rapidly.

2006 ENETS TNM System (Tables 98.4 and 98.7)

In 2006, the ENETS proposed a TNM staging system of foregut NETs (including pNETs), which also included a grading system [25]. The 2006 ENETS grading and TNM staging system effectively separated staging from grading. It was realized that unlike poorly differentiated endocrine carcinomas (PDECs), where the behavior of the tumor is more aggressive and predictable, it was difficult to predict the behavior of well-differentiated pNETs, which could range from being indolent to the more aggressive forms. It was therefore decided to subdivide well-differentiated pNETs into two grades to help prognosticate them better based on proliferation markers of mitoses and Ki-67 labeling index. They proposed that mitoses should be counted in at least 40 high-power fields (HPFs) in areas where they are most frequent, and expressed as number of mitoses per 10 HPFs (2 mm^2). Only clear-cut mitotic figures should be counted. For Ki-67 protein assessment, they recommended that the labeling index should be assessed in 2000 tumor cells in areas where the highest nuclear labeling is observed. Ki-67 is a nuclear protein expressed in dividing cells closely associated with the nucleolus and heterochromatin. The monoclonal MIB-1 antibody is used for labeling.

Pancreatic NETs were divided into three tumor categories: grade 1 (G1), grade 2 (G2), and grade 3 (G3), based on the number of mitoses seen per 10 HPFs and/or the percentage of tumor cells that stain for Ki-67. In general, G1 and G2 referred to well-differentiated pNETs, and G3 indicated poorly differentiated neuroendocrine carcinoma.

Table 98.7 2006 ENETS TNM classification and disease staging system for endocrine tumors of the pancreas.

T definition	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Limited to the pancreas and size <2 cm
T2	Limited to the pancreas and size 2–4 cm
T3	Limited to the pancreas and size >4 cm or invading duodenum or bile duct
T4	Invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)
	For any T, add (m) for multiple tumours
N definition	**Regional lymph nodes**
Nx	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M definition	**Distant metastases**
Mx	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis
Stage definition	
Stage 1	T1, N0, M0
Stage IIa	T2, N0, M0
Stage IIb	T3, N0, M0
Stage IIIa	T4, N0, M0
Stage IIIb	Any T, N1, M0
Stage IV	Any T, any N, M1

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2010 WHO classification system (Table 98.6)

The aim of the 2010 WHO classification system was to further standardize the classification of gastroenteropancreatic (GEP)-NETs [3]. It used a proliferation-based grading system together with the classic histologic features-based classification. It emphasized the malignant potential of pNETs.

It divided pNETs into "neuroendocrine tumours" (NETs), which include low-to-intermediate grade, well-to-moderately differentiated pNETs, and "neuroendocrine carcinomas" (NECs), which include high-grade, moderately-to-poorly differentiated pNETs. The 2010 WHO classification endorsed the ENETS 2006 TNM staging and grading system [25]; based on the proliferative rate of the tumor (mitotic count/10 HPF and/or Ki-67 labeling index), pNETs were divided into three grades: grade 1 (G1) and grade 2 (G2) tumors referred to NETs, whereas NECs were all uniformly high-grade tumors (G3). In cases of discordance between mitotic count and Ki-67 labeling index in assessing proliferation rate, the 2010 WHO classification system recommended use of the higher grade of either mean.

Unlike the 2004 classification system [24], the 2010 WHO classification system separated grading from staging. Classification is primarily based upon the proliferative rate of the tumor rather than stage-pertinent features such as size of tumor, regional invasion or distant metastases. The 2010 classification system recognized the need for a separate staging system, and together with the AJCC, endorsed the TNM staging system developed in 2009 by the UICC (UICC/AJCC/WHO 2010 TNM) [26,27]. This separation of grading from staging, which was earlier proposed by the ENETS in 2006, allowed for prognostication of pNETs even when insufficient information is available for staging, a fairly frequent scenario in clinical practice, when only small biopsy specimens are available for assessment of tumor grade but detailed clinical assessment, including size and invasion, is missing.

However, it was soon realized that there was a discrepancy between grading and differentiation in the grade 3 pancreatic neuroendocrine carcinoma (pNEC) group as classified in the 2010 WHO system; a few morphologically well-differentiated pNETs with a high Ki-67 labeling index were technically classified as grade 3 NEC [31]. However, these well-differentiated NETs, classified as grade 3 NEC, have a better prognosis than, and are generally not as sensitive to the chemotherapy regimen used for, poorly differentiated grade 3 NEC. Thus, the definition of grade 3 NEC based solely on mitotic index and/or Ki-67 labeling index was too broad, and failed to distinguish between grade 3 NET and grade 3 NEC, leading to inappropriate treatment decisions and unsatisfactory clinical outcomes.

2017 WHO Classification System (Tables 98.5 and 98.6)

To correct the above discrepancy, the latest 2017 WHO classification system has not only taken cellular proliferation but also cellular differentiation into consideration, and has thus changed the definition of grade 3 NEC [28]. Grade 3 NEC has now been divided into two groups: a new subset of grade 3 pNETs has been introduced, which includes morphologically well-differentiated pNETs with high mitotic index and/or Ki-67 labeling index (>20%), and the earlier grade 3 pNEC now includes only the morphologically poorly differentiated pancreatic neuroendocrine carcinoma with high mitotic index and/or Ki-67 labeling index (>20%) [28]. The 2017 WHO classification system retains the earlier pNETs grade 1 and grade 2 categories. It has also changed the nomenclature for mixed adenoneuroendocrine carcinoma (MANEC), as described in the 2010 classification system, to mixed endocrine nonendocrine neoplasm (MiNEN). This change has been made to acknowledge the fact that not all mixed tumors are high-grade malignant carcinomas; moreover, the nonendocrine component may include carcinomas other than adenocarcinoma, including acinar cell carcinoma or squamous cell carcinoma. Table 98.6 lists the differences between the 2010 and 2017 WHO classification systems for pNETs.

Tumor-Node-Metastasis (TNM) Staging System
(Tables 98.7, 98.8 and 98.9)

The TNM staging system is an instrument for prognostication, allowing death risk assessment at diagnosis and guiding therapy. The ability to stratify patients into different stages at diagnosis reflecting increasingly worsening prognosis allows for planning of progressively more aggressive therapy. The success of the TNM staging system depends to a large extent on its ability to reflect the biology and natural history of the cancer. Well-differentiated pNETs, which are much more common than the more aggressive poorly differentiated pNETs, are biologically different from adenocarcinoma of the pancreas; they are larger in size, more indolent, late to metastasize, run a long course despite widespread metastases, and overall have a much better prognosis than adenocarcinoma of the pancreas.

A TNM staging system for pNETs was first proposed in 2006 by the ENETS [25]. Subsequently, in 2009, the UICC released the seventh edition of the TNM classification of malignant tumors, which included a TNM staging system for well-differentiated pNETs [26]; this staging system was subsequently endorsed by both the AJCC and the WHO in 2010 [27]. However, tumor definition and the derived stages differed slightly between the two staging systems; as a result, although both systems used identical TNM terminology, they referred to

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Table 98.8 TNM classification and disease staging for well-differentiated endocrine tumors of the pancreas (eighth edition of the AJCC/UICC 2018)

Definitions	UICC/AJCC/WHO 2010 TNM
T definition	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Limited to the pancreas and <2 cm in greatest dimension
T2	Limited to the pancreas and 2–4 cm in greatest dimension
T3	Limited to the pancreas, >4 cm or invading the duodenum or common bile duct
T4	Tumor invades adjacent structures
N definition	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M definition	**Distant metastasis**
M0	No distant metastasis
M1 M1a M1b M1c	Distant metastasis Metastasis confined to liver Metastasis in at least one extrahepatic site Both hepatic and extrahepatic metastasis
Stage definition	
Stage I	T1, N0, M0
Stage II	T2–T3, N0, M0
Stage III	T4, N0, M0 Any T, N1, M0
Stage IV	Any T, any N, M1

slightly different extent of disease. The major source of contention was the tumor stage T3: the 2010 UICC/AJCC/WHO TNM staging system defined it as peripancreatic tumor spread without major vascular invasion whereas the 2006 ENETS system defined it as tumor 4 cm in size, confined to the pancreas, or invading the duodenum or bile duct.

The 2006 ENETS TNM staging system has subsequently been validated by a number of series reporting on pNETs [32–35]. Since its introduction in 2006, it has been widely used in Europe, with good prognostic discriminatory power amongst the various stages of pNETs. In contrast, although a number of centers in the United States were mandated to use the 2010 UICC/AJCC/WHO TNM staging system, independent validation of this system is limited [36]. Rather, there was a significant overlap of survival between stages II and III when using the 2010 UICC/AJCC/WHO TNM staging system.

Overall, both these TNM staging systems are predictive of patient outcome, and when combined with classification based on histologic and proliferative features, help stratify pNETs into groups of increasing malignant potential. However, a comparison between the 2006 ENETS and the 2010 UICC/AJCC/WHO TNM staging systems, analyzing 891 patients from eight European centers, found the 2006 ENETS TNM staging system to be superior and more accurate than the 2010 UICC/AJCC/WHO TNM staging system [34].

The limitations and inconsistencies in the seventh edition of the AJCC/UICC 2009/2010 staging system led to the introduction of the eighth edition in 2018 for well-differentiated pNETs [29]. Just as in the seventh edition, pancreatic neuroendocrine carcinomas continue to be staged similar to pancreatic ductal adenocarcinoma. The criterion for peripancreatic tumor spread of well-differentiated pNETs to define T3 in the seventh edition has been removed in the eighth edition; rather, as with the ENETS staging system for well-differentiated pNETs, tumor staging is mainly based on size. The M1 category has been further subdivided in the eighth edition into three stages depending upon the metastatic sites.

However, despite these changes, there still remains discrepancy in the derived stages between the 2006 ENETS staging system and the 2018 AJCC/UICC staging system. The 2006 ENETS system subdivides stage II and III into IIA/IIB and IIIA/IIIB whereas the 2018 AJCC system classifies well-differentiated pNETs into four simple stages, without dividing any of the stages into subcategories (Table 98.9).

The eighth edition of the AJCC/UICC staging system for pNETs has been validated recently; it was found to provide better discrimination in overall survival rate and disease-free survival rate than the 2006 ENETS and the seventh edition of AJC/UICCC staging systems [37].

Further modifications of the TNM staging system of pNETs are to be expected in the future. However, such modifications should be undertaken only after carefully analyzing the ability of the two existing systems, namely the 2006 ENETS and the 2018 AJCC/UICC TNM staging systems, in prognosticating pNETs, which should be assessed by collecting data using uniform protocols in a prospective manner. Until the adoption of such a unified TNM staging system, one should clearly mention which of the two systems has been used for TNM staging to allow for comparison between reported series using the alternate TNM staging system.

The current staging system for poorly differentiated pancreatic neuroendocrine carcinomas is unsatisfactory. pNECs account for approximately 15% of all pancreatic neuroendocrine tumors [38,39]. The vast majority of participants studied to design the 2006 ENETS TNM staging system had well-differentiated pNETs, and

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Table 98.9 Differences between the 2006 ENETS, the seventh and eighth editions of the AJCC/UICC 2018 TNM stating systems for well-differentiated pancreatic NETs.

Definitions	ENETS 2006	UICC/AJCC/WHO 2010 7th UICC/AJCC (2009/2010)	UICC/AJCC 2018 8th UICC/AJCC
T definition			
T1	Confined to pancreas, <2 cm	Confined to pancreas, <2 cm	Confined to pancreas, <2 cm
T2	Confined to pancreas, 2–4 cm	Confined to pancreas, >2 cm	Confined to pancreas, 2–4 cm
T3	Confined to pancreas, >4 cm, or invades duodenum or bile duct	Peripancreatic spread, without major vascular invasion	Confined to pancreas, >4 cm, or invades duodenum or bile duct
T4	Invasion of adjacent organs or major vessels	Invasion of adjacent organs or major vessels	Invasion of adjacent organs or major vessels
N definition			
N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis	Regional lymph node metastasis
M definition			
M0	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	M1a—metastasis confined to liver M1b—metastasis in at least one extrahepatic site M1c—both hepatic and extrahepatic metastases
Stage definition			
Stage I	T1, N0, M0	Divided into IA and IB	T1, N0, M0
Stage IA	–	T1, N0, M0	–
Stage IB	–	T2, N0, M0	–
Stage II	Divided into IIA and IIB	Divided into IIA and IIB	T2–T3, N0, M0
Stage IIA	T2, N0, M0	T3, N0, M0	–
Stage IIB	T3, N0, M0	T1–T3, N1, M0	–
Stage III	Divided into IIIA and IIIB	T4, any N, M0	T4, N0, M0 *or* Any T, N1, M0
Stage IIIA	T4, N0, M0	–	–
Stage IIIB	Any T, N1, M0	–	–
Stage IV	Any T, any N, M1	Any T, any N, M1	Any T, any N, M1a, M1b, or M1c

participants with pNECs were underrepresented. The 2010 UICC/AJCC/WHO system and the updated eighth edition of the AJCC/UICC TNM staging system recommended using the same staging system for pNECs as used for exocrine pancreatic malignancies. The tumor definitions and derived stages for pNECs from the 2006 ENETS and the seventh and eighth editions of UICC/AJCC TNM staging systems differ [40].

The major difficulty in designing a pNEC-specific TNM staging system stems from the fact that because of its rarity, most studies on pancreatic neuroendocrine tumors have included very few participants with pNECs. A recent study that included 644 participants with pathologically confirmed pNECs from the SEER database found that the seventh edition of the AJCC/UICC TNM staging system was superior to the eighth edition and the 2006 ENETS staging systems for predicting the prognosis of pNECs [40]. However, the study authors suggested minor modifications in the seventh edition of the UICC/AJCC TNM staging system to allow for more accurate and reliable prediction of pNEC prognosis.

As with the staging of pNETs, further modifications of the TNM staging system of pNECs is to be expected in the future. Until the adoption of such a unified TNM staging system for pNECs, one should clearly mention

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which system has been used for the TNM staging to allow comparison between reported series using the alternate TNM staging system.

Conclusion

Pancreatic NETs should be classified based on the 2017 WHO classification system into morphologically well-differentiated NET (grade 1, 2 or 3) or morphologically poorly differentiated NEC (grade 3). Grading should be assessed using both the number of mitoses per 10 HPFs and the Ki-67 labeling index; however, if the specimen size is small, such as a biopsy specimen, with insufficient HPFs for mitoses examination, then grading can be based solely on the Ki-67 labeling index. In the rare event of discordance between the two markers of proliferation rate, use the higher grade. Pancreatic NETs should also be staged, whenever possible, using one of the two current TNM staging systems (2006 ENETS or 2018 AJCC/UICCTNM). Care should be taken to mention the TNM staging system used. The 2017 WHO 2010 classification and a TNM staging system should be applied to all pNETs irrespective of whether they are functional or nonfunctional, syndromic or sporadic.

Further refinements in the classification and TNM staging systems of pNETs can be expected to allow for better prognostication and death risk assessment at diagnosis, and to guide therapy. Collection of prospective data from multiple centers using unified management protocols over the coming years is the key for future refinement of the classification system of well-differentiated pNETs, and hopefully the emergence of a unified TNM staging system. Moreover, the current system for staging poorly differentiated pNECs is rather unsatisfactory and further modifications of the TNM staging system of pNECs is to be expected in the future. However, until that time, the 2017 WHO 2010 classification system, together with the use of either one of the two TNM staging systems (2006 ENETS or 2018 AJCC/UICC), should remove much of the earlier controversy surrounding the classification of these rare endocrine tumors of the pancreas, allowing proper prognostic stratification, guiding appropriate stage- and grade-specific therapy, enabling evaluation of new therapies and comparison of results of published therapeutic trials on pNETs.

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Pathology of Neuroendocrine Neoplasms

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Definition, Terminology, and Classification of PanNEN

Pancreatic neuroendocrine neoplasms (PanNENs) are malignant epithelial neoplasms with neuroendocrine differentiation. Based on the current World Health Organization (WHO) classification published in 2019 for digestive organs and in 2022 for endocrine pancreas, PanNENs are divided into neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and mixed nonneuroendocrine and neuroendocrine neoplasms (MiNENs) [1,2]. The same classification system and terminologies are applied to NENs in other digestive organs [1].

A NET is a well-differentiated NEN and is classified into NET G1, G2, and G3 based on one of the higher values of Ki-67 proliferation index (%) and mitotic counts in 2 mm^2 (Table 99.1).

The grading of pancreatic NETs (PanNETs) is significantly associated with patient outcome [3]. The Ki-67 proliferation index is a percentage of nuclear labeling of tumor cells counted in at least 500 tumor cells. Mitotic counts are number of mitotic figures evaluated in 2 mm^2 of the tumor area. The Ki-67 proliferation index is distinctly higher than mitotic counts in most cases and predicts patient survival in PanNETs [4,5]. NET G3 was first proposed in the WHO classification for endocrine pancreas and has been applied for all digestive systems in the 2019 WHO classification [1,2]. PanNET G3 accounts for 2% of primary PanNETs [3] and 15% of primary and metastatic PanNETs [6]. Pancreas is the most frequent origin for NET G3 among digestive organs [6]. The relevant tumors have also been recognized in nondigestive organs including lung and thymus [6–8].

PanNETs smaller than 5 mm are termed pancreatic neuroendocrine microtumors. Microadenomatosis is a multifocal occurrence of microtumors.

PanNETs can be associated with clinical syndromes (functioning/syndromic PanNETs) caused by abnormal hormone secretion by tumor cells. These include mainly insulinomas, gastrinomas, glucagonomas, VIPoma and other rare hormone-secreting PanNETs, such as ACTH and serotonin.

Functioning PanNETs account for less than 40% of all PanNETs [9]. Nonfunctioning PanNETs are not associated with clinical symptoms by abnormal peptide hormone secretion. Nonfunctioning PanNETs are often diagnosed incidentally; 30–70% of patients with multiple endocrine neoplasia type 1 (MEN 1), caused by a germline mutation of a tumor suppressor gene *MEN1* located on chromosome 11q13, develop PanNETs [2]. MEN 1-associated PanNETs are typically multiple microtumors (microadenomatosis) and macrotumors (NETs), of which often one functioning PanNET (i.e., insulinoma) is present [10]. In addition, patients typically develop small duodenal gastrinomas that lead to Zollinger–Ellison syndrome [10]. About 12% of patients with von Hippel–Lindau syndrome (VHL), caused by a germline mutation of the *VHL* tumor suppressor gene on chromosome 3q25, develop PanNETs and the VHL-associated PanNETs are so far all nonfunctioning [11]. PanNETs may arise in 3–9% of patients with tuberous sclerosis [12,13]. Tuberous sclerosis (TSC) is an autosomal dominant disorder caused by a germline mutation of the tumor suppressor gene *TSC1* or *TSC2*. The TSC-associated PanNET can be both functioning and nonfunctioning sclerosis [12,13]. Neurofibromatosis 1 (NF1), caused by a germline mutation of *NF1*, may be associated with somatostatin-producing periampullary NETs.

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Table 99.1 World Health Organization 2022 classification of neuroendocrine neoplasms of the digestive system.

	Mitotic index (per 2mm^2)	Ki-67 index (%)
Well differentiated NENs		
NET G1	<2	<3
NET G2	2–20	3–20
NET G3	>20	>20
Poorly differentiated NENs		
NEC	>20	>20

Pancreatic NECs (PanNECs) are classified into large cell and small cell types based on cellular morphology and both types are aggressive neoplasms. PanNECs have a common molecular genetic background as pancreatic ductal adenocarcinomas and are distinct from those of PanNETs (see Chapter 100 Molecular genetics of neuroendocrine tumors) [14,15].

Pancreatic MiNENs are composed of both NEN and non-NEN, each component constituting more than 30% of the total tumor tissue. Most pancreatic MiNENs are mixed ductal neuroendocrine carcinomas.

In the TNM classification system created by the Union for International Cancer Control (UICC), PanNETs and PanNECs are treated separately but the differences are limited, only seen in pT1, pN1, and pM1 categories (Table 99.2) [16].

Macroscopy

PanNETs can arise in all parts of the pancreas. Smaller PanNETs are usually well circumscribed, showing a monotonous colored, whitish tan to yellowish cut surface (Fig. 99.1a). Larger PanNETs often show a multinodular

Table 99.2 TNM classification of pancreatic neuroendocrine tumors proposed by the European Neuroendocrine Tumor Society (ENETS TNM) and by the International Union for Cancer Control/American Joint Cancer Committee/WHO in 2017 (UICC/AJCC TNM, 8th edition). Source: [16]/John Wiley & Sons.

	Well differentiated neuroendocrine tumors	Poorly differentiated neurondocrine carcinoma
Primary Tumor (T)		
TX	Cannot be assessed	Cannot be assessed
T0	Not evident	Not evident
T1	Limited to the pancreas, <2 cm	T1a Limited to the pancreas, 0.5 cm or less
		T1b Limited to the pancreas, 0.5 cm ≤, < 1 cm
		T1c Limited to the pancreas, 1 cm ≤, < 2 cm
T2	Limited to the pancreas, 2-4 cm	Limited to the pancreas, 2-4 cm
T3	Limited to the pancreas, >4 cm, or invasion of duodenum or bile duct	Limited to the pancreas, >4 cm, or invasion of duodenum or bile duct
T4	Invading adjacent organs (stomach, spleen, colon, adrenal grand) or the wall of large vessels (celiac axsis or the superior mesenteric artery)	Invading adjacent organs (stomach, spleen, colon, adrenal grand) or the wall of large vessels (celiac axsis or the superior mesenteric artery)
Regional Lymph Node (N)		
NX	Cannot be assessed	NX Cannot be assessed
N0	No regional lymph node involvement	N0 No regional lymph node involvement
N1	Regional lymph node involvement	N1 Metastasis in 1–3 regional lymph nodes
		N2 Metastasis in 4 or more regional lymph nodes
Distant Metastasis (M)		
M0	No distant metastasis	M0 No distant metastasis
M1	M1a Only hepatic	M1 Distant metastasis
	M1b Extrahepatic metastasis	
	M1c Hepatic and extrahepatic	

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

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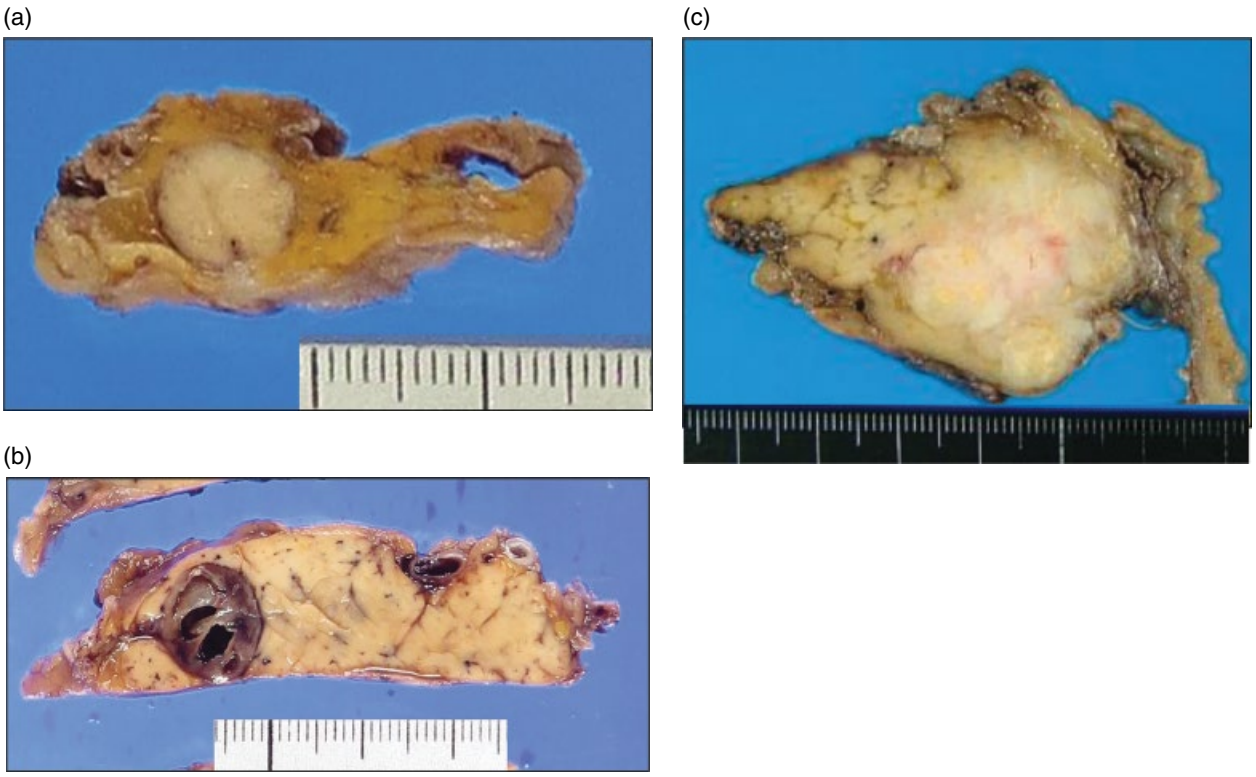


Figure 99.1 Macroscopic images of pancreatic neuroendocrine neoplasms (PanNENs). (a) A round to oval-shaped, well-circumscribed tumor with a whitish-tan cut surface observed in pancreatic neuroendocrine tumor (PanNET) G1. (b) A well-demarcated tumor with cystic changes observed in PanNET G1. (c) A tan-white and focally yellowish tumor with unclear boundaries observed in pancreatic neuroendocrine carcinoma (PanNEC) large cell type.

and heterogenous cut surface. Tumor size at the time of surgery varies from 0.5 cm to 20 cm in diameter. Insulinomas are generally detected as small lesions (<2 cm), whereas nonfunctioning PanNETs are usually detected as larger lesions. Cystic degeneration is not rare and is often associated with glucagon production by the tumor cells (Fig. 99.1b) [17]. PanNECs exhibit unclear boundaries (Fig. 99.1c). Necroses are not uncommon in NETs G3 and NECs (Fig. 99.1c).

Microscopy

PanNETs are characterized by solid and trabecular growth patterns. Solid tumor cells show either a solid-nested or paraganglioma-like pattern. The trabecular growth patterns include trabecular NOS, trabecular-reticulated (Fig. 99.2a,b), trabecular-gyriform and trabecular-glandular patterns (Fig. 99.2c). Capillary or fibrocapillary stroma intervenes within tumor cell nests (Fig. 99.2a). Tumor cells of PanNETs are uniform in size and shape, having round to oval nuclei, with a coarsely granular (so-called salt and pepper) chromatin pattern (Fig. 99.2a). Nucleoli may be observed but are mostly inconspicuous (Fig. 99.2a). Cytoplasm of the tumor cells is mostly granular and appears to be slightly eosinophilic. The extent of fibrosis or hyalinosis varies among cases. Stromal amyloid deposition is occasionally observed in functioning PanNETs, especially insulinoma (Fig. 99.2e).

Oncocytic PanNETs exhibit abundant eosinophilic cytoplasm due to abnormal mitochondrial accumulation. Oncocytic PanNETs tend to display larger nuclei and conspicuous nucleoli (Fig. 99.2f) and tend to have a higher incidence of lymph node metastasis [18]. Clear cell PanNETs have abundant clear cytoplasmic vacuoles or foamy microvesicular cytoplasm (Fig. 99.2g). Nuclei are pushed by lipid vacuoles and appear to be polygonal and pyknotic. Clear cell features have been described in VHL-associated PanNETs [19,20]. Pleomorphic PanNETs present large and hyperchromatic nuclei with marked pleomorphism, without high proliferative activity or necrosis (Fig. 99.2h) [21]. Hepatoid PanNETs are characterized by polygonal cells, prominent nucleoli, and pale acidophilic cytoplasm [21].

PanNECs are characterized by diffuse or solid sheet-like patterns with geographical necrosis. Tumor cells of the large cell type have a high degree of nuclear pleomorphism,

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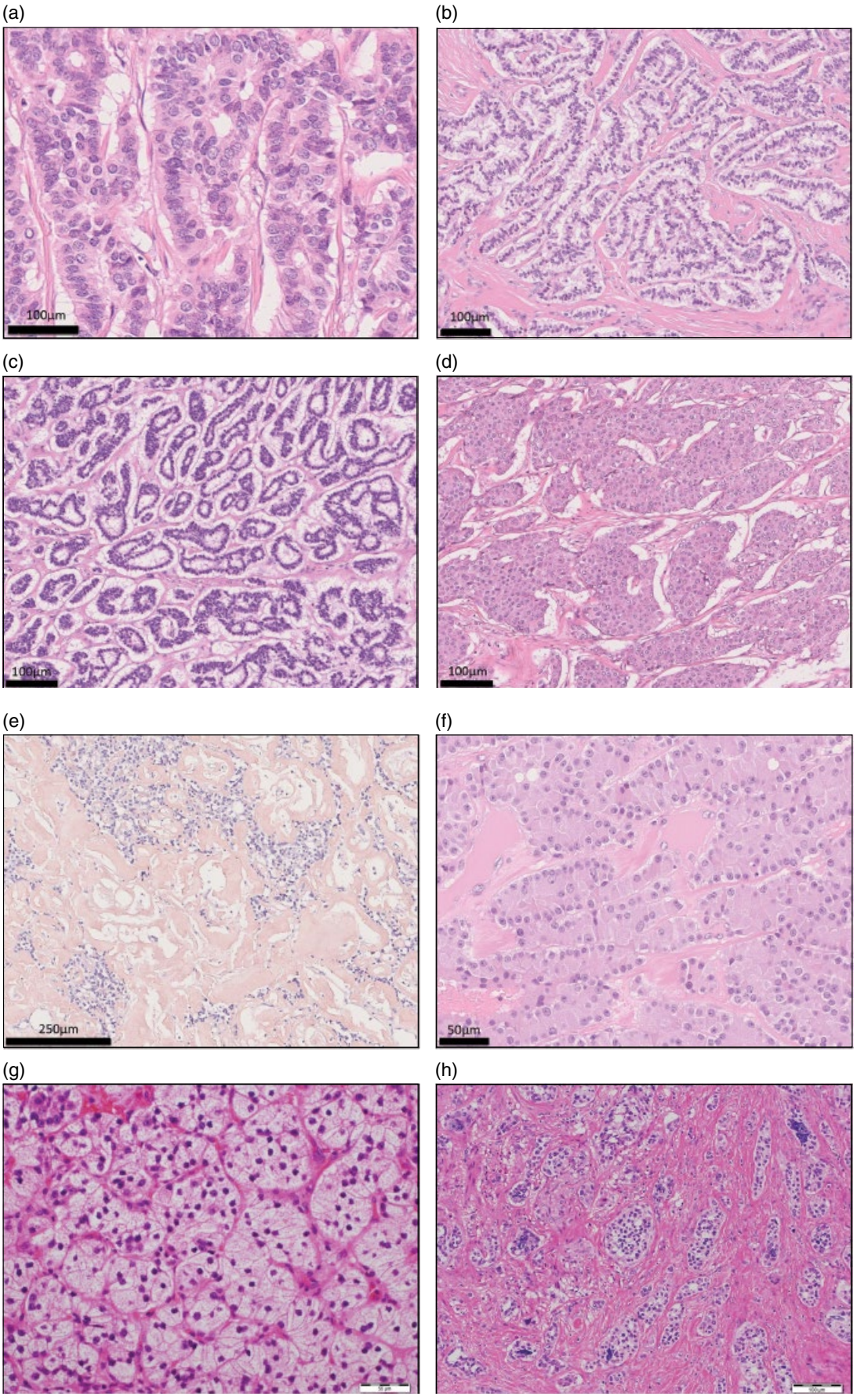


Figure 99.2 Microscopic images of pancreatic neuroendocrine tumors (PanNET). (a) Tumor cells display round to oval nuclei with coarsely granular, so-called "salt and pepper" chromatin distribution. (b) Tumor cells arranged in anastomosing ribbon-like nests, (c) gland-like features or (d) solid cell nests. (e) Marked amyloid deposition in insulinoma detected by direct fast scarlet staining. (f) An oncocytic variant of PanNET. (g) A lipid-rich variant of PanNET. (h) A pleomorphic variant of PanNET. Abundant capillary or fibrocapillary stroma observed within tumor cell nests (a–h).

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nuclear enlargement, and high nuclear–cytoplasmic ratio. Necrosis is abundant in most cases. Small cell NECs are characterized by a diffuse growth of cells with scant or elongated nuclei, finely granular chromatin, and inconspicuous nucleoli (Fig. 99.3a). The tumor cells are polygonal or uniform round with rich cytoplasm and large nuclei with prominent nucleoli (Fig. 99.3b). Ki-67 proliferation index of NECs mostly exceeds 50%.

Most MiNENs arising in the pancreas consist of two components: either ductal adenocarcinoma or acinar cell carcinoma and neuroendocrine carcinoma. The different components are either intimately intermingled or morphologically distinguishable. In rare cases, the neuroendocrine components show a well-differentiated morphology of the corresponding NET.

Cytology

Due to development of endoscopic ultrasound-guided fine needle aspiration, cytology assessment has become a standard pathologic diagnostic tool for PanNET. Nuclei of tumor cells display a monotonous appearance; they are uniformly round to oval shaped, with a salt and pepper chromatin pattern or, often, plasmacytoid epithelial cells (Fig. 99.4a,b). Tumor cells of PanNETs show loosely cohesive clusters. Single cells are also frequently observed (Fig. 99.4a). Tumor cells surrounding and loosely attached to capillary vessels are frequently observed (Fig. 99.4b). A rosette-like arrangement is highly specific to PanNETs, but rarely seen in cytology specimens.

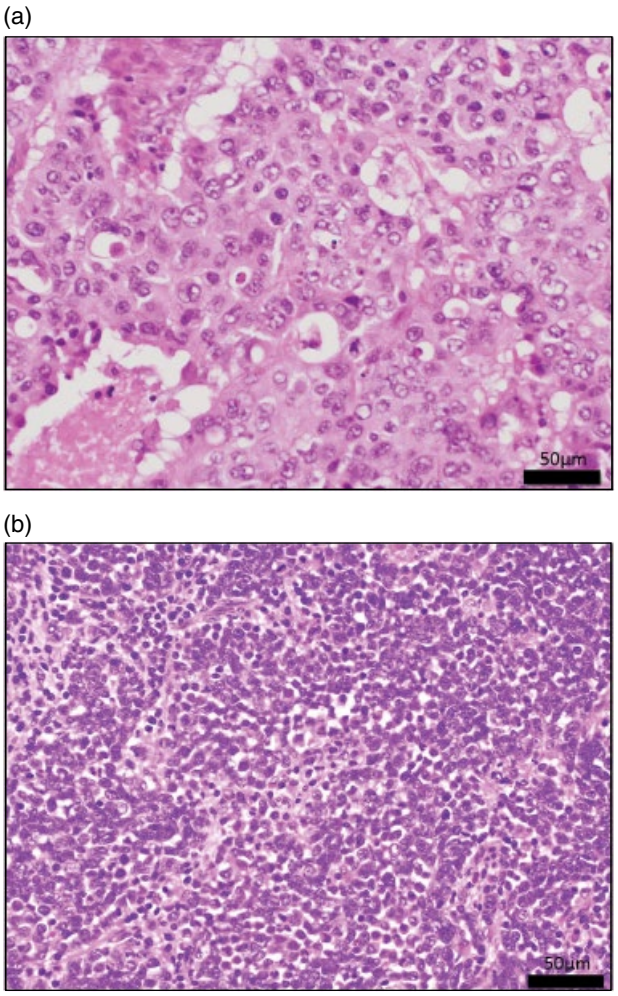


Figure 99.3 Microscopic features of pancreatic neuroendocrine carcinoma (PanNEC). (a) Large cell NEC displaying highly pleomorphic tumor cells showing diffuse growth pattern. Necrosis is also observed. (b) Small cell NEC composed of small round tumor cells with high nuclear-cytoplasmic ratio.

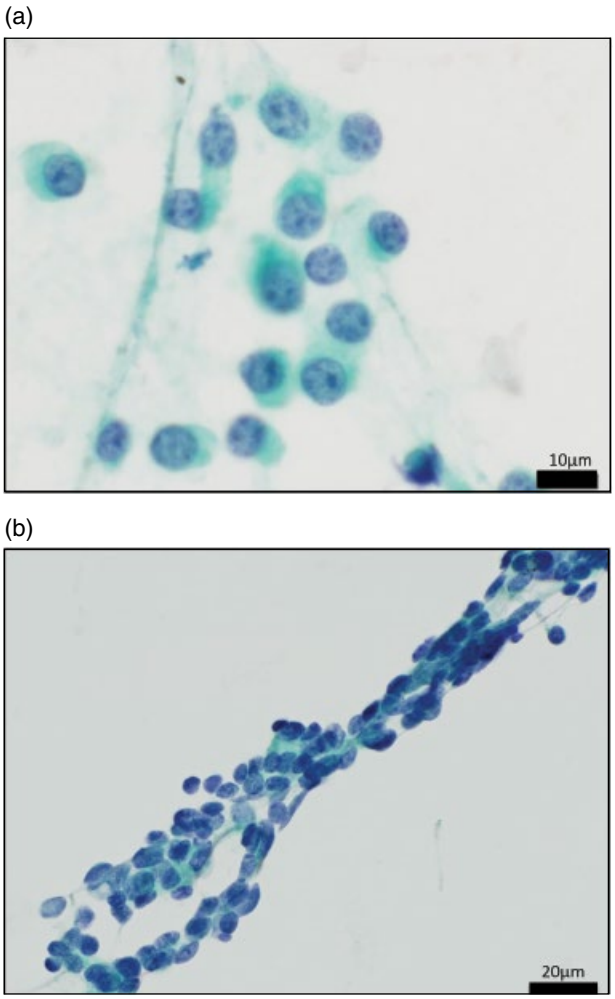


Figure 99.4 Cytology images of pancreatic neuroendocrine tumors (PanNET). (a) Loosely cohesive plasmacytoid epithelial cells with round to oval-shaped nuclei showing "salt and pepper" chromatin pattern. (b) Tumor cells surrounding capillary vessels.

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Immunohistochemistry

PanNETs diffusely and strongly express cytokeratin, chromogranin A, and synaptophysin. The other neuroendocrine markers, such as CD56 and neuron-specific enolase (NSE), are not specific. Nuclear expression of insulinoma-associated 1 (ISNM1) is a new neuroendocrine marker and is consistently positive in PanNETs [22].

In PanNECs, extent of cytokeratin and chromogranin A expression is variable, sometimes showing only focal and dot-like positivity. Normal expression of p53 and retinoblastoma 1 (Rb1) is highly suggestive for NETs, while abnormal expression of p53 and loss of Rb1 is suggestive for NEC [6,15]. Membranous expression of somatostatin receptor 2A (SST2) is expressed in more than 70% of PanNETs, but less than 10% of PanNECs, so is a powerful marker in distinguishing NETs from NECs [15,23,24].

ISLET-1, a transcription factor, is expressed in more than 90% of PanNETs and therefore, together with pancreatic peptide hormones (e.g., glucagon, PP), is a helpful marker to separate from NETs originated from other organs [25]. CDX2 is usually expressed in intestinal NETs but may also be expressed in about 50% of PanNETs [26]. Peptide hormone expressions are occasionally associated with certain morphologic patterns in PanNETs [17]. PanNETs with a trabecular-reticulated pattern often show a cystic growth and express glucagon. PanNETs with a solid paraganglioma-like pattern and with psammoma bodies often contain somatostatin-positive cells [27]. PanNETs that express serotonin often show a sclerotic stromal change and a solid-trabecular growth pattern [10].

Differential Diagnosis

PanNETs and PanNECs show distinct morphology in most cases but some PanNETs G3 may morphologically resemble large cell PanNECs and overlap Ki-67 proliferation index. Immunohistochemistry of normal expression of p53 and Rb1 and membranous expression of SST2 (see above), as well as loss of DAXX and ATRX expression, are suggestive for PanNETs and helpful to differentiate from PanNEC [15,28].

PanNETs showing a paraganglion-like pattern are morphologically like paraganglioma occurring in peripancreatic tissue. Paragangliomas show a strong and diffuse expression of neuroendocrine markers but are consistently negative for cytokeratin and positive for GATA3 and differ from PanNETs. S-100-positive sustentacular cells are characteristic in paraganglioma but may occasionally be seen in PanNETs [27].

Solid-pseudopapillary neoplasms (SPN) show low-grade cellular atypia and may resemble PanNETs. SPNs have characteristic pseudopapillary architectures, PAS-positive globules, hyalinosis, cystic degeneration, myxoid degeneration or solid and large calcification. Nuclear expression of β-catenin and somatic *CTNNB1* mutation are diagnostic features of SPN. In PanNETs β-catenin is expressed in cell membrane. Synaptophysin and cytokeratin 8/18 expression are not uncommon in SPN, but chromogranin A is consistently negative [29,30].

The architectural pattern of acinar cell carcinomas is variable, such as acinar, solid, trabecular, and diffuse, and these patterns are usually intermingled. Tumor cells have hyperchromatic nuclei, eosinophilic granular cytoplasm. PanNETs, especially NET G3, with a solid or solid-trabecular pattern, are important in the differential diagnosis of acinar cell carcinomas. Diagnosis of acinar cell carcinoma is confirmed and separated from PanNETs by expression of trypsin, BCL10 or lipase. Acinar cell carcinomas may also focally coexpress chromogranin A and synaptophysin. Acinar cell carcinoma that expresses neuroendocrine markers in more than 30% of all tumor cells is regarded as a MiNEN [31].

Pancreatic neoplasms that exhibit clear cytoplasm, e.g., clear cell variant of SPN, metastasis of clear cell renal cell carcinoma and solid-type serous cystic neoplasm, can be mimics of the clear cell variant of PanNET. Tumor cells that contain abundant lipid vacuoles appear to be mimics of adrenocortical neoplasm.

Mesenchymal or nonepithelial neoplasms including Ewing sarcoma, desmoplastic small round cell tumor, metastatic melanoma, SMARCB1-deficient neoplasms, and sclerosing epithelioid mesenchymal neoplasm occasionally express synaptophysin and may morphologically mimic PanNENs, mainly large cell PanNECs [32]. Ewing sarcomas are characterized by CD99, NKX2.2, and FL1, and 5–10% of Ewing sarcomas express synaptophysin [33]. Desmoplastic small round cell tumors express desmin and WT1, and variably (16–100%) express synaptophysin. Mesenchymal neoplasms usually express no or only focal cytokeratin and are negative for chromogranin A [32].

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Molecular Genetics of Neuroendocrine Tumors

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Introduction

Low-grade pancreatic neuroendocrine tumors (PanNETs) are the second most common malignancy of the pancreas, accounting for approximately 2% of newly diagnosed pancreatic malignancies. The increased diagnosis of patients with this disease has mainly been due to better imaging and diagnostic tools, and the increased use of imaging which has led to a larger number of incidentally detected tumors [1–4]. Although PanNETs are not as lethal as pancreatic adenocarcinoma (PDCA), more than 50% of patients have metastatic disease at diagnosis and the 10-year survival rate is about 40% [5]. High-grade pancreatic neuroendocrine carcinomas (PanNECs) are extremely rare, and highly lethal [6–9].

Well-differentiated PanNETs are classified as functional or nonfunctional, with the latter group being most common [10]. Functional PanNETs produce clinical syndromes with systemic effects related to the hormones that they secrete. The most common functional PanNETs are insulinomas, while glucagonomas, gastrinomas, somatostatinomas, VIPomas, and some PanNETs of mixed function comprise the rest of this group. Nonfunctional PanNETs do not secrete clinically significant hormones; rather, they grow silently, and patients often present with either an asymptomatic pancreatic mass or abdominal pain resulting from compression due to a large tumor. Surgery can be curative in the case of primary PanNETs and some cases of metastasis, but many patients present with unresectable tumors or extensive metastatic disease.

Most PanNETs are sporadic; however, they can also arise in patients with familial syndromes, most commonly in those with multiple endocrine neoplasia type 1 (MEN 1), followed by von Hippel–Lindau (VHL), neurofibromatosis type 1 (NF1) and tuberous sclerosis (TSC) [11]. Patients with one of these syndromes have germline mutations in the gene(s) that are responsible for the predisposition to the familial syndromes.

PanNECs, defined as poorly differentiated neuroendocrine neoplasms with dramatic atypia and proliferation rates typically >50%, are highly malignant neoplasms, and include entities previously classified as "small cell" and "large cell" neuroendocrine carcinomas [6–9]. There are some neoplasms which have a proliferation rate >20% but which retain an otherwise well-differentiated morphology, and these neoplasms harbor genetic alterations similar to well-differentiated PanNETs, and not those of the high-grade PanNECs [12,13]. These later neoplasms have therefore been designated as grade 3 PanNETs [14].

We now know that cancer takes many years to develop and is caused by the sequential alteration of a small number of genes that affect a smaller number of cellular processes [15]. The genomic landscapes of many tumor types have been determined, and although not everything is fully understood, these studies have provided sufficient information for developing effective approaches to reducing cancer morbidity and mortality. For similar reasons, much progress has been made in understanding the genetic alterations that underlie PanNET and PanNEC tumorigenesis. This chapter will describe what is known about the genetic landscape and epigenetics of PanNETs and PanNECs, and their clinical applications.

Genetics of Sporadic PanNETs

In order to gain insight into the genetic basis of PanNETs, whole-exome sequencing (WES) was performed in 10

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clinically homogeneous nonfunctional PanNETs [16]. Then, the most commonly mutated genes were analyzed for mutations in 58 additional nonfunctional PanNETs. The most commonly mutated genes identified encode proteins that are involved in chromatin modification. *MEN1* had inactivating mutations in 44% of the PanNETs. *ATRX* and death domain-associated protein (*DAXX*) had mutually exclusive inactivating mutations in 18% and 25% of the PanNETs respectively, resulting in the inactivation of the ATRX/DAXX complex in 43% of the PanNETs. Approximately 14% of the PanNETs had mutations predicted to result in the activation of the mTOR pathway. Tuberous sclerosis complex 2 (*TSC2*) was inactivated in 9% of the samples, and phosphatase and tensin homolog (*PTEN*) was inactivated in 7% of the samples. In addition, there was an activating mutation in *PIK3CA*, which encodes the p110 α catalytic subunit of PI3K. *TP53* was only inactivated in 3% of the PanNETs (Table 100.1). Overall, there were about 8–23 mutations/tumor with a mean number of 16 mutations, which is low compared to most other solid tumors. Mutations in oncogenes are rare in most solid tumors, so it was not unexpected that only one sample had an activating oncogenic mutation [15].

This lack of activating mutations in oncogenes underlies the overall challenge for developing targeted therapies for PanNETs. As a result, understanding the pathways involved in the development and progression of cancers has become pivotal for developing therapeutics. A good example is the mTOR pathway. Existing therapeutic agents that inhibit this pathway do not target commonly mutated genes in the pathway, but rather target mTORC1, a downstream effector in the pathway.

As we will discuss later, inactivating mutations in *ATRX* and *DAXX* correlated with the ALT phenotype. In fact, protein expression studies in 68 PanNETs indicated that all samples with *ATRX* or *DAXX* inactivating mutations exhibited the ALT phenotype [17]. Interestingly, tumors negative for nuclear labeling of either ATRX or DAXX also showed the ALT phenotype, indicating that *ATRX* or *DAXX* genes were inactivated either by a rearrangement such as large deletions not identifiable by exome sequencing, or via epigenetic mechanisms. This study indicated that inactivation of *ATRX* or *DAXX* occurred in approximately 60% of the PanNET samples, of which 43% were caused by exomic mutations and the remaining cases most likely resulted from large deletions or epigenetic gene inactivation.

To alleviate some of the limitations of WES mentioned above, the whole genomes of 98 PanNET samples were subsequently analyzed for somatic mutations, germline mutations, and telomere repeat content [18]. Overall, the results of this study validated the major findings reported by WES analysis with small differences in the percent of samples with somatic mutations in the major driver genes involved in the tumorigenesis of PanNETs. The most frequently mutated gene was *MEN1* with 37% of the samples having inactivating mutations. *DAXX/ATRX* were inactivated in 34% of the samples and associated with the presence of ALT. Rearrangements and fusion genes, including *PTPRD* and Ewing sarcoma 1 (*EWSR1*) gene, were observed in three samples without *ATRX/DAXX* mutations. Consistent with previous results, somatic mutations in *TSC1*, *TSC2*, *PTEN*, and *DEPDC5* were observed that were predicted to activate the mTOR signaling pathway. Germline analysis revealed mutations in *MUTYH* in five patients, *BRCA2* in one patient and *CHEK2* in four patients, suggesting the involvement of DNA damage repair pathways in a subset of PanNETs. In addition, there were five patients with *MEN1,* and one patient each with *CDKN1B* or *VHL* germline mutations.

In glial tumors, *ATRX* inactivating mutations and *TERT* promoter mutations are mutually exclusive, presumably because each type of mutation results in preservation of the telomeric length appropriate for cell growth [19]. To evaluate the possibility of this occurring in PanNETs, the samples analyzed for *ATRX* and *DAXX* mutations were also evaluated for *TERT* promoter mutations. None of the 68 PanNETs had TERT promoter mutations at the hot spots shown to be mutated in many other tumor types; thus, we presume that TERT is expressed in these tumors.

The exome of sporadic functional PanNETs has only been sequenced in insulinomas. In a set of 10 insulinomas, the most commonly mutated gene was the transcription factor Ying Yang 1 (*YY1*) [20]. Sequencing of *YY1* in an additional 103 insulinomas identified a hot spot mutation in 31 of them. Overall, 30% (34/113) of the insulinomas possessed the T372R mutation in *YY1*. A more recent study focusing on the Caucasian instead of Asian population identified a much lower prevalence (13%) of *YY1* mutations in sporadic insulinomas. In the Caucasian population, the T372R mutation appeared to stratify with women and older age [21].

Pathways Altered in PanNETs

ATRX/DAXX Pathway

As noted above, approximately half of PanNETs have inactivating mutations in *ATRX* or *DAXX*. *ATRX* is located on chromosome X, and only the active copy needs to be inactivated to result in total loss of the ATRX protein expression. On the other hand, *DAXX* is located on chromosome 6, and both copies need to be inactivated for DAXX protein loss. The mutations that occur in the *DAXX* gene include single nucleotide base substitutions and indels that create frameshifts, and larger deletions of single or multiple exons, all accompanied by

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Table 100.1 Comparison of commonly mutated genes and their prevalence in PanNETs and other pancreatic neoplasms.

Gene	Nonfunctional PanNETs	Syndromic microadenomas	NECs	PDAC	Insulinomas	Intracellular pathway	Clinical application	Future opportunity
MEN1	44%	100%	0%	0%	2.50%	Chromatin methylation	Not available	Synthetic lethality
ATRX	18%	0%	0%	0%	2.50%	Chromatin remodeling - ALT	Prognostic/ Diagnostic	Synthetic lethality
DAXX	25%	0%	0%	0%	0%	Chromatin remodeling - ALT	Prognostic/ Diagnostic	Synthetic lethality
TSC2	9%	Not Tested	Not Tested	0%	0%	mTOR	Target treatment - mTOR inhibitors	Improved mTOR inhibitors
PTEN	7%	Not Tested	<10%	0%	0%	mTOR	Target treatment - mTOR inhibitors	Improved mTOR inhibitors
PIK3CA	1%	Not Tested	Not Tested	0%	0%	mTOR	Target treatment - mTOR inhibitors	Improved mTOR inhibitors
TP53	3%	Not Tested	95%	85%	0%	TP53	Not available	Synthetic lethality, or bispecific antibodies
KRAS	0%	Not Tested	30%	100%	0%	KRAS	Not available	Sotorasib target therapy
CDKN2A	0%	Not Tested	50%	25%	0%	Cell cycle	Not available	Synthetic lethality
SMAD4	0%	Not Tested	10%	27%	0%	TGFβ	Not available	Synthetic lethality
RB1	0%	Not Tested	74%	0%	0%	Cell cycle	Not available	Synthetic lethality
YY1	0%	Not Tested	0%	0%	13 - 30%	Transcription	Not available	Target therapy

ALT, alternative lengthening of telomeres: mTOR, mammalian target of rapamycin NEC, neuroendocrine carcinoma; PanNET, pancreative neuroendocrine tumor; PDAC, pancreatic adenocarcinoma: TGFβ, transforming growth factor β.

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loss of heterozygosity (LOH). The mutations in both *ATRX* and *DAXX* lead to inactivation of the respective gene and tumors with these mutations lack nuclear protein immunolabeling for the respective proteins, in accordance with them being tumor suppressors. The mutations are also mutually exclusive, consistent with the two genes working within the same pathway [15,17].

ATRX is a chromatin remodeling protein that interacts with DAXX and together they function as a histone chaperone complex that deposits the histone variant H3.3 into pericentric, telomeric, and ribosomal repeat sequences [22–24]. Although the mechanism underlying the action of ATRX remains unclear, recent progress has been made. ATRX is thought to be recruited, perhaps by interacting with histones, to G-quadruplex DNA where it is involved in chromatin remodeling, with consequences for gene expression and relief of replication fork stalling [25]. Consequently, its absence can impair both nonhomologous end-joining DNA repair and formation of protein complexes, resulting in changes to the epigenetic state of the DNA [26–28].

Perhaps more intriguing is the connection between the lack of ATRX or DAXX protein expression and the ALT phenotype [29]. There is telomere length attrition with every cell division resulting in telomeric lengths that are not compatible with limitless growth. Cancer cells must circumvent this issue. Telomeric length is usually maintained by TERT [30]; however, TERT is not always active. Cells with the ALT phenotype have very long telomeres whose lengths are maintained by recombination instead of by the enzymatic action of TERT [31]. Mutations in *ATRX* or *DAXX* that abolish protein expression of these proteins in PanNETs correlated with ALT [17,19,32]. *ATRX* inactivating mutations concomitant with ALT have also been identified in extrapancreatic tumor types, including glial tumors, neuroblastomas, and sarcomas, in cancer cell lines, as well as in *in vitro* immortalized ALT cell lines [19,33]. Furthermore, loss of wild-type *ATRX* expression in somatic cell hybrids segregated with ALT, whereas *ATRX* expression led to inhibition of ALT [34,35]. A greater understanding of how *ATRX* loss may result in the ALT phenotype and its connection to increased chromosomal instability was provided by a study which showed that loss of *ATRX* in cancer cells lines can promote sister telomere cohesion associated with increased recombination between sister telomeres [36].

PanNETs are also unique in that *DAXX* mutations are predominant over *ATRX* mutations, even though *DAXX* mutations are extremely rare in other tumor types with ALT, which almost exclusively have *ATRX* mutations [16,37]. The differences in the spectrum of *ATRX* mutations in various diseases and the preferential inactivation of *DAXX* in PanNETs provide fertile ground for understanding the intricacies of this pathway and its tumor-specific ALT phenotype, with the hope that a deeper understanding will lead to the therapeutic targeting of the pathway.

MEN1 Pathway

MEN1 is the most frequently somatically mutated gene in PanNETs [16,38]. This gene encodes the transcriptional regulator menin, which recruits the H3K4me3 histone methyltransferase mixed-lineage leukemia (MLL) complex [39,40]. Menin interacts with many proteins and regulates gene expression and intracellular cell signaling; it is associated with numerous cellular processes including the regulation of SMAD3 to inhibit TGFβ1-mediated inhibition of proliferation, and repression of JunD activity, regulation of homeodomain gene expression, and repression of telomerase expression [41–44]. *MEN1* mutations in PanNETs inactivate both alleles either by inactivating mutations or a combination of mutation coupled with LOH. Thus, by definition, *MEN1* is a tumor suppressor.

It appears that tumorigenesis in PanNETs is driven by alterations in both histone modification and chromatin remodeling as the overlap of *MEN1* with *ATRX/DAXX* mutations is significant (74%). *MEN1* and *ATRX/DAXX* are epigenetic drivers of cancers resulting in a plethora of epigenetic changes in the cell. Thus, it is important to determine which epigenetic alterations are the key drivers of PanNET tumorigenesis, which has obvious implications for therapeutic exploitation of the associated pathways.

mTOR Pathway

The mTOR signaling pathway integrates environmental signals to regulate growth and homeostasis. mTOR is an atypical serine/threonine protein kinase that interacts with several proteins to form two key complexes in the pathway named mTOR complex 1 (mTORC1) and 2 (mTORC2), each of which mediates different upstream inputs and has different downstream outputs.

A number of tumor suppressors and oncogenes commonly mutated in cancers are upstream of mTORC1, including the PTEN/PIK3CA pathway, the RAS/RAF pathway, TSC1/2, NF1, and LKB1. Sequencing of PanNETs revealed somatic mutations in *TSC2*, *TSC1*, *DEPDC5*, *PTEN*, and *PIK3CA* genes in 16% of samples, all of which are predicted to activate the mTOR pathway, conasistent with its progrowth effects on cells. Downstream effectors of the pathway involve 4E-BP1, which in turn regulates hypoxia inducible factor 1 (HIF1a), a target of VHL, and S6K1 resulting in increased

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proliferation signals, regulation of metabolism, and increased protein synthesis [reviewed in 45]. Inhibitors of the mTOR pathway have shown benefit in patients with different tumor types, including PanNETs; however, correlations between pathway mutations and the observed benefits have not yet been fully established [46].

Based on results from other tumor types, we hypothesize that patients with tumors with mTOR pathway mutations will respond better to therapies targeting this pathway [41]. However, in clinical trials, the number of patients with PanNETs that benefited from treatment with everolimus, which targets the mTOR pathway, was larger than the number of PanNETs with mutations in the mTOR pathway [16,46]. However, this is an extrapolation as the PanNETs from the patients included in the study were not tested for mutations. It is worth noting that for such a complicated pathway, there could be other means of activation besides mutations. Related to this, expression studies resulted in the observation that expression of genes in the mTOR pathway is upregulated in PanNETs [47]. Nevertheless, a good study to test the companion diagnostic potential of the mutational status of the pathway would be important.

High-grade Neuroendocrine Carcinomas

In contrast to well-differentiated PanNETs, the *DAXX/ATRX* and *MEN1* genes are not targeted in most high-grade PanNECs [6,48,49]. Instead, the *RB1* and *TP53* genes are commonly somatically mutated in PanNECs [6]. Yachida and colleagues extensively studied a series of PanNECs (small cell and large cell neuroendocrine carcinomas) and found the p53 expression was altered in 95% and Rb in 74% of the PanNECs [6]. Abnormal immunolabeling of p53 and Rb proteins correlated with the intragenic mutations in the *TP53* and *RB1* genes. By contrast, DAXX and ATRX labeling was intact in virtually all of these same carcinomas. These genetic differences indicate that the biology and process of tumorigenesis are distinct in PanNETs and PanNECs, and that poorly differentiated PanNECs do not result from progression of the well-differentiated PanNETs to a less differentiated state.

The increased genetic understanding of these neoplasms resulted in changes in the 2019 WHO classification [16]. Tumors with a high proliferation rate (>20%) that maintain their well-differentiated neuroendocrine cytology are now classified as grade 3 PanNETs as they have the same mutational profile as do lower grade PanNETs. In addition, PanNECs with small cell morphology are lumped together with PanNECs with large cell morphology because of their overlapping mutational profiles [50].

A comprehensive analysis of 115 cases of neuroendocrine neoplasms of gastrointestinal system (GIS-NEN), specifically 60 GIS-NECs (18 pancreatic, 14 gastric, 10 biliary, nine colorectal, six ampullary, three esophageal) and 55 GIS-NETs (48 pancreatic, six colorectal, one nonampullary duodenal), that included WGS/WES, transcriptome sequencing, DNA methylation, and ATAC-seq, allowed comparison of genetic and epigenetic features of these neoplasms [51]. This study validated that PanNETs are genetically distinct from PanNECs. Overall, GIS-NECs are genetically distinct from GIS-NETs. Although there were overlapping features between NECs of different organ sites, there were significant differences between PanNECs and extrapancreatic NECs. Furthermore, the authors of the study proposed a classification of PanNECs into two groups, a "ductal-type" and an "acinar-type."

Comparison of PanNET Genetic Landscape to Other Pancreatic Neoplasms

The genetic landscape of well-differentiated PanNETs is fundamentally different from that of the more aggressive pancreatic adenocarcinoma (PDAC) (see Table 100.1). *KRAS* mutations that are not found in neuroendocrine tumors are present in almost 95% of PDACs. In addition, PDACs have a high prevalence of mutations in *SMAD4*, *CDKN2A*, and *TP53* genes, but no mutations in *DAXX*, *ATRX*, or *MEN1* [52,53].

The genetic alterations found in PanNETs are also distinct from those found in the other neoplasms of the pancreas. Serous cystic neoplasms are characterized by *VHL* gene mutations, solid-pseudopapillary neoplasms by *CTTNB1* mutations, intraductal papillary mucinous neoplasms by alterations in *KRAS*, *GNAS*, *RNF43*, *p16/CDKN2A*, and *TP53*, mucinous cystic neoplasms by mutations in *KRAS*, *RNF43*, *p16/CDKN2A*, and *TP53*, and acinar cell carcinomas by multiple complex alterations including mutations in *JAK1*, *BRAF*, and *APC*, among others [52,54,55].

The distinct mutational profile of each tumor type of the pancreas suggests that mutational analyses may be used to help classify tumor type in the future [56].

Finally, among neuroendocrine tumors, the targeting of the *ATRX/DAXX* pathway and ALT is relatively specific for those tumors that arise in the pancreas. This suggests that ALT status could be used to clarify organ of origin in metastatic neuroendocrine tumors of unknown primary [57].

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Familial Syndromes

MEN 1 is an autosomal dominant syndrome caused by germline mutations in the *MEN1* gene on chromosome 11, which is the gene most frequently somatically mutated in sporadic PanNETs [58]. As previously mentioned, *MEN1* is a tumor suppressor gene that follows the two-hit paradigm. The first hit in individuals with MEN 1 is an inactivating inherited mutation. The second hit, an inactivating somatic mutation or loss of heterozygosity of the remaining wild-type allele, occurs in the tumors. Tumors of the pancreas are the second most common manifestation of the MEN 1 syndrome. Most of the PanNETs in MEN 1 patients are nonfunctional, although about 10% of them are insulinomas. They typically appear as multiple microadenomas (<0.5 cm); however, in many cases, like the sporadic PanNETs, they can grow larger and even metastasize to other organs [59,60].

Study of the genetics of PanNETs in the context of the MEN 1 syndrome has shown that *MEN1* inactivation precedes *ATRX/DAXX* inactivation and the concomitant appearance of ALT [32]. In this study, 109 well-differentiated PanNETs from 28 patients with MEN 1 syndrome were tested for expression of ATRX and DAXX and for the presence of ALT by immunolabeling as a proxy for the genetic inactivation of the genes that encode for these proteins. The lesions included 47 neuroendocrine microadenomas (<0.5 cm), 50 pancreatic neuroendocrine tumors (>0.5 cm), and 12 pancreatic neuroendocrine tumor lymph node metastases. All of the lesions had loss of function of the MEN1 protein by definition, since they were present in patients with MEN 1 syndrome; thus, this was the first and presumably the initiating event in these tumors. ATRX/DAXX expression was intact in all of the 47 microadenomas, which were also negative for ALT. Loss of ATRX/DAXX expression was only observed in tumors larger than >3 cm. These tumors were also ALT positive, which is consistent with the already documented role of ATRX/DAXX loss in the development of ALT. In addition, in the samples with concurrent metastases, the genetic alterations in the primary and metastatic tumors were the same. The progression from *MEN1* inactivation to *ATRX/DAXX* inactivation and appearance of ALT as the tumor size and the risk of metastasis increased, which was observed in the MEN 1 syndrome-associated PanNETs, most likely exists in the sporadic PanNETs as well. However, *ATRX/DAXX* inactivation in sporadic pancreatic neuroendocrine microadenomas was much higher [61].

Von Hippel–Lindau syndrome is caused by germline mutations in the tumor suppressor *VHL* on chromosome 3. The VHL protein controls the degradation via ubiquitination of HIF1, and loss of VHL leads to tumor growth and angiogenesis. HIF1 regulation also has been proposed to be downstream of the mTOR pathway. Patients with VHL syndrome develop a number of different benign and malignant neoplasms, and approximately 12–15% of them develop nonfunctional PanNETs. Most of these tumors have a clear cell morphology and are well differentiated, but some are aggressive, and they can metastasize [62,63].

PanNETs also arise, albeit less frequently, in patients with NF1 and TSC syndromes [11]. NF1 is caused by germline mutations in *NF1*, whereas TSC results from germline mutations in *TSC1* or *TSC2*. All three of these genes are tumor suppressors and are associated with the extensive mTOR pathway [64,65]. NF1 acts more distally upstream of mTORC1, regulating the KRAS arm of the pathway. The TSC1/TSC2 complex inhibits mTORC1 activation. Mutations in *TSC2* were the most common mTOR pathway mutations observed in sporadic PanNETs.

The prevalence of PanNETs in these syndromes is in accordance with the presence of the affected pathways in sporadic PanNETs, with *MEN1* mutations occurring in 44% of PanNETs and mTOR only occurring in 16% of these tumors [16]. Further studies on the genetic changes in syndromic PanNETs will provide an understanding of the pathways that drive PanNET tumorigenesis.

Epigenetics

PanNETs can be classified into three groups according to their RNA profiles: well-differentiated islet cell tumors/insulinomas, poorly differentiated tumors, and gene mutation-enriched subtypes. The first two classification groups are not surprising as PanNETs and PanNECs are two different tumor types. The differences between well-differentiated and gene mutation-enriched groups are intriguing in that they could reflect groups with different clinical behaviors.

Targeted CpG promoter methylation analysis of 46 PanNETs revealed hypermethylation in *MEN1* in 19% of tumors tested and in *MGMT* in 17% in tumors tested [66]. Genome-wide methylation analysis of 53 PanNETs identified significant differences in methylation profiles between tumors of different grades and between tumors with or without *ATRX*/*DAXX* mutations. However, this clustering was not perfect as some tumors with mutations in these genes clustered with normal controls. Interestingly, there were significant differences in the methylation profiles between PanNETs with *ATRX* mutations and those with *DAXX* mutations [37].

RNA sequencing followed by RNA expression analysis of 33 PanNETs, 19 with mutations in *ATRX/DAXX/MEN1*

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and 14 without mutations in these genes, identified two distinct clusters [67]. The profile of the PanNETs with mutations in *ATRX/DAXX/MEN1* was reminiscent of that from a pancreatic α cell with highly expressed aristaless-related homobox gene (ARX) and low expression of pancreatic duodenal homeobox 1 (PDX1), suggesting a possible cell origin of the tumor. Similar results based on enhancer signatures were reported by Cejas et al. [68]. Genome-wide DNA methylation profiling of PanNETs classified them in α-like and β-like, stratifying with mutations in *ATRX/DAXX/MEN1* and no mutations in these genes along the lines presented in Chan et al. [67,69]. However, the classification included an intermediate profile indicating the need for further refinement of the groups.

Another study classified 84 sporadic PanNETs into three groups based on DNA methylation which also stratified with genetic alterations. PanNETs in the T1 group did not have mutations in *ATRX/DAXX/MEN1* and were enriched in functional tumors. PanNETs in group T2 had mutations in *ATRX/DAXX/MEN1* and high expression of *MGMT*. PanNETs in group T3 had mutations in *MEN1* with recurrent loss of chromosome 11. This group was enriched in grade G1 PanNETs [70]. The aforementioned studies provide concordant results in that there is a genetic classification of PanNETs accompanied by epigenetic changes reflected in RNA expression and methylation profiles; however, these classifications do have overlap and are not yet well defined. Furthermore, these studies include both functional and nonfunctional PanNETs.

Clinical Implications

The genetic landscape reflects the different biology and clinical manifestations of pancreatic neuroendocrine neoplasms and has clinical ramifications. First, genetics can be used to unambiguously classify the different lesions. Second, the differences in the genetics suggest different types of treatment. Unfortunately, treatments are not available that can target the most common mutations in PanNETs, *MEN1* and *ATRX/DAXX* mutations. The relationship between loss of *ATRX/DAXX* with ALT, recombination and DNA repair suggests that synthetic lethality could be feasible with agents that interfere with these pathways. However, this has not yet been proven.

ATRX/DAXX mutations in PanNETs have been associated with prognosis. In a study of 142 well-differentiated PanNETs, loss of ATRX and DAXX and presence of ALT correlated with higher tumor stage and a worse prognosis, perhaps a reflection of *ATRX/DAXX* mutations being a late event in PanNET tumorigenesis [71]. However, when only the subset of metastatic patients was considered, loss of ATRX and DAXX was associated with longer survival [62]. This latter observation is in accordance with the initial observation that patients with metastatic PanNETs harboring *MEN1*, *ATRX*, and *DAXX* mutations showed better prognosis and longer survival [18]. Similarly, in an independent study of 43 patients with liver metastasis managed with resection, loss of ATRX/DAXX was associated with better overall survival [57]. One interpretation of this is that tumors with *ATRX/DAXX* inactivating mutations comprise a subgroup with a different clinical presentation than the PanNETs without inactivation of these genes.

Furthermore, as noted earlier, in a comparison between metastatic lesions in the liver from patients with PanNETs or gastrointestinal carcinoid tumors, the presence of ALT in the metastatic lesion was a useful biomarker to predict that site of origin of metastatic lesions to the liver is a neuroendocrine tumor of the pancreas in cases where the primary site is unknown [57].

Although the classifications of PanNETs mentioned above based on epigenetic profiles indicate that different PanNETs have different potential clinical outcome [67–69], it is not yet clear which biomarkers provide accurate prognosis for nonfunctional PanNETs. Expression of ARX and PDX1 by immunolabelling, as well as mutational status of *ATRX/DAXX* by immunolabelling and fluorescence *in situ* hybridization (FISH) for ALT, were evaluated in 1322 NETs from multiple institutions. All NETs were nonfunctional, 561 primary PanNETs, 107 metastases of PanNETs, and 654 nonpancreatic nonfunctional primary and metastases NETs. ATRX/DAXX and ALT status were independent prognostic factors. ATRX/DAXX-negative and ALT-positive PanNETs had worse five-year relapse-free survival (RFS). In contrast, ARX/PDX1 expression did not independently correlate with RFS [72]. These data provide evidence that ATRX/DAXX immunolabeling and ALT FISH should be considered as prognostic biomarkers for nonfunctional PanNETs [72]. Given the issues with diagnosis of certain neuroendocrine neoplasmas [73], ATRX/DAXX and ALT are highly diagnostic biomarkers to indicate the origin of NET metastasis of unknown primary tumor [72].

Of all the mutations identified in PanNETs, those in the mTOR pathway show promise as therapeutic target, as it is thought that PanNETs with mTOR pathway mutations upstream of mTORC1 will derive benefits from mTOR inhibitors. However, this has yet to be proven in clinical trials. A trial has been reported that will test this hypothesis [74]. It is worth noting that the mTOR pathway is complex; thus, mutations in other genes or via epigenetic mechanisms may activate this pathway in

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PanNETs. Even so, not only people with tumors with the described mTOR pathway mutations will show benefit from the therapies, but also people with "cryptic," at least for now, alterations of the mTOR pathway.

Everolimus was approved by the FDA in 2011 for patients with advanced PanNETs, based on the results of the RADIANT III trial [46]. In this trial, single therapy with everolimus was compared to the best supportive care for advanced PanNETs. The majority of patients had previously been treated with different therapies. Compared to placebo, everolimus led to increased progression-free survival (11 vs 4.6 months).

Sotorasib, a KRAS inhibitor, has been approved for the treatment of lung cancers. In the future, this could be a possible therapeutic option for PanNECs with *KRAS* mutations. A potential future therapy for tumors with *TP53* mutations has been proposed based on bispecific antibodies that target mutant p53 [75]. This approach is in the very early stages but if successful, it could be considered for treatment of *TP53* mutant PanNECs.

Conclusion

Over the last several years, the studies mentioned above have increased our understanding of the genetic alterations and intracellular pathways that drive PanNET tumorigenesis. Although much remains to be determined, for example identification of the driver genes in PanNETs that do not have mutations in *MEN1*, *ATRX*, or *DAXX*, we have enough information to develop clinical applications based on the genotype of these tumors [76]. Future studies should clarify which companion diagnostics should be available for therapies, such as everolimus, as many patients do not respond to this drug. In those who are responsive, the overall increase in survival is months rather than years. New therapies are needed for the management of patients with PanNETs. Therefore, efforts should be invested in understanding and therapeutically targeting the ATRX/DAXX and MEN1 pathways. It is clear that molecular genetics have provided new opportunities to improve the clinical management of patients with PanNETs.

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What is the Origin of Pancreatic Endocrine Tumors?

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Introduction

Historically, Pierre Masson proposed an origin of gastroenteropancreatic neuroendocrine tumors (GEP-NET) from gastrointestinal endocrine cells [1]. This idea was challenged by the APUD-oma concept of Pearse with the hypothesis that GEP-NETs would arise from APUD (amine precursor uptake and decarboxylation) cells, which migrated to endoderm from the neural crest [2]. More recent work based on transcriptomic data, such as expression of transcription factors, as well as genetically engineered mouse models established the original idea of diffuse neuroendocrine cells as the origin of GEP-NETs. Lately, DNA methylation markers have been shown to be useful in providing information on the potential cell of origin in different cancer types [3,4].

In pancreatic neuroendocrine tumors (PanNETs), different molecular subtypes based on mutational pattern and gene expression have been reported, and some of these changes show associations with type of hormone production and thereby possibly cell of origin [5]. Recent data support the islet α- and β-cells as a potential origin of PanNETs [6,7]. Additional PanNET subgroups may also arise from other endocrine cell types as well as from precursors. Interestingly, pancreatic neuroendocrine carcinoma (PanNEC) could arise from acinar or ductal cells in addition to precursors [8].

Mouse Models

Genetically engineered mouse models (GEMMs) have been instructive in the understanding of tumorigenesis and the role of various genetic and nongenetic modifications (Table 101.1). Over the years, numerous GEMMs have been developed, aiming to understand the cell of origin and the role of various genetic alterations during the progression of PanNETs [9–11]. Most of the studies have focused on three cell types: the pancreatic progenitors, and the endocrine α- and β-cells. Herein, we focus on studies examining the role of the most frequently mutated genes in PanNETs, i.e., *MEN1*, *DAXX/ATRX*, *VHL*, and mTOR pathway genes (e.g., *Pten*), and the role of the p53 and pRb tumor suppressors [12–14]. Although *TP53* and *RB1* gene mutations are exceptionally rare in PanNETs, alterations of upstream regulators often lead to their inactivation [15,16].

Inactivation of the *Men1* in mouse progenitor cells of the endocrine and exocrine pancreas using a Pdx-1 driven Cre leads to development of only endocrine tumors with expression of insulin, without any exocrine malignancy [17]. The specific derivation of insulinomas could be due to the persistent Pdx-1 expression in mature β-cells, which presumably allows for complete *Men1* inactivation, in contrast to the transient expression in the progenitor cells (Figure 101.1). It might also be due to the unique susceptibility of β-cells to *Men1* inactivation; however, this is unlikely, since as mentioned below both α- and β-cell specific *Men1* deletion leads to tumorigenesis. Genetic inactivation of *Men1* along with *Daxx* in the pancreatic progenitor cells using the Pdx-1 driven Cre resulted in the generation of insulinomas that had the same overall survival as *Men1* inactivation [18]. Inactivation of the *Vhl* gene in pancreatic progenitors using the Pdx-1 driven Cre leads to the development of pancreatic cysts, microcystic adenomas, and some hyperplastic islets [19]. The latter phenotype recapitulates the nonfunctioning neoplasms in patients with VHL disease [20]. Notably, *Vhl* specific deletion in either

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Table 101.1 PanNET mouse models with respective cells of origin

Tumor model (mouse strain)	Cell of origin	Promoter	Genetic modification	Phenotype	Metastasis	Reference
PDX1-Cre; $Men1^{loxP/loxP}$	Pancreatic progenitor cells/ β-cells	PDX1 promoter	*Men1* inactivation	Insulinoma	Not reported	[17]
PDX1-Cre; $Men1^{loxP/loxP}$; $Daxx^{loxP/loxP}$	Pancreatic progenitor cells/ β-cells	PDX1 promoter	*Men1* and *Daxx* inactivation	Insulinoma	Not reported	[18]
PDX1-Cre; $Vhl^{loxP/loxP}$	Pancreatic progenitor cells	PDX1 promoter	*Men1* inactivation	Cysts, microcystic adenomas (hyperplastic islets)	Not reported	[19]
Glu-Cre; $Men1^{loxP/loxP}$	α-Cells	Glu promoter	*Men1* inactivation	Glucagonoma; insulinoma (via transdifferentiation)	Not reported	[21]
Ren-Cre; $p53^{loxP/loxP}$; $Rb^{loxP/loxP}$	α-Cells	Renin promoter	*Tp53* and *Rb1* inactivation	Glucagonoma	LN and liver (glucagon positive)	[23]
RIP-Cre; $Men1^{loxP/loxP}$	β-Cells	Rat insulin promoter	*Men1* inactivation	Insulinoma (progressive downregulation of insulin expression)	Not reported	[24]
MIP-Cre; $Men1^{loxP/loxP}$	β-Cells	Mouse insulin promoter	*Men1* inactivation	Insulinoma	Not reported	[25]
MIP-Cre; $Men1^{loxP/loxP}$; $Pten^{loxP/loxP}$	β-Cells	Mouse insulin promoter	*Men1* and *Pten* inactivation	Insulinoma	Not reported	[25]
RIP1-Tag2 (RT2;C57Bl/6N)	β-Cells	Rat insulin promoter	SV-40 TAg-mediated inhibition of p53 and pRb	Insulinoma (rare nonfunctional MLP PanNETs)	Rare	[26]
RIP1-Tag2 (RT2;AB6F1)	β-Cells	Rat insulin promoter	SV-40 TAg-mediated inhibition of p53 and pRb	Insulinoma (IT) and nonfunctional (MLP) PanNETs	LN and liver (from nonfunctional MLP PanNETs)	[29]

LN, lymph node; MLP, metastasis-like primary; PanNET, pancreatic neuroendocrine tumor.

α- or β-cells has no phenotype, indicating a susceptibility of pancreatic progenitor cells to *Vhl* inactivation [19].

α-Cell specific inactivation of *Men1*, using glucagon-driven Cre, leads to glucagonomas [21]. Intriguingly, glucagonomas transdifferentiate to insulinomas in advanced stages of the disease [21]. Similarly, in humans the rarely occurring malignant insulinomas share molecular features closer to nonfunctioning (ATRX-DAXX-MEN1 mutant) PanNETs, indicating that such a transdifferentiation could also occur [22]. Conditional deletions of *Tp53* and *Rb1* using a Renin-driven model also leads to transformation of α-cells and development of glucagonoma [23]. However, in contrast to the *Men1* inactivation, the authors did not report transdifferentiation to insulinomas. Notably, the glucagonomas with deleted *Tp53* and *Rb1* gave rise to aggressive tumors that metastasized to the lymph nodes and liver [23], indicating a possible malignant PanNET phenotype originating from α-cells.

β-Cell specific inactivation of *Men1*, using a transgenic mouse in which Cre is expressed under the rat-insulin promoter, leads to the development of insulinomas [24]. During the progression of the disease, the authors observed marked downregulation of insulin, suggesting dedifferentiation and progression towards nonfunctional (NF) PanNETs. β-Cell specific inactivation of *Men1* and *Pten*, using mouse lines expressing Cre under either the mouse-insulin promoter or the rat-insulin promoter, dramatically accelerated disease progression compared to inactivation of *Men1* alone [25]. The expression of insulin levels in advanced lesions was not characterized; therefore, it is unknown whether *Men1* along with *Pten* inactivation also leads to dedifferentiation. According to the studies mentioned above, inactivation of *Men1* alone or with *Pten* activation does not lead to metastasis.

The SV40 large T antigen (TAg) protein suppresses the function of the tumor suppressor proteins p53 and pRb. Therefore, cell specific TAg expression resembles suppression of the p53 and pRb protein function due to the increased levels of upstream negative regulators during the progression of PanNETs. Specifically, β-cell specific

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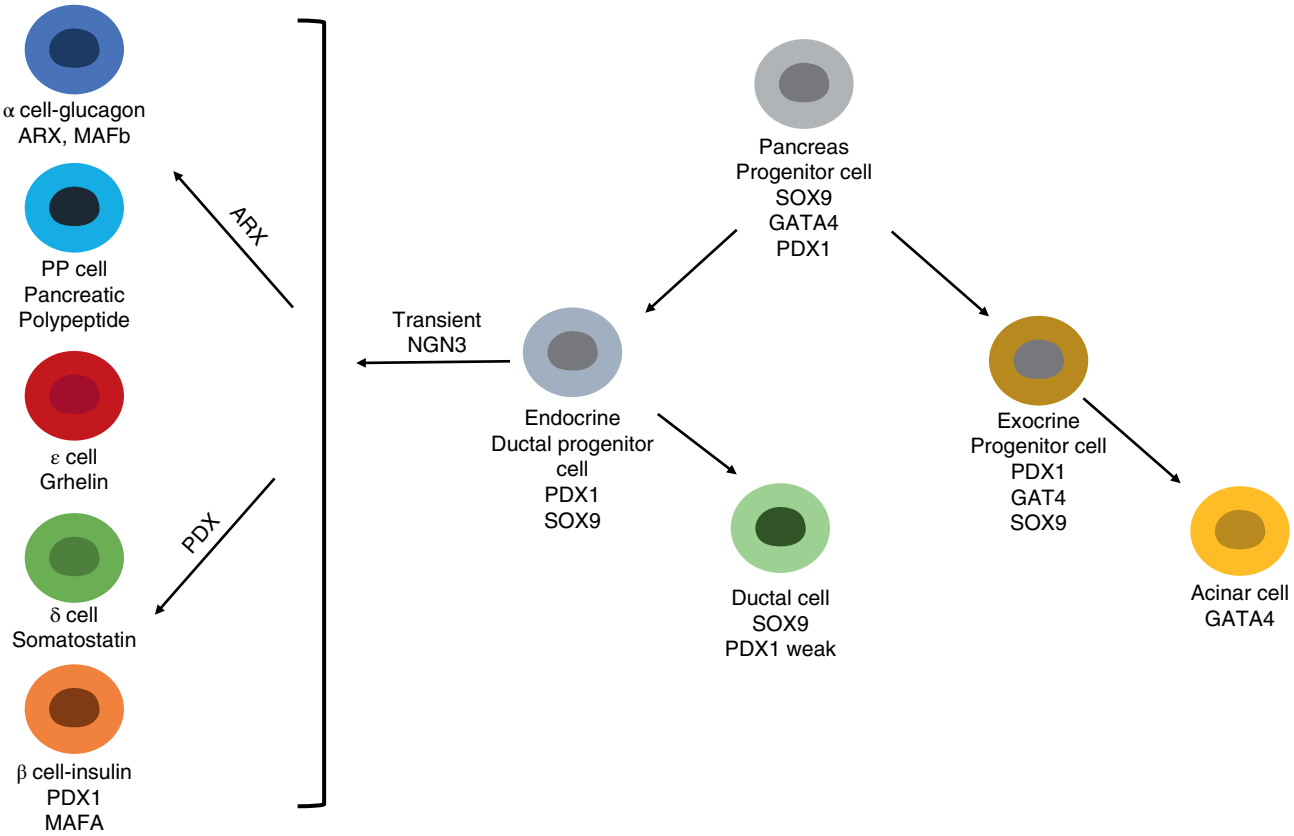


Figure 101.1 Simplified scheme of development of pancreatic cells.

TAg expression using the rat insulin promoter, in the RIP1-Tag2 (RT2) mouse model, leads to a stepwise development of insulinomas [26].

Transcriptomic characterization of primary lesions in the RT2 PanNET mouse model revealed two distinct molecular subtypes: islet tumor (IT) subtype and metastasis-like primary (MLP) subtype [27,28]. The IT subtype comprises insulinoma tumors that are not invasive and rarely metastatic, while the MLP subtype is characterized by highly invasive and metastatic tumors, that have a similar transcriptomic program to liver metastasis. Sadanandam et al. have shown that IT and MLP subtypes also exist in human PanNETs [28]. The IT subtype is made up mostly of functional G1-PanNETs and the MLP subtype by nonfunctional G3-PanNETs. Saghafinia et al. demonstrated that MLP tumors (i.e., high-grade, NF-PanNETs) arise from IT tumors (i.e., low-grade, insulinomas) via dedifferentiation following a reverse trajectory along the developmental pathway of β- cells [29]. This dedifferentiation results in the downregulation of mature β-cell markers and the activation of pancreatic progenitor markers (see Fig. 101.1).

In the RT2 mouse model, the IT-to-MLP transition takes place during the early stages of tumorigenesis and constitutes a distinct step of tumorigenesis. Notably, this transition temporarily precedes the accelerated proliferation of cancer cells. The latter suggests that some patients with low-grade PanNETs, e.g., low proliferation/Ki67 index, might have already undergone dedifferentiation, i.e., IT-to-MLP switch, and acquired prometastatic capabilities.

In addition to origin of α-, β-, and progenitor cells, the various GEMM models revealed the cell plasticity of PanNETs, which can lead to phenotype and subtype switch via mechanisms of trans- and dedifferentiation. Additional mouse models are necessary to systematically examine the effect of the inactivation (or activation) of the combination of genes associated with PanNET progression as well as to better define the cell of origin. For example, while current studies support the notion that inactivation of the p53 and pRb pathways facilitates the development of more invasive and metastatic lesions, further studies are needed to examine this in the context of *Men1* and *DAXX*/*ATRX* inactivation.

Human PanNET/Familial Syndromes

Observation of the very early steps of tumorigenesis allows us to gain insights into the microanatomic localization of tumorigenesis and thereby indicate (localization of) cells

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of origin. While such early tumors are difficult to detect, the multiple endocrine neoplasia (MEN) familial endocrine tumor syndromes are characterized by development of multiple tumors in various organs as well as within the same organ. For example, the multiple endocrine neoplasia type 1 (MEN 1) and vonHippel–Lindau syndromes are characterized by the presence of microadenomatosis of the pancreas—the occurrence of multiple microscopic endocrine microtumors.

A detailed analysis of over 300 microadenomas from pancreatic resection specimens of patients suffering from PanNET in the setting of the MEN1 syndrome showed most frequently expression of glucagon (53%), followed by pancreatic polypeptide (20%), insulin (15%), and somatostatin (5%) [30]. This distribution does not represent the abundance of respective islet cells, suggesting an increased susceptibility of α- and PP-cells to *MEN1* mutations. While these microadenomas express one hormone homogeneously, single interspersed cells expressing other islet hormones were observed, indicating islet origin of microadenomas and thereby islet origin of PanNET.

Knowing that allelic loss of the *MEN1* wild-type allele is a very early step in tumorigenesis in MEN 1 patients, a combined immunofluorescence/FISH analysis for insulin, glucagon, and the *MEN1* locus (on 11q13) enables the detection of potential monoclonal lesions inside or outside islets. Microadenomas of the pancreas showed allelic loss of the *MEN1* region in the vast majority of cases. Different patterns of loss of heterozygosity (LOH) with or without concomitant loss of centromere 11 show that individual microadenomas had independent second hits and were therefore unrelated. Single interspersed cells with expression of different islet hormones showed retention of both *MEN1* alleles, and therefore were not part of the microadenomas. This observation supports the scenario of development of microadenomas in islets [31] (Fig. 101.2). Furthermore, small clusters with expression of one single hormone were detected, both in islets (5×) as well as in ducts (1×) or in the exocrine parenchyma (1×). These monohormonal endocrine cell clusters (MECCS) all showed LOH of the MEN1 locus, and therefore represent tiny neoplastic lesions (see Fig. 101.2).

These results suggest that the genesis of PanNET is most frequently in islets, and rarely in ducts or the parenchyma. Overall, these results support the notion of development of glucagon- and insulin-positive PanNET in islets, where normal α- and β-cells are located, and the rare development of PanNET in ducts and the exocrine stroma, where rare interspersed endocrine cells can be found. The possibility of development of PanNET from putative endocrine stem cells in islets, and more rarely ducts or parenchyma, cannot be excluded.

Hyperplastic islets are a very rare phenomenon in the setting of MEN 1. Indeed, enlarged islets with increased number of α- and β-cells in a disorganized fashion with slightly increased proliferation rate are observed, but this step seems unnecessary for the development of microadenomas. In the above study, only one MECC was found in such a hyperplastic islet.

In other genetic diseases that lead to microadenomatosis, a step of hyperplasia in the sequence of development of microadenomas is possible. Both in insulinomatosis (homozygous *MAFA* mutations) and glucagon-cell adenomatosis (homozygous glucagon receptor [*GCGR*] mutations), hyperplastic islets are a frequent finding besides microadenomas [32,33].

In summary, in MEN 1 patients microadenomas frequently develop in islets, as indicated by nonneoplastic islet cells found in microadenomas and by the presence of MECCS in islets. Glucagon-producing microadenomas are the most frequent, while insulin-producing microadenomas are rare despite the much higher number of β-cells compared to α-cells, indicating a higher susceptibility of α-cells to *MEN1* mutations.

Molecular Evidence on Human PanNET

Mutation Signatures Depending on Hormone Production

Sporadic PanNETs present a heterogenous pattern of genetic drivers. As for the familial disease, *MEN1* is mutated in almost 44% of sporadic PanNETs [12]. Mutations in *DAXX* (death domain-associated protein) and *ATRX* (α-thalassemia/mental retardation syndrome X-linked) are found in almost 40% of PanNETs, often in association with *MEN1* [34]. Other less frequent mutations include members of the mTOR pathways such as *PTEN*, *TSC2*, and *PIK3CA*, and the epigenetic regulators *SETD2* and *MLL3* [12].

Insulinomas, which are the most common functioning PanNET, have a unique genetic background with recurrent mutations (T372R) in the transcription factor gene *YY1* (Ying Yang 1) in about 25% of cases [35]. *YY1* mutations have not been identified in patients with NF-PanNETs. On the other hand, insulinomas only rarely present mutations in *MEN1* and *DAXX/ATRX* [13]. Therefore, insulinoma and NF-PanNET development seems to follow different molecular pathways, which presumably reflects a different cell of origin. Indeed, while, not surprisingly, insulinomas express PDX1 (pancreatic and duodenal homeobox 1), a transcription factor responsible for β-cell differentiation, the majority of NF-PanNETs are positive for ARX (aristaless related homeobox), which

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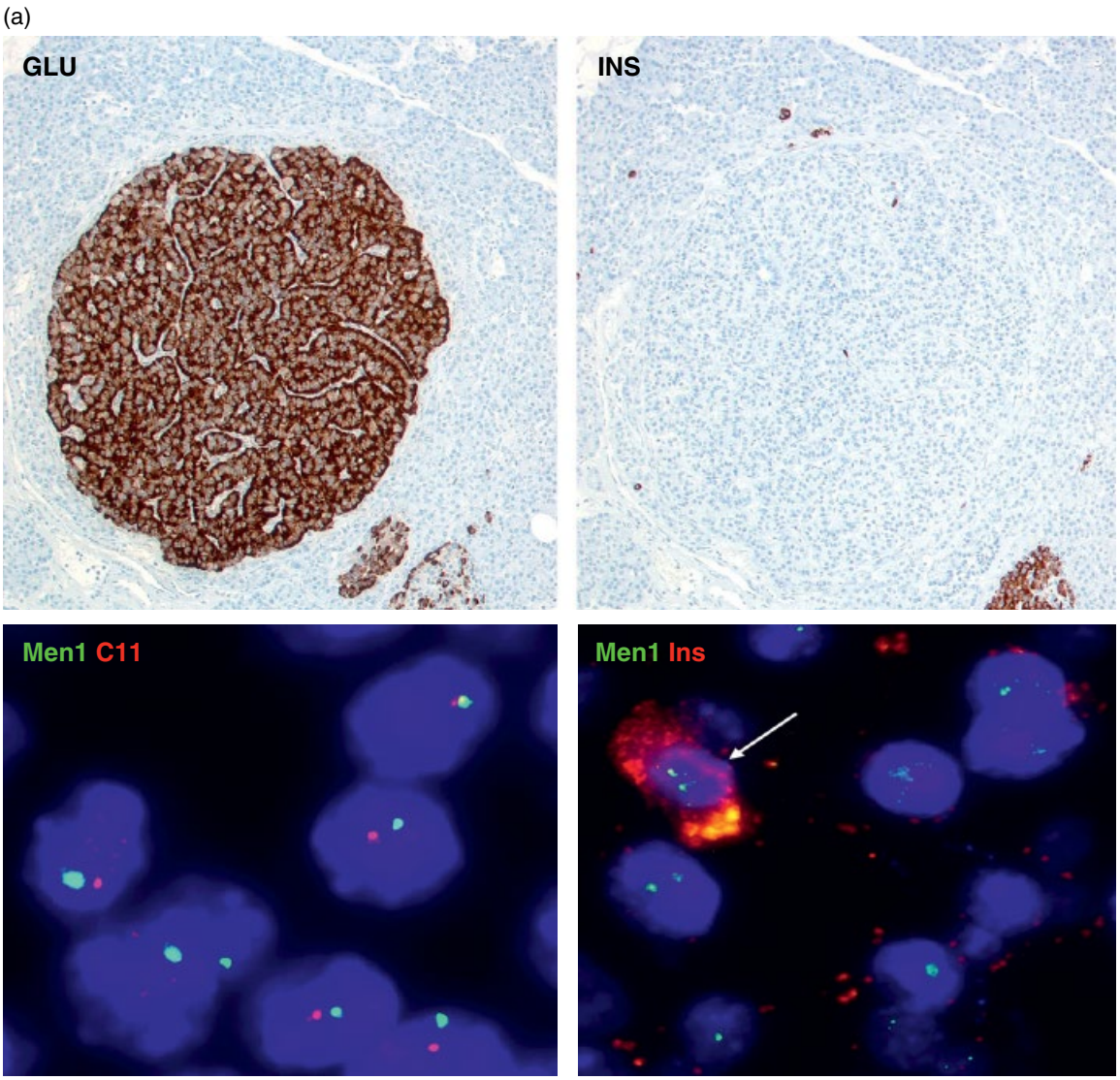


Figure 101.2 (a) Glucagon-producing microadenoma with nonneoplastic β-cell. GLU: Immunohistochemical staining for glucagon showing monohormonal expression typical for microadenomas. Tumor cells show loss of both MEN1 locus and C11 locus. Note the normal distribution of α-cells in nonneoplastic islets on the lower right. INS: Immunohistochemical staining for insulin showing single nonneoplastic β-cells, showing a retained *MEN1* allele in the FIHS analysis (red insulin, green MEN1 locus). (b) PanNET precursors (MECC): monohormonal endocrine cell clusters (MECC) arising in islets, parenchyma, and duct. Monoclonality by FISH was shown in glucagon-positive trabecular parts. These MECC are surrounded by cytologically normal rim of β-cells and α-cells, retaining islet structure.

instead drives the differentiation [6,7,22] of the α-cell lineage (Fig. 101.3). Interestingly, DAXX/ATRX loss is found only in malignant insulinomas in correlation with ARX positivity [22], indicating a transdifferentiation from α-cells, as observed in some mouse models.

Malignant and indolent insulinomas seem to follow different tumorigenic mechanisms: while indolent small insulinomas express the β-cell differentiation marker PDX1 consistent with β-cell origin, malignant ones express the endocrine transcription factor ARX inconsistent with normal β-cell differentiation.

Epigenetic Similarities to α- and β-Cells

Epigenetic signatures and specifically methylation patterns are now considered a robust method to identify cells of origin across tissues and different cancer types [36,37].

The methylation state is established during embryonic development. This generates a tissue-specific chromatin template, which is extremely stable and maintained for the rest of an organism's life. Each tissue type has specific DNA methylation profiles, which differ minimally across individuals. This allows identification of cell and tissue

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(b)

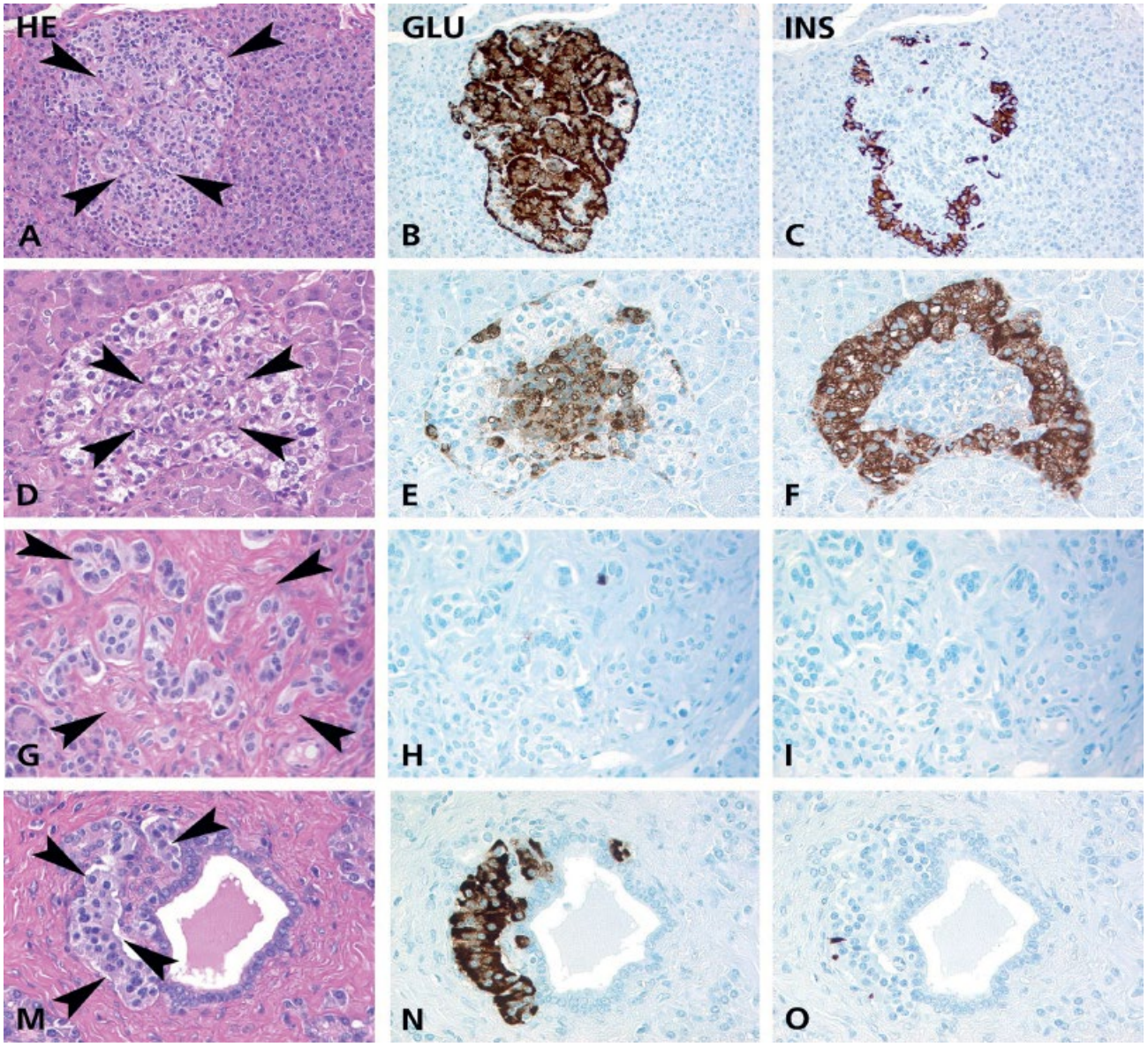


Figure 101.2 (Continued)

type based on DNA methylation profile. In addition, DNA methylation pattern allows discrimination of stem and progenitor cells from adult tissues [36]. For these reasons, DNA methylation profiles are extremely powerful in identifying subgroups of tumors as well as tissues of origin [36,38].

Recently, H3K27ac super enhancer profiles identified two major subtypes of PanNETs [6]. These subtypes comprise tumors with an α-like signature expressing ARX and tumors with a β-like signature expressing PDX1. A small fraction of PanNETs presented expression of both transcription factors or neither of them. DNA methylation profiles also classified PanNETs according to epigenetic similarity to α-cells and β-cells [7,39,40]. Specifically, based on DNA methylation profiles, three main groups of PanNETs can be distinguished: β-like and α-like tumors, respectively very similar to β- and α-cells, and a group of intermediate tumors, which seem to progressively lose cell differentiation [7]. β-Like PanNETs mainly include insulinomas while α-like PanNETs include small, grade 1 PanNETs enriched for *MEN1* mutations only. Intermediate PanNETs are instead of advanced stage, with high metastatic risk, mainly mutated in *MEN1* together with *DAXX/ATRX*.

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Intermediate PanNETs mutated in *MEN1/DAXX/ATRX* (*ADM*) maintain some features of α-cells, including specific transcription factors profiles [7] Both α-like and intermediate tumors express ARX, while β-like PanNETs are PDX1 positive.

These data suggest that α-like tumors mutated in *MEN1* originate from endocrine α-cells and can progress into intermediate-ADM tumors upon *DAXX/ATRX* mutation acquisition and progressive loss of cell differentiation (see Fig. 101.3). While occasionally stem cell markers are expressed in intermediate tumors, an origin from progenitor or stem cell is not yetproven. Of note, ARX is already expressed in endocrine precursor and in both α- and γ-cells [41,42].

β-Like tumors instead seem to originate directly from β-cells, giving rise to insulinoma. These tumors separate very clearly from the rest according to the β-cell transcription factors [7]. Interestingly, a group of aggressive tumors (metastasis-like primary, MLP) feature markers of pancreatic progenitor cells with progressive loss of insulin expression [29]. On the other hand, in rare cases, α-like NF-PanNETs may transdifferentiate by acquiring the ability to secrete insulin, usually presenting with a larger tumor size and aggressive phenotype [22].

Taken together, these studies reveal the presence of distinct NF-PanNET subgroups based on epigenetic signatures of endocrine differentiation, resembling either mature α- or β-cells.

Neuroendocrine Carcinomas

High-grade PanNENs consist of well-differentiated PanNET G3 and poorly differentiated neuroendocrine carcinoma (NEC). PanNET G3 share mutations with G1-G2 PanNET, including *MEN1*, *DAXX*, *ATRX*, *PTEN*, and *TSC2*, but they also have distinct ones such as *TP53*, while PanNECs are commonly mutated in *TP53*, *KRAS*, *BRAF*, and *PIK3CA/PTEN* [43–45]. The PanNEC mutational spectrum is similar to that of pancreatic ductal carcinoma, which may indicate a different cell of origin followed by transdifferentiation towards a neuroendocrine phenotype. Indeed, neuroendocrine transdifferentiation has been observed in ductal pancreatic adenocarcinoma in a MYC-dependent manner [46]. It is not uncommon to observe heterogeneous expression of cell markers of the exocrine lineage such as trypsin, MUC1, and CEA which may indicate cell plasticity and a possible clonal transdifferentiation [41] as well as a different cell of origin.

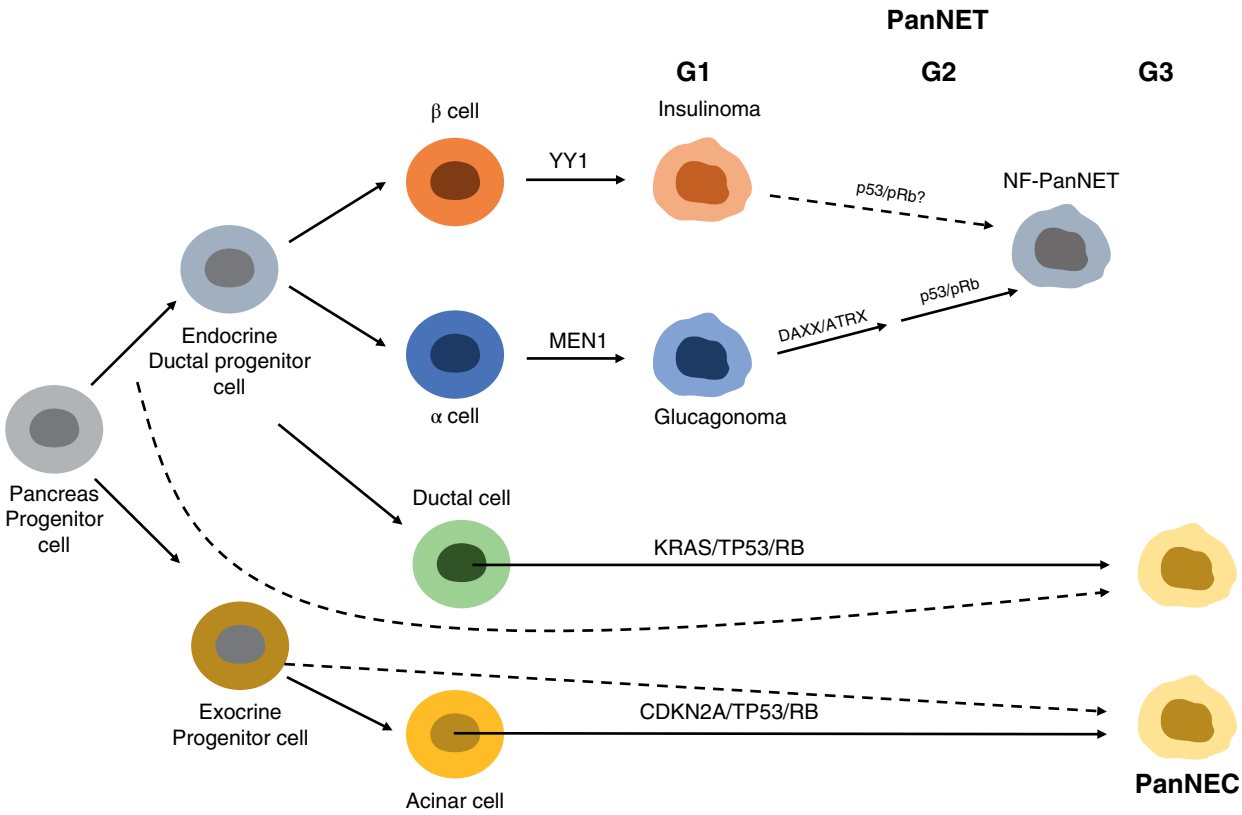


Figure 101.3 Proposed model of cell of origin with driving mutations of PanNEN.

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A very recent study, based on mutational spectrum and epigenetic profiles, suggested that PanNECs include two different groups of tumors: PanNEC with acinar origin and PanNEC with ductal origin [14]. Ductal PanNECs present mainly mutation in *KRAS* and *TP53*, RB loss, and overexpression of duct lineage markers such as SPP1 and CFTR. Interestingly, expression of the transcription factors SOX2 and ASCL1 associated with increased chromatin accessibility was also found in this subtype. SOX2 is expressed in embryonic stem cells and neuronal progenitor cells, and has been shown to be important for neuroendocrine transdifferentiation in prostate cancer [47]. Acinar PanNECs instead present characteristic alterations in *CDKN2A* and in WNT signaling.

DNA methylation pattern accurately distinguishes PanNECs from all PanNENs, including G3 PanNETs [8]. Notably, PanNECs cluster together and show epigenetic similarities to acinar cells, rather than to endocrine cells. PanNECs showed consistent positivity for SOX9 and loss of expression of endocrine transcription factors ARX and PDX1. SOX9 is a crucial differentiation factor in pancreas development, which is expressed in a multipotent progenitor state and confined to ductal and centroacinar cells in the adult pancreas (see Fig. 101.1) [48,49]. These data together suggest that PanNECs originate from exocrine or stem cells. In contrast, well-differentiated PanNET G3 cluster with G1-G2 featuring endocrine α- and β-cells [8]. Interestingly, a subset of PanNET G3 also expresess SOX9 while retaining endocrine cells epigenetic similarity; thus NET-G3 may originate from endocrine cells and progressively lose cell differentiation via reexpression of progenitor markers.

Conclusion

In summary, converging evidence exists that insulinomas and a subset of low-grade nonfunctioning PanNET seem to arise from β- and α-cells of the pancreatic islets, respectively. They are driven by at least two different molecular pathways, driven by *YY1* and *MEN1* mutations. There is also evidence for a combined genetic (DAXX/ATRX) and epigenetic malignant evolution in the α-cell lineage towards more aggressive, epigenetically intermediate higher grade PanNET. In this scenario, a hormonal switch to insulin production also seems to occur in both human and mouse models. Possibly, a subset of well-differentiated PanNETs may also arise from endocrine precursor cells, and it can be anticipated that upcoming studies using single cell techniques will shed light on this question (see Fig. 101.3).

Interestingly, high-grade PanNEC could arise from ductal and/or acinar cells and shares some mutational patterns with the respective adenocarcinomas. Besides these general lines, observations from human tumors indicate potential additional plasticity: cases of mixed IMPN/NET with combined mutational background as well as NET-like differentiation on the infiltrative front of acinic cell carcinomas cannot fit into the current simplified model and is indicative of rare events of increased plasticity as well as microenvironmental factors influencing divergent differentiation.

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Clinical Manifestation of Endocrine Tumors of the Pancreas

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Epidemiology of PanNEN

PanNEN represents 1–2% of all pancreatic tumors, and the annual prevalence is reported to be less than 1 per 100 000 individuals. According to the American SEER (Surveillance, Epidemiology and End Results) database, more than 60% of tumors registered between 1973 and 2004 were gastrointestinal NENs in which the ileum and rectum were sites of high incidence; 3.6% of these tumors were PanNENs [1]. However, according to the SEER study, the number of patients with this pathology has been increasing, with an annual incidence of 6.98 per 100 000 population in 2012, approximately seven times greater than the 1.09 per 100 000 population reported in 1973 [2]. Epidemiologic surveys for PanNEN were also conducted in Japan in 2005 and 2010 [3–5]. It was reported that approximately 2845 Japanese PanNEN patients were treated in 2005 whereas 3379 patients were treated in 2010; the number of PanNEN patients per 100 000 people was approximately 2.23 in 2005 and 2.69 in 2010. Moreover, the number of new patients per 100 000 people was estimated to be approximately 1.01 in 2005 and 1.27 in 2010. Hence, the number of NEN patients is definitely increasing in Japan as well.

Clinical Symptoms of PNET

As mentioned above, PanNET is broadly categorized into functional and nonfunctional entities. The clinical symptoms of functional PanNET are caused by excessive secretion of hormones. A Japanese epidemiologic study reports that approximately 35% of pancreatic NETs are functioning, indicating that most pancreatic NETs are nonfunctioning [5].

Functional PanNET

Three aspects must be taken into consideration when treating functional PanNET. First, multiple symptoms can be present because of the excessive levels of various hormones autonomously secreted by the tumors (Table 102.1) [6], possibly causing deterioration of the patient's quality of life or development of a life-threatening situation. Therefore, appropriate treatments for alleviating hormone symptoms are critical. Second, malignant functional NET may grow rapidly and can frequently metastasize to other organs during the course of the disease. Therefore, a multidisciplinary approach is of the utmost importance. Lastly, determination of multiple endocrine neoplasia type 1 (MEN 1) complications is also recommended [7,8].

Insulinoma

Insulinoma is characterized by hypoglycemic symptoms induced by excessive autonomous insulin secretion, and is categorized according to symptoms of the central nervous system and those of the autonomous nerve system. Central nervous system symptoms include headache, dizziness, disturbance of consciousness, and convulsions; they are sometimes mistaken for epilepsy or mental disease.

During hypoglycemic conditions, sympathicotonia can occur, followed by autonomic symptoms such as hunger, sweating, and tremors. As hypoglycemia improves upon consumption of food, a patient may tend to overeat,

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Table 102.1 Symptoms and recommended tests for pancreatic functional neuroendocrine neoplasm [6]/Springer Nature/Public Domian CC BY 4.0.

Functional neuroendocrine neoplasm	Symptoms and findings	Differential diagnosis (presence diagnosis)
Insulinoma	Central nervous system symptoms: impaired consciousness (67–80%), abnormal vision (42–59%), amnesia (47%), personality changes (16–38%), epilepsy (16–17%), headache (7%)	Differentiating hypoglycemia: Whipple's triad, exogenous insulin, oral hypoglycemic agents, endogenous insulin dyssecretion, insulin autoimmune syndrome
	Autonomic symptoms: sweating (30–69%), malaise (28–56%), hyperphagia/obesity (14–50%), tremor (12–14%), palpitation (5–12%), anxiety (12%)	Definitive diagnosis: 72-hour fasting test, mixed-meal test, 48-hour fasting test + glucagon tolerance test
Gastrinoma	Peptic ulcers: duodenal bulb (75%), distal duodenum (14%), jejunum (11%)	Fasting serum gastrin measurement, gastric pH measurement, intravenous calcium injection test
	Abdominal pain, steatorrhea	(MEN1 differential diagnostics: blood calcium measurement, intact PTH measurement)
Glucagonoma	Glucose intolerance/diabetes (30–90%), weight loss (60–90%), necrotizing erythema migrans (55–90%), mucosal symptoms (30–40%), diarrhea (10–15%), anemia (30–90%), hypoaminoacidemia (30–100%), venous thrombosis, psychoneurotic symptoms	Plasma glucagon measurement, serum albumin measurement, amino acid fraction measurement
VIPoma	Profuse watery diarrhea, hypokalemia, fatigue, muscle weakness, shortness of breath, muscle cramps	Stool osmotic gap measurement
	Diarrhea: dark brown, odorless, low osmotic gap and secretory	Blood VIP cannot be measured in Japan
Somatostatinoma	Weight loss, abdominal pain, diabetes, cholelithiasis, steatorrhea, diarrhea, hypoacidity, anemia (often asymptomatic)	Blood somatostatin cannot be measured in Japan. Diagnosis by biopsy
Carcinoid syndrome	Skin flushing (without sweating), diarrhea, pellagra symptoms, psychiatric symptoms (i.e., confusion), heart failure (especially right heart failure), bronchospasm, intraabdominal fibrosis	Urinary 5-HIAA excretion measurement, intake of serotonin-containing foods and drugs

HIAA, hydroxy-indole acetic acid; MEN1, multiple endocrine neoplasia type 1; PTH, parathyroid hormone; VIP, vasoactive intestinal polypeptide.

resulting in weight gain or obesity. Persistence of this condition can lead to memory disturbances or the development of intellectual impairment; such cases are sometimes regarded as dementia or cerebrovascular disorders. Some patients may fall into a coma without presenting with any autonomic symptoms beforehand; therefore, a cautious approach is necessary. Meanwhile, fasting hypoglycemic events are not the primary symptoms in some insulinoma patients; instead, excessive insulin secretion is noted after glucose loading (i.e., after eating a meal).

Gastrinoma

Gastrinoma occurs primarily in the duodenum and pancreas, which ectopically secrete gastrin, resulting in the Zollinger–Ellison syndrome (ZES), which is due to marked hypersecretion of gastric acid causing severe gastroesophageal peptic disease. Abdominal pain, heartburn, nausea/vomiting, gastrointestinal bleeding, and gastrointestinal perforation may occur, and are symptoms of refractory ulcers or excessive gastric acid. Digestion-absorption disorder may also occur because gastric acid is not neutralized in the duodenum, and pancreatic digestive enzymes are inactivated. As a result, fatty diarrhea, weight loss, and other symptoms may be observed. ZES patients have two management problems that must be dealt with: control of acid hypersecretion and control of the gastrinoma, which is malignant in 60–90% of cases. Most gastrinomas are sporadic, but 20–25% of patients have it as part of the MEN 1 syndrome [9].

Glucagonoma

Glucagonoma characteristically presents with a specific dermatitis (necrolytic migratory erythema), which frequently occurs on the face, perineum, and limbs, causing itchiness and pain and exhibiting chronic healing/

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recurrence cycles [9]. Excessive secretion of glucagon induces glucose intolerance, hypoaminoacidemia, hypoalbuminemia, weight loss, anemia, glossitis, angular cheilitis, venous thrombosis, mental symptoms, and other conditions. At presentation, glucagonoma is characterically large (>5 cm) and 50–80% of patients have advanced disease with metastatic liver lesions.

VIPoma

Secretion of electrolytes and water from the intestine is accelerated by autonomic excessive secretion of VIP (vasoactive intestinal polypeptide) from the tumor, resulting in severe watery diarrhea and hypokalemia as well as metabolic acidosis induced by massive excretion of bicarbonate ions. Owing to the secretin-like action of VIP, gastric acid becomes hypoacidic or anacidic. Various symptoms occur, including severe dehydration, weight loss, vasodilation-caused skin flushing, hypercalcemia caused by accelerated bone resorption, and glucose intolerance. Most patients with VIPomas present with advanced disease with liver metastases.

Somatostatinoma

Most cases of somatostatinoma in the literature do not have the clinical somatostatinoma syndrome, characterized by diabetes mellitus, gallbladder disease, diarrhea, weight loss, and steatorrhea, but are cases with no specific symptoms or found by chance that demonstrate immunohistochemical staining for somatostatin-like immunoreactivity.

Nonfunctional PanNET

No specific symptoms are present in patients with nonfunctional PanNET. As the tumor grows, nonspecific symptoms appear that include abdominal distension, abdominal pain, anorexia, and weight loss. Nonfunctional PanNET is often discovered following compression or invasion by the primary tumor or a distant metastasis. In the case of advanced liver metastasis, hepatic dysfunction and jaundice are observed.

According to the results of an epidemiologic study in Japan, approximately 22 months pass between the appearance of PanNET symptoms and disease diagnosis in symptomatic cases, on average [4,5]. While PanNET is not often encountered in actual clinical practice, it is important to consider it during differential diagnosis.

Diagnosis of PanNET

When repetitive hypoglycemic events or refractory gastrointestinal ulcers are investigated, differential diagnosis for functional PanNET is required, including insulinoma and gastrinoma. If functional PanNET is suspected on the basis of clinical symptoms, measurement of basal hormone levels in the blood and various loading tests are required to detect the presence of a hormone-producing tumor. If such a tumor is confirmed, its location should be accurately identified using imaging modalities; this is important for deciding the subsequent therapeutic strategy. Even if the presence of a tumor is first detected via imaging, as in the case of nonfunctional PanNET, the hormone-producing ability of the tumor as well as the presence or absence of metastasis should be investigated in detail. PanNET is often associated with MEN 1 so serum calcium and potassium levels should be determined upon initial examination to rule out excessive parathyroid hormone production. The following describes how to diagnose insulinoma and gastrinoma.

Diagnosis of Tumor Presence

Insulinoma

In the past, Whipple's triad (i.e., loss of consciousness on fasting combined with blood glucose levels <50 mg/dL, where symptoms improve upon consuming glucose) and Fajan's index for insulinoma (the ratio of plasma insulin concentration to fasting blood glucose >0.3) have been observed; however, false-negative findings should be ruled out. Testing such as a 72-hour fasting test and a mixed-meal test are recommended for definitive diagnosis [10], although there are recent reports of a 48-hour fasting test combined with a glucagon test [11].

Gastrinoma

The diagnosis of ZES should be suspected in any patient with peptic ulcer disease/gastroesophageal reflux disease (GERD) which is accompanied by diarrhea, personal or family history of endocrinopathies, or various laboratory findings (hypercalcemia, hypergastrinemia). Measurement of fasting serum gastrin and gastric acid secretion, and/or a 24-hour gastric pH monitoring test, are essential for diagnosis. It is important to inquire about the patient's medication history, as serum gastrin levels may increase owing to oral administration of proton pump inhibitors or H_2-blockers. For definitive diagnosis, a secretin or calcium stimulation test is useful, as gastrin secretion is increased by intravenous injection of secretin or calcium.

Localization Diagnosis

Many PanNETs are plethoric with inner uniformity; therefore, diagnosis is not difficult in typical cases. However, in atypical cases, it may be difficult to distinguish PanNET from a pancreatic ductal cancer or cystic

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pancreatic tumor on differential diagnosis. Furthermore, insulinoma and gastrinoma are often small in diameter, and accurate localization is important for surgery. Therefore, various imaging modalities are employed during actual examination.

To determine the localization of PanNENs, it is recommended to consider and perform imaging such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), or somatostatin receptor scintigraphy (SRS) on a case-by-case basis. When performing histology, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is recommended [12,13]. If microscopic insulinomas and gastrinomas cannot be localized by imaging, then a selective arterial secretagogue injection (SASI) test is useful [14,15].

Abdominal Ultrasonography

The more uniform the inside of tumor, the more likely the mass can be visualized on US. When the tumor is large, an irregular shape that reflects internal bleeding, necrosis, or cystic degeneration is sometimes observed. Abdominal US is easy to perform, and is the least invasive among imaging modalities. However, its diagnostic accuracy is low.

Abdominal Computed Tomography

When contrast medium is used, typical PanNETs are highly enhanced in the arterial phase (Fig. 102.1a). As contrast enhancement is weak in oligemic pancreatic ductal tumors, a CT image may be critical in distinguishing between PanNET and pancreatic ductal cancer. However, plethoric pancreatic tumors present the same contrast enhancement as PanNET, metastatic pancreatic tumor, and especially renal cancer; therefore, differential diagnosis should be carefully conducted. The diagnostic accuracy of CT is approximately 80% [16,17]. Further, liver metastases often show ringed enhancement (Fig. 102.1b).

Abdominal Magnetic Resonance Imaging

A T1-weighted MRI scan of a PanNET shows low intensity, whereas a T2-weighted scan shows high intensity (Fig. 102.2). On MRI, a tumor is visualized similarly to CT; however, the diagnostic accuracy of this method is approximately 70%, which is slightly lower than that of CT. On the other hand, for the detection of hepatic metastases from PanNET, enhanced MRI is more sensitive than enhanced CT (see Fig. 102.2) [17–19].

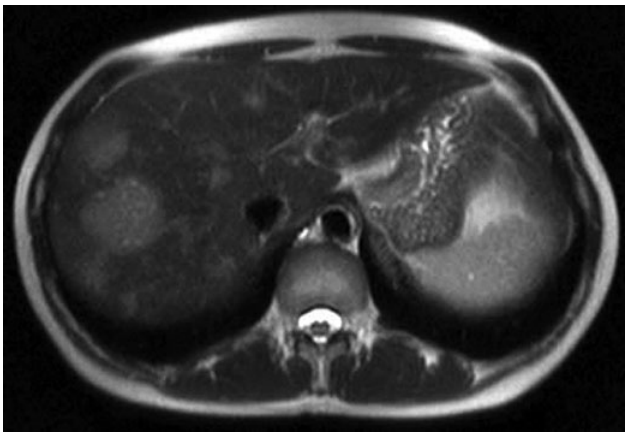


Figure 102.2 T2-weighted MRI findings of liver metastases in a patient with pancreatic nonfunctional neuroendocrine tumor.

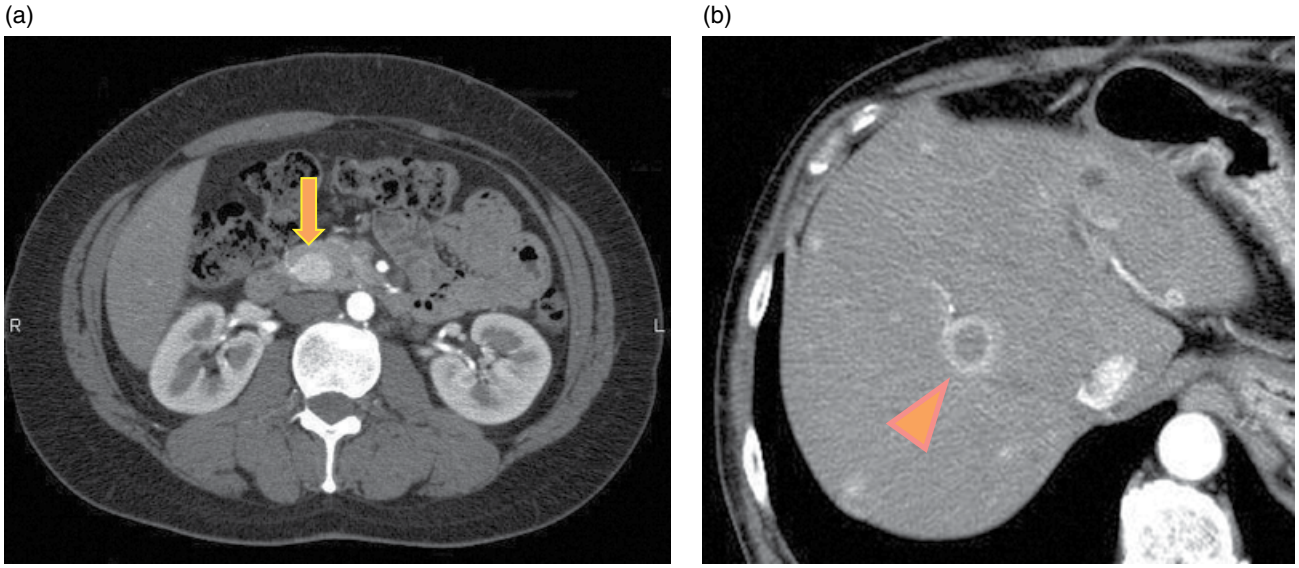


Figure 102.1 CT findings of nonfunctional neuroendocrine tumor in the pancreatic head lesion (a) and liver metastases (b).

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Endoscopic Ultrasonography/Fine Needle Aspiration (Fig. 102.3)

PanNET is visualized on EUS as a hypoechoic mass with border regularity and inner uniformity. EUS can screen the entire pancreas and detect lesions <1 cm. With a diagnostic accuracy of approximately 80–95%, this method is superior to CT and MRI and is thus a very useful testing modality [20–22]. Furthermore, EUS-FNA has become an essential assessment for the qualitative diagnosis of pancreatic neoplasms.

The role of EUS-FNA in the diagnosis of PanNEN is two-fold. Its first role is to identify pancreatic neoplasms by EUS and to correctly diagnose PanNEN. Its second role is to diagnose the degree of malignancy according to the WHO classification using the Ki-67 index and mitotic index to aid the development of a treatment strategy once the condition has been diagnosed as PanNEN.

Selective Arterial Secretin/Calcium Injection Test

At the time of abdominal arteriography, a catheter is placed in the hepatic vein for secretin/calcium infusion into the feeding artery of each pancreatic region. The level of gastrin/insulin in the hepatic venous blood is then measured. The tumor's location is determined based on the increase of gastrin concentration (>2-fold). As the supply vessel for the tumor is identified, localization becomes possible for those tumors that are difficult to visualize by imaging modalities. This technique is especially useful as a preoperative test for gastrinoma and insulinoma [15,23].

Somatostatin Receptor Scintigraphy

Somatostatin receptor scintigraphy was approved for use in Japan in January 2016 and is beneficial for identifying the distribution of NET throughout the body. This method may be explained as follows: octreotide, a somatostatin analog containing pentetreotide labeled with radioactive indium (^{111}In), is intravenously administered. Subsequently, the labeled compound specifically binds with and accumulates in somatostain receptors (SSTR) to make imaging of NET possible. Concomitant use of single photon emission computed tomography (SPECT) is useful for improving the detection rate of lesions. Recently, ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE have been used for detecting rate of lesions [24]. For cases of PanNEN, SRS is used for the purposes of (i) diagnosis of localization and metastasis [25,26], (ii) confirmation of SSTR2 expression [27,28], and (iii) follow-up [29,30]. Here, one case is presented. The patient had a nonfunctioning PanNET with liver metastasis, and ^{111}In-SRS was observed to have accumulated in the primary focus in the pancreatic head, and liver metastatic focus was detected by CT (Figure 102.4a–d). However, by the use of ^{111}In-SRS, bone metastasis, which was not detected by CT, was found (Figure 102.4e) [12].

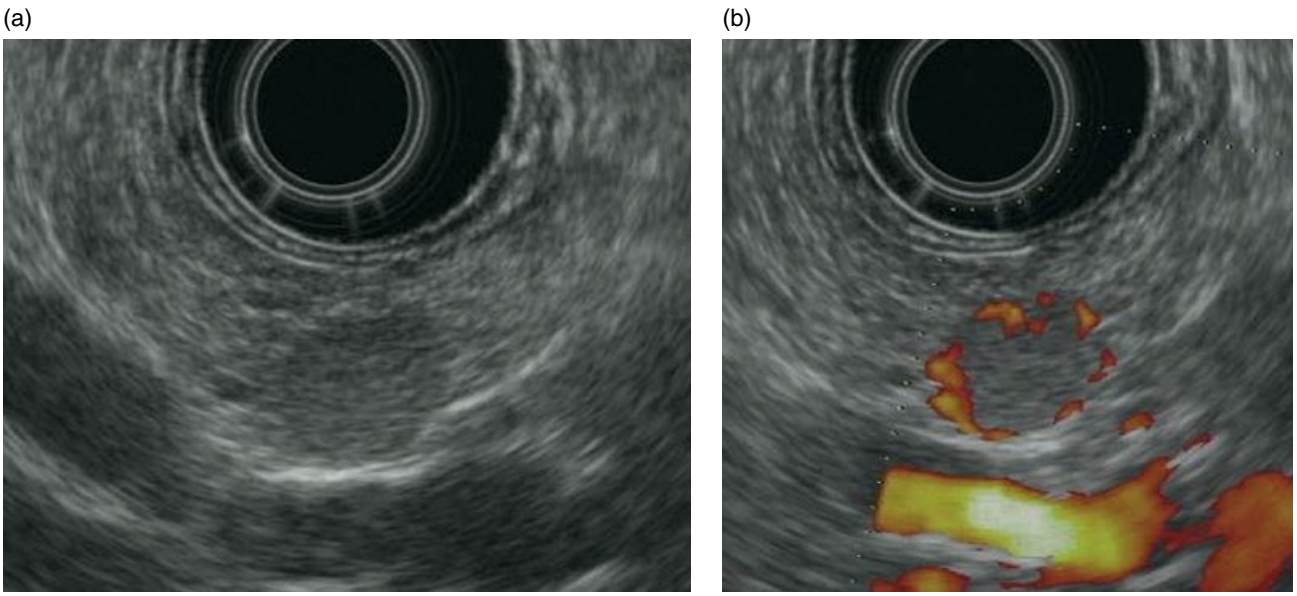


Figure 102.3 Endoscopic ultrasonography (EUS) findings of pancreatic neuroendocrine tumor. Typically, tumor is hypoechoic and homogeneous (a) and hypervascular on Doppler scanning (b).

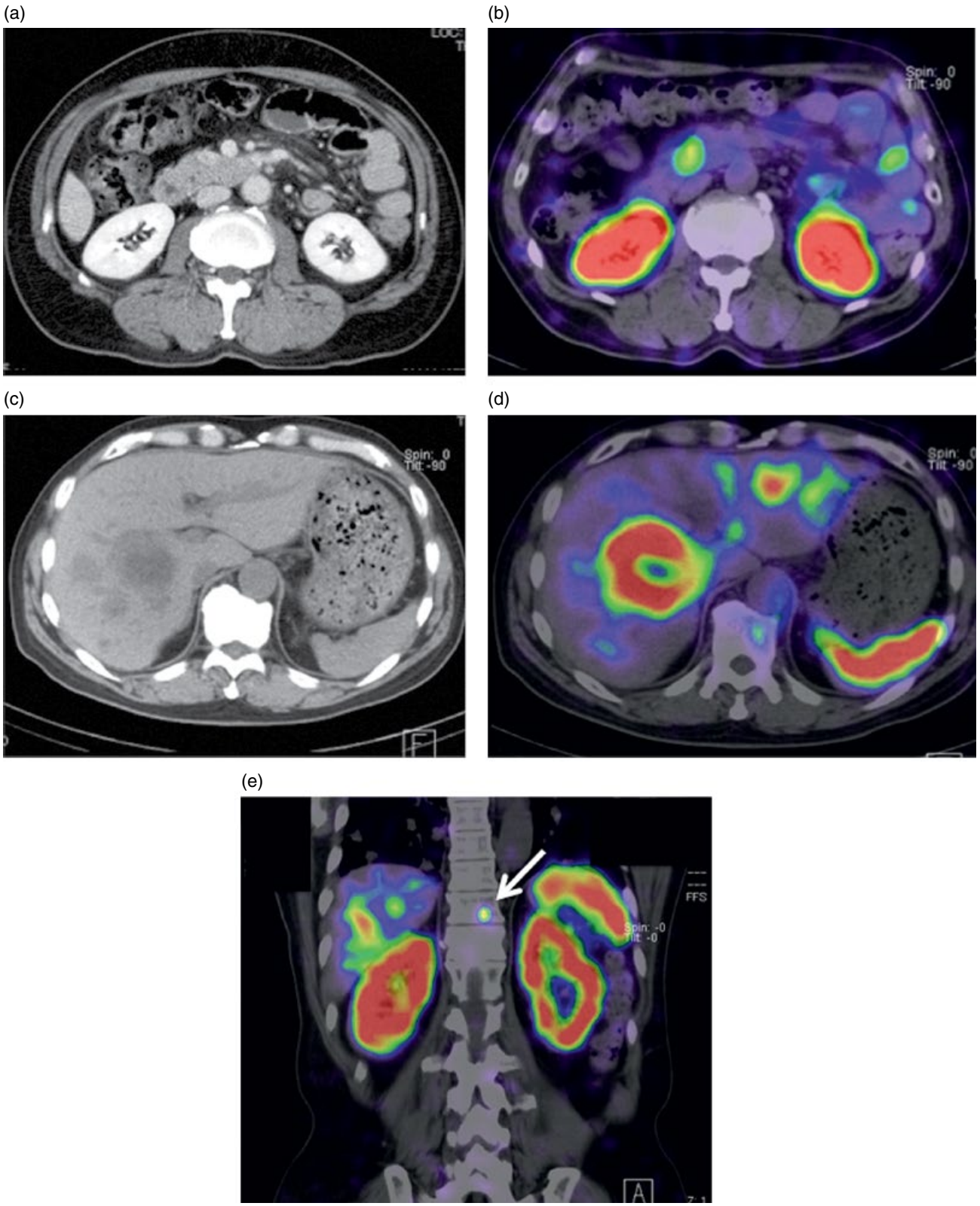


Figure 102.4 Somatostatin receptor scintigraphy (SRS) findings. The patient had a nonfunctioning pancreatic neuroendocrine tumor with liver metastasis. ^{111}In-SRS was observed to have accumulated in the primary focus in the pancreatic head, and liver metastatic focus was detected by CT (a–d). However, by the use of ^{111}In-SRS, bone metastasis, which was not detected by CT, was found (e).

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103

Evidence of Hormonal, Laboratory, Biochemical, and Instrumental Diagnostics of Neuroendocrine Tumors of the Pancreas

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Introduction

Pancreatic neuroendocrine tumors (pNETS) originate from neuroendocrine cells in the pancreatic islets and differ from other pancreatic neoplasms that originate from other pancreatic tissues. They often secrete a variety of molecules and overexpress somatostatin receptors (SSTR) on their cell surface. Traditionally, they have been divided into "nonfunctioning" and "functioning" pNETs.

In recent years, the rapid increase in pancreatic imaging has made the diagnosis of nonfunctioning pNETs as asymptomatic incidentalomas more frequent than functioning pNETs. These incidentalomas need to be distinguished from other pancreatic neoplasms for management and treatment decisions. In contrast, functioning pNETs pesent with clinical symptoms and signs and subsequently need imaging for localization and treatment.

The classic functioning pNETs are the insulinomas and glucagonomas which originate primarily from the pancreatic islets. Gastrinomas may originate from the duodenum and other parts of the gastrointestinal tract as well as the pancreas (see Chapter 102). These are rare, and many other hormones have since been reported from functional pNETs. They are even more rare, and often present with nonspecific symptoms. A multidisciplinary approach is best in the diagnosis and management of pNETS.

This chapter will describe the serum-based laboratory investigations followed by the various conventional and more recent pNET-specific radionuclide imaging investigations.

Serum-based Laboratory Investigations

Many pNETs, functioning or nonfunctioning, secrete "general NETs tumor markers" of which chromogranin A and neuron-specific enolase are the most useful [1]. Others include pancreatic polypeptide and chromogranin B, but these have lower specificity and sensitivity [1,2]. Finally, several centers have reported using "liquid biopsies," observing circulating tumor cells and serum DNA and RNA secreted by pNETS in unique patterns ("molecular signatures") as diagnostic and prognostic markers [3,4]. There is still a lack of standardization of the assays for these markers and thus there are difficulties in the interpretation of many of the laboratory-based investigations. Guidelines are updated frequently in Europe and North America.

Nonfunctioning pNETs frequently present as incidentalomas and do not secrete biologically active hormones giving rise to any symptoms or signs. However, many do secrete general NETs markers, and the most useful is still chromogranin A (ChA). Functioning pNETs present with classic syndromes to endocrinologists or gastroenterologists and need accurate diagnosis and assessment. Insulinomas and glucogonomas predominantly originate from pancreatic islets and metastasize elsewhere, but other pNETs secreting gastrin, serotonin, vasoactive intestinal polypeptide (VIP), SS, and many other hormones may originate from both pancreatic and extrapancreatic sites. Often, there may be incomplete or defective processing of the hormone and they may not be functionally active but still be identified in tissue immunochemistry, and be measurable in the serum in some

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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commercial assays. This may cause confusion as to whether they are "functioning" or not. Measurement of the relevant hormone, functioning or not, if elevated, remains useful for diagnostic and prognostic purposes.

All of these serum-based investigations should be carried out with the appropriate precautions and need to be interpreted carefully. Endocrine hormones may also be affected by their own dynamic regulation, food intake, and many commonly prescribed drugs.

Non-specific Biochemical Markers in pNETS

Many pNETS secrete molecules, which, if present, may be useful as biomarkers for diagnosis and prognosis [1,2]. These are useful in indicating a diagnosis of a pNET in incidentalomas of the pancreas, or where a nonfunctioning pNET is suspected. They include ChA, other chromogranins [5], neuron-specific enolase, pancreatic polypeptide, human chorionic gonadotrophin (hCG) subunits, synaptophysin, and pancreastatin (a derivative of ChA) [6]. Of these, only ChA has proved consistently useful as a marker, especially for monitoring for most functioning and nonfunctioning pNETs, except for insulinomas which are unusual in not secreting ChA. It is important to remember that ChA may also be elevated in other nonpancreatic neuroendocrine tumors, liver and kidney disease, and to a lesser and variable degree in atrophic gastritis and with the use of proton pump inhibitors. Neuron-specific enolase is useful mainly in poorly differentiated pNETs, and pancreatic polypeptide may be useful in nonfunctioning pNETs. However, all of these may be absent in many pNETs.

Insulinomas

Insulinomas are the most frequent functioning pNET and almost always originate in the pancreatic islets. Insulinomas are unlike other pNETS and rarely secrete ChA or overexpress SST receptors. Insulinomas may be sporadic or be associated with multiple endocrine neoplasia 1 (MEN 1) where they present as multiple pancreatic tumors (see Chapter 104 – MEN chapter). Diagnosis of an insulinoma requires the clear demonstration of inappropriately elevated serum insulin concentrations in the presence of hypoglycemia, and exclusion of other causes. They are usually benign at the time of diagnosis.

The gold standard for diagnosis is the supervised prolonged fast (72 hours) with regular venous blood sampling every 4–6 hours for glucose, insulin, and c-peptide. The fast is terminated if there is hypoglycemia (glucose <55 mg/dL or <3.0 mmol/L) with symptoms and signs. The presence of inappropriately elevated serum insulin and c-peptide concentrations (even within the normal range) during hypoglycemia is diagnostic, but sulphonylurea abuse has to be excluded [7]. Absolute cut-off values have to be interpreted within the context of the laboratory, as both insulin and c-peptide assays are not standardized. A 48-hour or 24-hour fast, followed by vigorous exercise, with or without the aid of continuous glucose monitoring, has been reported to be nearly as good in making a conclusive diagnosis [8]. With the improvement in imaging, provocative tests with infusion of arginine, calcium, and glucagon are no longer recommended.

An elevated insulin concentration with a low c-peptide value indicates surreptitious exogenous insulin administration. An elevated plasma proinsulin to insulin ratio, if available, supports the diagnosis of an insulinoma. Urine or plasma sulphonyurea should be measured, as both insulin and c-peptide are elevated in patients taking these drugs surreptitiously [7]. In ethnic East Asians, anti-insulin autoantibodies should also be measured to exclude insulin autoimmune syndrome [7,9]. Care should also be taken in the interpretation of elevated insulin levels values and hypoglycemia if there has been bariatric surgery within recent years [10,11].

Imaging investigations should proceed only after establishing a laboratory diagnosis (see below). If available, exendin-based positron emission tomography (PET) scanning would be valuable in localization prior to surgery (Fig. 103.1) [11,12].

Gastrinomas

Gastrin-secreting pNETS occur sporadically and in association with MEN 1 (1 in 4 in some series). They are often multiple and malignant and are present mostly in the duodenum as well as the pancreas at diagnosis. The hypergastrinemia causes severe gastric hyperacidity, with abdominal pain, increased gut motility and diarrhea, giving the classic Zolinger–Ellison syndrome. Many patients are already on acid suppression drugs, and the proton pump inhibitors (PPIs) are effective for the symptoms. However, all acid suppression medications will cause hypergastrinemia and need to be stopped before investigations.

The diagnosis of a gastrinoma requires stopping preexisting acid suppression drugs (seven days or longer for proton-pump inhibitors [PPIs], two days for others) and measurement of fasting serum gastrin. Fasting serum gastrin is usually markedly elevated [1]. However, difficulties arise because of the lack of standardization of gastrin assays and the absence of normal population ranges. Elevated fasting serum gastrin may also be present in chronic kidney disease, atrophic gastritis, and short bowel syndrome. Finally, several molecular forms of

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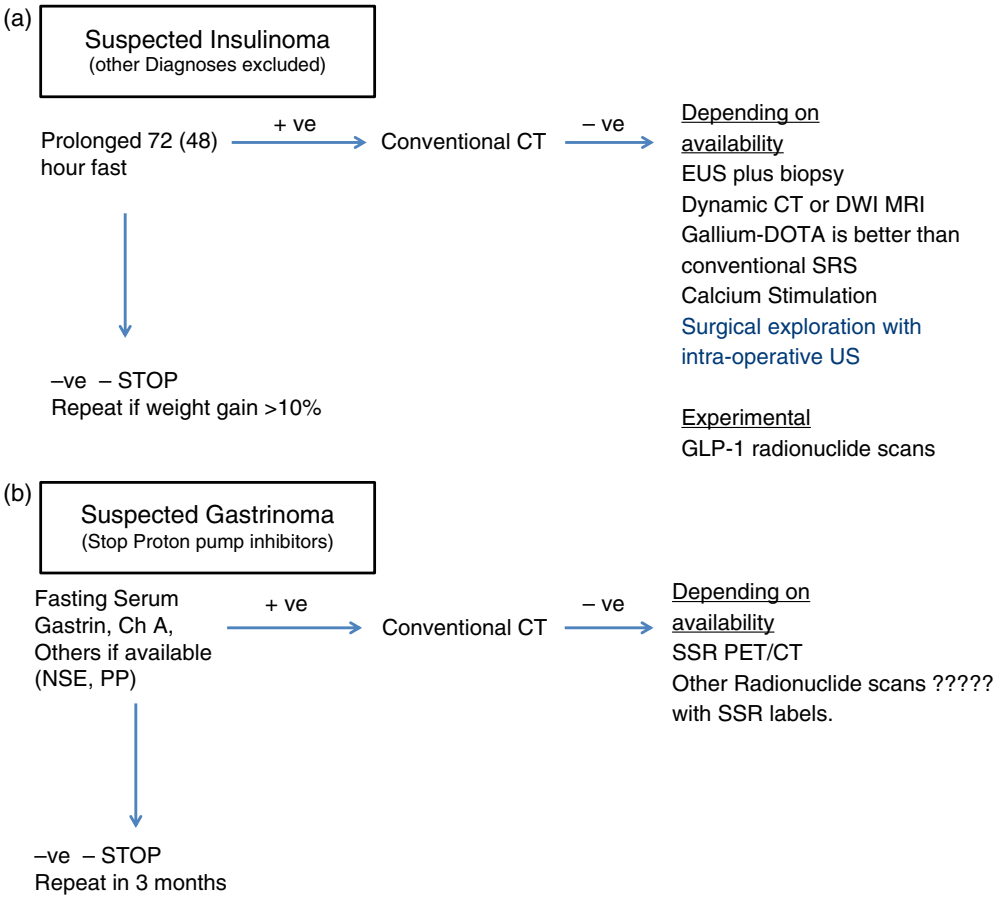


Figure 103.1 Flow chart for investigations in suspected pNETs.

gastrin may be secreted which may or may not be accurately measured by many of the available commercial assays [13]. Thus, care has to be taken in the preparation of the patient before taking measurements, and in the interpretation of the results. Many patients with gastrinomas are *H. pylori* negative, and the presence of multiple peptic ulcers in such patients should raise the index of suspicion.

The secretin stimulation test has been reported to be useful, especially when hyperacidity symptoms are too severe to permit withdrawal of acid suppression drugs. A 2 U/kg bolus of secretin is administered intravenously after an overnight fast and serum gastrin is measured at 0, 2, 5, 10, and 15 minutes. An increase in serum gastrin of >200 pg/mL is considered diagnostic. However, false-positive results may still occur and care has to be taken in the interpretation of these tests [1,14].

Imaging studies should proceed if there is clear suspicion of a gastrinoma based upon the presence of severe hyperacidity or multiple peptic ulcers on endoscopy. Somatostatin-based PET/computed tomography (CT) may be necessary if other imaging modalities are negative.

Glucagonomas

Glucagon-secreting pNETs are very rare and almost always originate from the pancreas. They are usually sporadic but may rarely be associated with MEN 1. The classic clinical syndrome of diarrhea, weight loss, hyperglycemia, and necrolytic migratory erythematous rash [15] is usually recognized late, when the tumor is often large, with liver and other metastases already present (see Chapter 102). Mild anemia and recurrent venous thromboembolism are common. The grossly elevated concentrations of fasting serum glucagon, and imaging findings, will give a clear diagnosis. However, glucagon measurements in the absence of clinical signs are difficult to interpret.

Secretion of glucagon is affected by many factors, and many smaller glucagon-like molecules, including glucagon-like peptide-1 (GLP-1), are present in the blood and may give falsely elevated results [16]. Elevated fasting glucagonemia may be found in liver cirrhosis, chronic kidney disease, acromegaly, and hypercortisolism.

A conventional CT is usually sufficient to identify the tumor because of the late presentation and diagnosis.

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Vasoactive Intestinal Peptide (VIPomas)

VIPomas are rare and sporadic and more than 90% are located in the pancreas at diagnosis [17]. Like gastrinomas and glucagonomas, they are diagnosed late, often with metastases at presentation. The classic presentation is that of severe watery diarrhea, hypokalemia, hypochlorhydria and occasionally facial flushing (Verner–Morrison syndrome or the pancreatic cholera syndrome). Serum VIP concentration is grossly elevated and is usually diagnostic. In the early stages, VIP secretion may be intermittent and should be measured during episodes of watery diarrhea. Elevated VIP concentrations may also be found in chronic kidney disease, short bowel syndrome, and radiation enteritis. Diagnosis is more difficult in countries with endemic cholera but infective causes are usually milder and self-limiting.

Imaging studies with SSTR radionuclides may be helpful in the detection of this rare pNET.

ACTH-secreting pNETs

The diagnosis of Cushing syndrome due to ectopic adrenocorticotrophic hormone (ACTH) secretion is often difficult and usually presents as a diagnostic challenge to the endocrinologist [18]. A pNET may be one of the rare possibilities. The initial screening test for hypercortisolemia is the 1 mg overnight dexamethasone test; an adequate suppression of serum cortisol excludes hypercortisolemia in most cases. In the event of uncertainty, hypercortisolemia should be confirmed with a formal three-day 2 mg low-dose dexamethasone suppression test. The plasma ACTH should then be measured to distinguish between an adrenal cause and an ACTH-dependent hypercortisol state. If the ACTH concentration is inappropriately elevated, then further investigations are necessary to distinguish between a pituitary tumor and an ectopic ACTH-secreting tumor. This may include a corticotrophin hormone (CRH) test, inferior petrosal sinus sampling, or a combination of the two.

In ectopic ACTH-dependent Cushing syndrome, imaging and localization studies for the extrapituitary NET will begin with the pancreas, lung, and thymus. Imaging of the pancreas with fine-cut CT may reveal an ACTH-secreting pNET. Rarely, pNETS may secrete CRH. Measurements for serum CRH are not widely available, and interpretation is difficult.

Imaging with SSTR radionuclides is useful if conventional CT or MRI do not reveal a tumor.

Other Functional pNETS (Somatostatin, Serotonin, Ghrelin, Growth Hormone-releasing Hormone, Parathyroid Hormone, PTH-related Peptide)

There are increasing reports of pNETS secreting other functioning hormones, usually as case reports or small series. The hormones include somatostatin (SST), serotonin, ghrelin, growth hormone-releasing hormone (GHRH), parathyroid hormone (PTH), PTH-related peptide (PTH-RP), renin, and erythropoietin. Many of these hormones are not routinely measured and, moreover, measurements are not standardized or readily available. If the pNET is diagnosed as a small incidentaloma, the secretions may not have caused severe enough clinical signs and symptoms, and thus it may be treated without measurement of these hormones. Many of the secretions are episodic, and levels may be difficult to interpret. The existing guidelines do not recommend routine measurement of these hormones in the absence of symptoms and signs. However, it is important to be aware of the possibility of rare secretions from pNETs and thus reduce the delay in diagnosis [19].

Somatostatin-secreting pNETs are thought to be very rare and sporadic, usually arising from the pancreas but may also be found in the duodenum. Symptoms are usually mild and nonspecific and include hyperglycemia, weight loss, abdominal pain, gallbladder stasis, and diarrhea [20]. Liver and other metastases are usually present at diagnosis. Elevated SST levels are diagnostic but like other rarely measured hormones, available assays vary considerably in characteristics and ranges. Elevated serum SST may also be found in medullary thyroid tumors, small cell lung tumors, pheochromocytomas, and paragangliomas.

Serotonin (5 hydroxytryptamine, 5-HT)-secreting NETs originating in the pancreas are very rare, as these classic "carcinoid tumors" are more frequent in the hindgut and other locations [21]. When found as a pNET, they are usually large and present with metastases at diagnosis. The 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), measured in a 24-hour urine collection sample, is still the investigation of choice and is elevated in most patients with the classic symptoms of facial flushing, diarrhea, and right heart failure.

Ghrelin-secreting and GHRH-secreting NETs orginate from the pancreas and other gastrointestinal tract tissues. They are very rare, and are usually sporadic or associated with MEN 1. Ghrelin and GHRH cause classic acromegaly, which presents to the endocrinologist. There should be suspicion of an ectopic extrapituitary

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location if there is elevated GH in the presence of a generally enlarged pituitary gland on MRI without a defined pituitary adenoma. Ghrelin and GHRH assays are not standardized and some have reported elevated ghrelin without any symptoms and signs of acromegaly [22].

Many other functioning pNETS have been reported as case reports, and include the following: PTH- and PTH-RP-secreting pNETS causing hypercalcemia, renin-secreting pNETS causing hypertension, erythropoietin (EPO)-secreting pNETS causing polycythemia, and calcitonin, cholecystokinin and neurotensin all usually presenting with nonspecific symptoms. It is likely that there will be more reports when more assays become available and our understanding of the pathophysiology of these various hormone-secreting pNETS improves.

Somatostatin analogue radionuclides have been very useful in the diagnosis and localization of these tumors but are not often necessary as these tumors are often large enough at presentation to be diagnosed with conventional CT or magnetic resonance imaging (MRI).

Serum RNA and DNA Measurements in pNETS

Recent advances in measurement of circulating serum DNA, RNA, and circulating tumur cells have led to studies of their usefulness in the diagnosis and management of pNETs. Studies on serum DNA, together with fresh tissue from patients with NETs, have been reported to identify DNA patterns and secretion into the circulation. Similarly, serum RNAs, including microRNAs (miRNA) and long noncoding RNAs (lcRNA), have been measured in various pNETs. These various patterns ("signatures") have been reported as potentially useful in distinguishing NETs from other pancreatic tumors. A commercial assay has become available and has been reported to be better than ChA [23,24] as a biomarker for NETs.

Table 103.1 gives a list of the more common functional pNETS and summarizes the useful laboratory and imaging investigations.

Imaging

Asymptomatic pancreatic "incidentalomas" are increasingly being diagnosed as a result of a general increase in frequency of abdominal imaging and greater awareness of these lesions among radiologists. Various features of these "incidentalomas" suggest different possible diagnoses, with isolated nonfunctioning pNETs as one of them. Although some features on imaging may suggest a pNET, a tissue diagnosis is needed for management decisions. For classic functioning pNET with suggestive symptoms and signs and biochemical evidence, ultrasound, conventional CT, MRI, and radionuclide scans all play a part in the localization and assessment of the tumor.

There has been rapid progress in many of the investigations for pNETs with better dynamic enhanced CT and MRI techniques, and novel radioisotope linked ligands and molecules for nuclear imaging. Radionuclide imaging based on the unique specific expression of the SSTR and/or unique metabolic features is particularly important in the detection and investigation of pNETs. The introduction of the copper-64 marker Cu-64, linked to somatostatin analogues, has improved PET images further [25].

Conventional CT and MRI

Conventional CT and MRI are useful and adequate for the diagnosis and localization of most functioning larger pNETS (around 1 cm in diameter or more). Recent developments in multiphase contrast-enhanced CT and dynamic MRI have reported good results for earlier detection and characterization of smaller and nonfunctioning pNETs [19,20], and for staging [26]. Pancreatic NETS are usually densely hypervascular and therefore appear as well-circumscribed masses with early strong enhancement from the arterial to pancreatic phase. Diffusion-weighted MRI (DWI) has also been reported to be useful, alone or in conjunction with SST-based radionuclide imaging, in the detection of some pNETs [27,28].

Pancreatic NETs usually appear as low intensity images on T1 and high intensity on T2, with clear gadolinium enhancement. These findings may be adequate in the localization of many pNETS, especially when sophisticated and expensive specialized radionuclide SSRT and other PET/CT imaging facilities are unavailable. However, despite all the advancements, conventional CT and MRI are less able to identify the full extent of metastases.

Conventional PET Scans

Conventional 18-fluorodeoxyglucose (^{18}FDG) PET scans (including PET/CT) identify tumor cells with high glucose utilization, and identify aggressive tumors with higher metabolic rates. More indolent tumors, like many pNETs, are not identified using ^{18}FDG scans. They are therefore not as helpful in the investigation of pNETS as in other pancreatic tumors.

To identify pNETs, other radionuclides have been studied actively – those based on the specific metabolic

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Table 103.1 More common functional pNETS and useful laboratory and imaging investigations.

	Differential diagnosis	Pancreatic origin (versus other locations)	Laboratory investigations	Imaging investigations	Other special investigation
Suspected functioning pNET					
Insulinoma	Factitious; autoimmune disease	>90%	Prolonged fast with glucose, insulin and c-peptide measurements Chromogranin A often negative	Endoscopic ultrasound	Selective intraarteriolar calcium infusion (used in some centers still) GLP-1 analogue (exenatide) radionuclide scan
Gastrinoma	Acid-suppressing medications (proton pump inhibitors)	<50% Often in duodenum	Fasting serum gastrin; secretin test – if available; chromogranin A	Endoscopy/EUS MRI	SSTR imaging (preferentially gallium labeled)
Glucagonoma	Secondary diabetes from other causes	>90%	Serum glucagon Chromogranin A	Conventional imaging	Conventional CT/MRI usually adequate Rarely SSTR imaging
VIPoma	Other causes of hypokalemic diarrhea	>90%. May be in other GIT sites	Serum VIP Chromogranin A	Conventional imaging	SSTR imaging
Somatostatinoma		<50% Other sites include duodenum and other foregut sites	Serum somatostatin Chromogranin A		Unknown. SSTR imaging may be useful
ACTH	Nonpancreatic ectopic ACTH tumor	<10% More often in lung and other sites	Dexamethasone suppression test CRH stimulation test	Endoscopic US and conventional imaging	Exclusion of pituitary Cushing syndrome SSTR imaging
Ghrelin, GHRH	Nonpituitary acromegaly with high GH	<5% Most often in pituitary	Ghrelin, GHRH	Endoscopic US and conventional imaging	Exclusion of pituitary acromegaly SSTR imaging
Others – PTH-RP Renin Erythropoietin	Other causes of symptoms and signs	<50% Can be any GIT or other site	Chromogranin A	Endoscopic US and conventional imaging	Unknown. SSTR imaging may be useful
Serotonin	Classic "carcinoid" syndrome	<10% More often in lower GIT and lung	24-hour urine 5-HIAA Chromogranin A	Endoscopic US and conventional imaging	SSTR imaging
Nonfunctioning pNET			Chromogranin A, neuron-specific enolase, human pancreatic polypeptide, serum DNA signatures	Dynamic CT or MRI	SSTR imaging

PET-CT with SSTR radionuclides: Ga^{68} DOTA-TOC, DOTA-TATE and DOTA-NOC, or Cu^{64} DOTA-TATE.
Non-SSTR radionuclides are not widely available and include PET/CT with Ga^{68} DOTA-exendin 4, PET with Fl^{18} DOPAMINE.
ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; CT, computed tomography; EUS, endoscopic ultrasound; GH, growth hormone; GHRH, growth hormone-releasing hormone; GIT, gastrointestinal tract; GLP, glucagon-like peptide; HIAA, hydroxy-indole acetic acid; MRI, magnetic resonance imaging; PTH-RP, parathyroid hormone-related peptide; SSTR, somatostatin receptor; VIP, vasoactive intestinal polypeptide.

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characteristics (and those based on cell surface receptor expression, see below) of pancreatic islet cells. Dopamine is a major metabolite of many NETs and dopamine-based radionuclide studies have been reported using 18-fluorodopamine (^{18}F-Dopa), 11C-L-dopamine (^{11}C-L-DOPA), and 11C-5-hydroxytryptophan (^{11}C-5-HTP) for serotonin pNETs [29]. However, these have been reported to be of use only in pNETs with negative or minimal SSTR expression and the development of the SST radionuclides has diminished their potential.

Somatostatin and Other Peptide Receptor-based Radionuclide Imaging

Most differentiated functioning (except insulinomas) and nonfunctioning pNETS overexpress cell surface SSTRs. This has led to the development of radionuclides based on somatostatin analogues. Of the five SSTR subtypes, pNETs usually overexpress SSTR subtype 2. The main radionuclide used is octreotide, which selects for SSTR-2, and has a longer half-life than native somatostatin. Octreotide was initially used with the tracers iodine I-123 and indium In-111 (commercialised as Octreoscan®) and subsequently technetium Tc-99m. However, these have been superseded by PET/CT scanning with gallium Ga-68 linked to octreotide analogues via the chelating molecule DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid).

Three main DOTA compounds have been extensively studied and compared in large numbers of pNETs: DOTA-TOC (DOTA-Tyr-octreotide), DOTA-TATE (DOTA-Tyr-octreotate), and DOTA-NOC (DOTA-Nal-octreotide). They are all able to identify both functioning and nonfunctioning pNETs and their metastases with a high specificity and sensitivity (>80%). The differences reported in different pNETs of differing histologic stages are minor and may be the result of different study populations [29]. More recently, copper-64 has been used instead of gallium-68 as the radioactive tracer, linked to octreotate with the chelating molecules DOTA or with NODAGA (1,4,7-triazacyclononane,1-glutaric acid) (Cu-64-NODAGA) with improved imaging qualities, lower costs, and greater flexibility in the timings of injections and imaging and thus better results [30,31].

Other Radionuclide Scans

Other peptide receptors have been identified in pNETS and attempts have been made to utilize these for imaging (and therapy) in the less common pNETs with less overexpression of SSTR. These would have the greatest potential in insulinomas where the GLP-1 receptor and the glucose-dependent insulinotropic peptide (GIP) receptor are expressed in abundance. The GLP-1 analogue exendin-4 linked to Ga68-DOTA has shown promising results [11,12] but its usefulness will remain restricted to insulinoma and its metastases. Other peptide receptors are being actively investigated at present and may have potential in pancreatic and other NETs, including cholecystokinin-2/gastrin, gastrin-releasing peptide, neuropeptide-Y, and bombesin [32].

A multitargeted approach using a cocktail of three different radioligand peptide receptors at the same time, targeting the SSTR, GLP-1 R and GIP R, suggested better results than single radioligand imaging [33]. While this approach will save time, the costs will invariably be much higher. Moreover, interpretation may be difficult as normal tissues have different levels of expression of these peptide receptors, and thus false-positive and -negative rates will have to be confirmed in other centers. In addition, in peptide receptor radionuclide therapy (PRRT – see Chapter XX), information is necessary on the relative abundance of single receptor types, as the therapeutic doses of the therapeutic radioisotope, most commonly lutetium-177 or yttrium-90 (Y90), are bound to single analogues. This information will be lost if a cocktail of radionuclides is utilized for imaging.

Instrumental and Invasive Investigations

Even when biomarkers and imaging characteristics are indicative of a pNET, small nonfunctioning pancreatic incidentalomas often still require instrumental and invasive investigations to obtain tissue biopsies for accurate diagnosis and grading of the tumor. Endoscopic US combined with guided fine needle aspiration cytology and/or core biopsy will therefore remain the gold standard for accurate diagnosis in small nonfunctioning pNETs. This may be dependent on the availability of expertise and experience.

Apart from asymptomatic incidentalomas, some small functioning pNETs may require invasive investigations to locate the tumor within the pancreas, for tissue diagnosis and grading, and to diagnose multiple tumors. Despite all the advances in MRI and radionuclide imaging, endoscopic US of the pancreas may still have some advantages [34], and in combination with radiofrequency ablation will potentially be very useful in treatment of small pNETs or other pancreatic tumors. This would be especially useful in small biochemically proven insulinomas or VIPomas. Both insulinomas and VIPomas are almost always confined to the pancreas. Insulinomas rarely secrete ChA and are not detectable on SSTR radionuclide imaging. If all these investigations still are unable to localize a biochemically confirmed insulinoma, progressive partial pancreatectomy may be necessary,

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which may reveal single or multiple tiny insulinomas or diffuse nesidioblastosis.

Conclusion

Pancreatic NETs are rare and heterogeneous tumors. Biochemical investigations are essential, but interpretation may be difficult at times because of the use of nonstandardized assays. Advances have been made in conventional CT and MRI and rapid progress is being made in the development of new radionuclide tracers and chelators. The unique overexpression of SSTR in most pNETs has made this an essential modality for diagnosis, staging, and therapy. Advances in endoscopic ultrasound have been refined, and endocscopic US-guided biopsy of pNETS has facilitated tissue diagnosis and tumor grading and therapy.

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Pancreatic Neuroendocrine Tumors in Multiple Neoplasia Syndromes

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Introduction

Neuroendocrine tumors, including pancreatic neuroendocrine tumors (PanNETs), are on the rise and, probably owing to improved imaging techniques and better awareness, especially localized disease is more often diagnosed [1]. Although most of these tumors are sporadic, in about 17% of PanNETs there is a hereditary background with multiple endocrine neoplasia type 1 (MEN 1) being the most relevant family cancer syndrome for PanNETs [2]. Early diagnosis of the hereditary syndrome is of diagnostic and therapeutic relevance for the patient and their kindreds. Diagnostic procedures, follow-up, and treatment should be managed by a multidisciplinary team with experience in the management of MEN 1 [3]

MEN 1 should always be suspected in patients with PanNETs with multiple lesions, a positive family history, a second MEN 1 typical manifestation such as hyperparathyroidism or pituitary tumor, in patients with insulinoma in young age (<30 years) or in cases of gastrinoma/Zollinger–Ellison syndrome (ZES) even in the absence of a positive family history. In addition to the classic "three-P triad" of **p**arathyroid tumor (90–100% of cases), **p**ituitary tumor (20–60%), and **p**ancreatic tumor (60–80%), patients with MEN 1 may also develop adrenocortical tumors, lipomas, carcinoid tumors, including thymic, gastric, and lung carcinoids, facial angiofibromas, collagenomas, and meningiomas and may also have an increased risk for other nonendocrine malignant tumors such as lymphoma, myeloma, melanoma, renal cell cancer, ovarian tumors, breast cancer, and sarcoma [4,5]. This chapter focuses on the management of PanNETs in MEN 1.

Epidemiology

With an estimated prevalence of 0.02–0.2 per 1000 inhabitants, MEN 1 is one of the most common familial cancer syndromes; in an old autopsy study, the reported incidence was 0.25% [6–8]. Duodenopancreatic neuroendocrine tumors are the second most frequent manifestation of MEN 1. Older studies probably underestimated the prevalence of PanNETs in MEN 1 syndrome and with more sensitive diagnostic tools and regular screening, about 90% of patients are found to develop PanNETs at the age of 70 [9]. PanNETs have an earlier age of onset in patients with MEN 1 than in patients without MEN 1. These tumors are typically multiple and can present with hormone syndromes or be nonfunctioning [10,11]. The most common hormone-active duodenopancreatic tumors are gastrinomas, followed by insulinomas, whereas vasoactive intestinal peptide-releasing tumors (VIPomas) and glucagonomas are rare. Approximately 20–30% of all patients with ZES will have MEN 1 [3,12].

Genetics

MEN 1 is an autosomal dominant inherited syndrome with high penetrance; nearly 100% of persons with germline MEN 1 mutation will develop symptoms of MEN 1 during life. In 1988, the *MEN1* gene locus was first mapped to the long arm of chromosome 11 (11q13) [13] and in 1997 the gene was identified and cloned [14]. It acts as a tumor suppressor gene and codes for the 610 amino acid protein menin, which is involved in transcription regulation, genome stability, and proliferation [3,14].

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In about 10% of MEN 1 cases, the germline mutation arises *de novo* and the family history is negative [3].

More than 1300 inactivating mutations involving all locations of the gene have been identified so far and in about 90% of clinically diagnosed MEN 1 cases, the mutation in the *MEN1* gene can be detected [3]. About 70% of the mutations are nonsense and frameshift mutations, resulting in truncation of the protein. Although there is no clear genotype–phenotype correlation and even in one family the manifestations may vary [15,16], a recent publication described an increased prevalence of PanNETs and increased risk of metastasis in patients harboring an exon 2 mutation [17]. The diversity of mutations makes mutational analysis in MEN 1 difficult and complete sequencing of the whole gene is necessary. In contrast, if the mutation of an index case in the family is known, family members only have to be analyzed to determine whether the known mutation is present or absent.

Diagnosis

Three diagnostic criteria for MEN 1 exist, each individually establishing the diagnosis of MEN1 [3,8].

- Genetic: identification of a germline MEN 1 mutation in the individual, or
- Familial: diagnosis of a MEN-associated tumor in a person who has a first-degree relative with known MEN 1, or
- Clinical: occurrence of two or more primary MEN 1-associated endocrine tumors.

The diagnosis of a PanNET may result either from symptoms (e.g., hypoglcycemia in a patient with insulinoma) or from biochemical (elevated levels of pancreatic polypeptide, gastrin, insulin, glucagon, vasoactive intestinal polypeptide [VIP]) or morphologic screening (identification of pancreatic lesions in computed tomography [CT], magnetic resonance imaging [MRI], endoscopic ultrasound, somatostatin receptor imaging).

In a patient with MEN 1 syndrome, initially at least annual biochemical and morphologic screening for PanNET is recommended [3] but the frequency of imaging should be individually adapted and intervals may be lengthened once it can be demonstrated that there is no rapid growth [8]. Endoscopic ultrasound (EUS) is more sensitive for detection and follow-up of small pancreatic lesions than CT or MRI [18,19] and can be combined with fine needle biopsy. MRI is a recommended alternative if EUS by an expert is not available [8].

In patients with gastrinoma, upper gastrointestinal endoscopy is indicated. Typically, gastrinomas in MEN 1 are small, multiple, and located in the duodenum, where the sensitivity of EUS is inferior compared with pancreatic lesions. In some publications and the recent guideline, a role for [^{68}Ga] DOTA-TOC (DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTA-TOC, DOTA-Tyr-octreotide) positron emission tomography (PET)/CT or DOTA-TATE (DOTA-Tyr-octreotate) PET/CT for exclusion of small metastases in patients with MEN 1 and PanNET has been suggested (Fig. 104.1) [8,20,21]. For insulinomas, somatostatin receptor-based imaging is less sensitive but glucagon-like peptide 1 receptor (GLP-1R)-based PET/CT has been

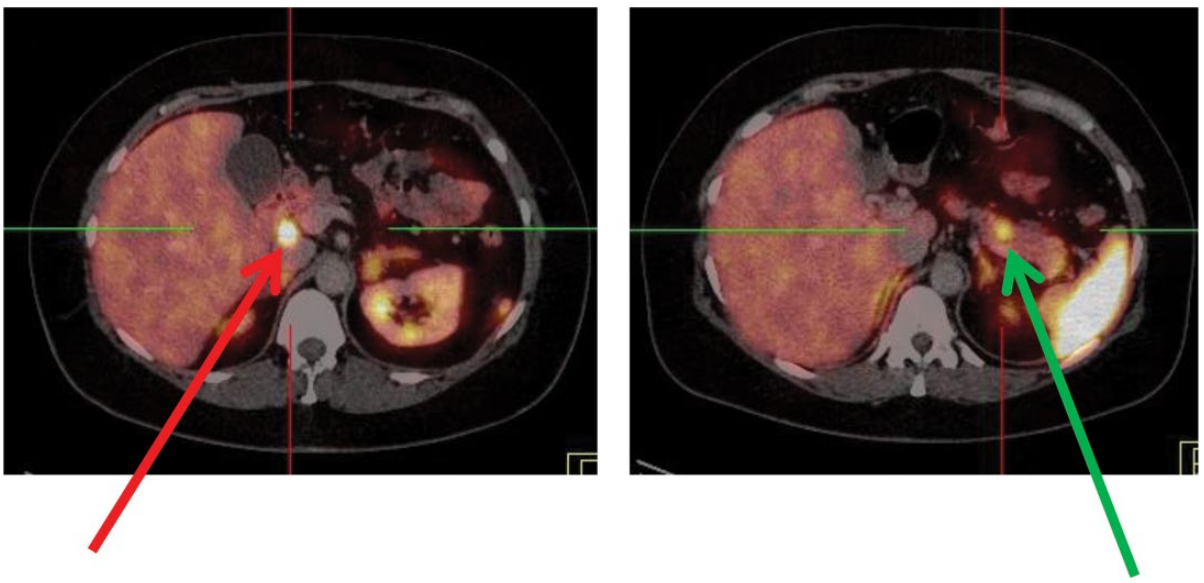


Figure 104.1 [^{68}Ga]DOTA-TOC PET/CT in a 41-year-old patient with known MEN 1 syndrome. She had undergone parathyroidectomy because of hyperparathyroidism 10 years earlier. At present she is diagnosed with hypergastrinemia without clinical manifestation of ZES. Red arrow, duodenal lesion. Green arrow, additional pancreatic lesion; no evidence of metastases.

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shown to localize insulinomas with high sensitivity [22,23] and may therefore help to differentiate insulinomas from nonfunctioning PanNETs in the preoperative setting.

Clinical Presentation

Nonfunctioning PanNETs are usually asymptomatic. In cases of advanced disease, they can cause unspecific tumor-associated symptoms such as abdominal or back pain, jaundice, or weight loss.

Gastrinomas cause the *Zollinger–Ellison syndrome* with clinical manifestations resulting from gastric acid hypersecretion such as severe peptic disease (peptic ulcerations), gastroesophageal reflux disease, and diarrhea. Peptic ulcer bleeding may be the presenting symptom in some patients. The use of proton pump inhibitors (PPIs), however, may mask the symptoms of ZES and delay diagnosis. Concomitant hyperparathyroidism may enhance hypergastrinemia-associated symptoms. With biochemical screening in patients with a known diagnosis of MEN 1, hypergastrinemia can be detected early before clinically relevant ZES develops. Patients with MEN 1 with ZES present at an earlier age (mean 32–35 years) than patients with sporadic gastrinomas.

Insulinomas present with symptoms of hypoglycemia (headache, diplopia, confusion, dizziness, abnormal behavior, amnesia, rarely seizures and coma) and symptoms resulting from the counterregulation of the autonomic nervous system (sweating, weakness, hunger, tremor, anxiety, palpitations). Patients often gain weight. The presence of a Whipple triad remains useful in suspecting underlying insulinoma [24]. The triad consists of symptoms of hypoglycemia, plasma glucose level <40 mg/dL, and relief of symptoms with administration of glucose. Insulinomas in patients with MEN 1 often occur at young age (many <20 years), whereas sporadic cases generally occur in patients aged >40 years [3].

A *glucagonoma syndrome* is found in <3% of patients with MEN 1 and is characterized by the presence of a necrolytic migratory erythema (a characteristic skin rash), weight loss, anemia, and glucose intolerance or diabetes. In clinical practice, the glucagnoma syndrome is rare and more often pancreatic lesions stain positive for glucagon with slightly increased glucagon serum levels, although without the clinical syndrome [3,8].

The *Verner–Morrison syndrome*, also called pancreatic cholera or WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria) is caused by hypersecretion of VIP. Patients suffer from excessive diarrhea with electrolyte and pH disturbances and dehydration. Less than 1% of patients with MEN 1 present with Verner–Morrison syndrome [3,8].

In a patient with MEN 1, more than one hypersecretion syndrome can develop over the years.

Surgical Treatment

A proven organic hyperinsulinism is an indication for surgical treatment due to the lack of adequate medical therapy. The surgical strategy has to be individualized, taking the localization and size of tumor(s) (about 30% multiple insulinomas) into consideration. The identification of the insulinoma(s) within multiple PanNETs can be challenging and new options with endoscopic fine needle biopsy and GLP1R-based PET/CT may be helpful but availability and data are limited. If only one tumor is visualized or one dominant tumor (<10 mm) with smaller (≤5 mm) additional PanNETs, enucleation or pancreatic segmental resection is recommended [8]. For larger insulinomas near the main pancreatic duct, spleen-preserving left pancreatectomy is indicated. Routine lymphadenectomy is not indicated. A partial pancreaticoduodenotomy (PPD) is rarely necessary only in case of a large insulinoma of the pancreatic head. Intraoperative ultrasound and determination of the insulin/glucose ratio have been suggested for assessing the success of removal of the insulinoma [25].

In patients with glucagonomas and VIPomas, the primary tumor is often located in the pancreatic tail and surgical removal with curative intention (left pancreatectomy with lymph node resection) is the treatment of choice. In metastasized cases with functioning pancreatic tumors, interdisciplinary discussion of operative debulking, medical treatment, peptide receptor radionuclide treatment (PRRT) and hepatic artery embolization or combinations thereof is necessary.

The indication for surgery and the operative technique in patients with MEN 1-associated ZES are controversial. About 90% of patients with MEN 1 have multiple tumors in the duodenum and a favorable long-term prognosis if only small tumors (<2 cm) or no tumors are present on preoperative imaging examination [26]. Although the gastrinomas in MEN 1 patients are usually duodenal, a PanNET of ≥2 cm has been suggested as a surrogate parameter to indicate surgery which always has to include duodenectomy and systematic lymphadenectomy [8]. The so-called Thompson procedure additionally comprises subtotal left pancreatectomy with preservation of the spleen and enucleation of tumors of the pancreatic head [27]. Most patients can be rendered eugastrinemic with this approach but cure is rare. Therefore, some centers suggest a more aggressive surgical approach with PPD to provide a higher rate of

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cure [28,29]. The increased likelihood of cure has to be weighed against an increased operative mortality and long-term morbidity in each individual case and the patient's preference must be considered.

Surgery may also have a role in metastatic disease if at least 90% or all of the identifiable tumor burden can safely be removed [8]. Cure by surgery in metastatic disease is rare (<10%); all patients should be discussed in an experienced multidisciplinary tumor board.

Nonfunctioning (NF) PanNETs also harbor the risk of malignant transformation and there is ongoing debate regarding the correct timing and extent for surgical intervention. Most centers and also the recent guideline recommend surgery for NF PanNETs of 2 cm size or larger or for smaller tumors demonstrating significant growth under surveillance [8,11]. A documented grade 2 PanNET is associated with higher malignant potential and therefore also judged as indication for surgery regardless of size [30,31].

There is no clear consensus on the extent of surgical resection. Most authors suggest left pancreatectomy with enucleation of tumors of the pancreatic head with lymphadenectomy, but sole enucleation and also more aggressive approaches have also been proposed. A recent metaanalysis demonstrated no differences in survival and reoperation rate in patients with sole enucleations compared to major pancreatic resections, but a higher recurrence rate and a lower rate of endocrine insufficiency [32].

Medical Treatment

The principles of medical treatment of PanNETs in MEN 1 are similar to those in sporadic cases as studies specifically for MEN 1 are very limited.

Medical Treatment in Functioning Tumors

In patients with gastrinoma, treatment with PPI is indicated to suppress hyperacidity. The recommended starting dose is equivalent to omeprazole 40–60 mg b.i.d. in MEN 1/ZES [26]. Long-acting somatostatin analogues such as octreotide-LAR or lanreotide autogel also control acid secretion and can be added to PPI, which is the basic treatment of choice because of its effectiveness and the ease of oral intake.

In patients with insulinoma, prior to mostly curative surgery, intravenous glucose administration in addition to frequent small carbohydrate meals may be necessary. Additional medical treatment is mainly indicated in the rare metastatic cases and includes diazoxide (in combination with diuretics), somatostatin analogues (SSA) (which should be started in the hospital to exclude worsening of hypoglycemia, which also has been reported), and the mammalian target of rapamycin (mTOR) inhibitor everolimus [33].

In patients with VIPomas and glucagonomas, SSA can control the hypersecretion syndrome. Electrolyte shifts and malnutrition should be treated before surgery. Particularly in patients with ZES, hyperparathyroidism should be corrected first (usually by surgery or if not possible, by calcium-sensing receptor agonists such as cinacalcet) as hypercalcemia worsens hypergastrinemia [8].

Medical Treatment for Tumor Control

Medical treatment with antiproliferative intention is usually started in patients with nonresectable or metastatic disease. Nevertheless, one retrospective study as well as a recent prospective study suggested that treatment with SSA in patients with MEN 1 syndrome and small (<2 cm) PanNETs may delay tumor progression and the need for surgery [34,35].

Somatostatin analogues can be administered for antiproliferative purposes in patients with metastatic PanNETs showing slow tumor growth. The CLARINET trial has proven the efficacy with respect to progression-free survival (PFS) in somatostatin receptor-positive (sporadic) gastroenteropancreatic neuroendocrine tumors with a proliferation rate Ki-67 not exceeding 10% [36].

In patients with a high tumor load or rapid tumor growth, chemotherapy with streptozotocin and 5-fluorouracil or temozolomide and capecitabine is indicated [37,38]; in patients with liver-predominant disease, chemoembolization is an alternative. Two molecular-targeted treatments are approved for metastatic PanNET: the multikinase inhibitor sunitinib and the mTOR inhibitor everolimus. In placebo-controlled trials, both drugs demonstrated a doubling of PFS compared with placebo [39,40]. Although the studies included mainly non-MEN patients (two patients with MEN 1 in the sunitinib trial; in the everolimus trial MEN status was not provided), it seems plausible that the results also apply for PanNETs in MEN 1 syndrome which is supported by a recent retrospective study [41].

Peptide receptor radionuclide treatment is also used for symptomatic as well as tumor control in receptor-positive PanNETs although currently prospective controlled data for the PanNET are lacking [42,43]. The efficacy for metastatic tumors with a hereditary background of MEN has been recently demonstrated in a case series [44].

Follow-up

Patients with MEN 1 syndrome or *MEN1* gene carriers should be offered a program of combined clinical, biochemical, and radiologic screening and follow-up; an

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Table 104.1 Suggested program of combined clinical, biochemical, and radiologic screening and follow-up.

Examination	Interval	Extent
Clinical evaluation	Annually	Extensive history of symptoms of tumor manifestations and physical examination
Biochemical screening	Annually	Ca, parathyroid hormone, gastrin, fasting glucose, insulin, CgA, glucagon, VIP, prolactin, IGF-1
Functional testing	No routine investigation, suspicion of gastrinoma	Gastric pH, secretin test, or Ca infusion test
	Suspicion of insulinoma	Fasting test
Abdominal imaging	Annually	EUS, MRI, or CT or [^{8}Ga] DOTA-TOC PET/CT
Imaging of the chest	Every 1–2 years	CT or MRI or [^{68}Ga] DOTA-TOC PET/CT
Imaging of the pituitary gland	Every 3 years	MRI

CgA, chromogranin A; IGF-1, insulin-like growth factor 1; for other abbreviations, see text.

example of a follow-up scheme is summarized in Table 104.1 [3]. The program should be individualized according to initial tumor size, Ki-67 value (if available), documented tumor growth rate, the patient's (family) history, and also patient preference. If rapid growth is excluded in initial follow-up, extension of the screening interval may be appropriate [8,45].

There is no consensus regarding the value of tumor markers like chromogranin A (CgA) or pancreatic polypeptide (PP) in follow-up nor for the best imaging technique (MRI, endoscopic ultrasound, [^{68}Ga]DOTA-TOC PET/CT, combinations therof) [8].

Prognosis

Despite the fact that life expectancy in patients with MEN 1 has increased in recent decades, 50–70% of patients with MEN 1 will die of causes directly related to MEN 1 [46]. Whereas in early series patients often died as a result of complications of hormonal effects of the tumors such as upper gastrointestinal bleeding resulting from ZES or renal complications as a consequence of hyperparathyroidism, today there is a shift toward death from malignancy [4]. PanNETs and especially the more aggressive thymic carcinoid tumors are associated with an increased risk of death [46] and the risk of dying from a malignant nonendocrine tumor is also elevated [4,5]. The presence of liver metastases is the most important prognostic factor. In the Dutch MEN 1 database, 10-year overall survival in patients with and without hepatic metastases was 50% and 86%, respectively [47]. Large PanNETs, grade 2 tumors, thymic NETs, presence of ZES, and male sex have also been reported as poor prognostic factors [4,30,47,48].

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Nonfunctioning Pancreatic Neuroendocrine Neoplasms: Diagnosis and Management Principles

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Definition

Among pancreatic neuroendocrine neoplasms (PanNENs), nonfunctioning PanNEN (NF-PanNEN) is defined as tumor with no specific symptoms due to excess of hormonal secretion. Therefore, PanNENs with a high level of serum hormone or positive result for specific hormone on immunohistochemical assessment, while no specific symptoms are observed, are managed as NF-PanNENs.

Pathology

According to the World Health Organization (WHO) classifications of 2017 and 2019 [1,2], NENs, including PanNENs, are divided into well-differentiated neuroendocrine tumor (NET) and poorly differentiated neuroendocrine carcinoma (NEC). NETs are graded using mitotic count and/or Ki-67 labeling index as G1 (mitotic count <2 per 10 high power fields [HPF] and/or <3% Ki-67 index), G2 (mitotic count 2–20 per 10 HPF and/or 3–20% Ki-67 index), and G3 (mitotic count >20 HPF and/or >20% Ki-67 index). Poorly differentiated NECs are further divided into small cell type and large cell type, and NECs usually show mitotic count >20 HPF and/or >20% Ki-67 index. A combination of NEN and other pathologic subtypes such as adenocarcinoma and acinar cell carcinoma is classified as mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN).

Positive staining for specific neuroendocrine markers such as chromogranin A and/or synaptophysin is necessary to make a definitive diagnosis of NEN. Of note, some NF-PanNENs show positive staining for several specific hormones including insulin, glucagon, pancreatic polypeptide, or serotonin on immunohistochemical assessment, although staining pattern is focal and thus there is no specific symptom [3].

Mechanism of Tumorigenicity

Neoplastic cells of PanNETs are considered to originate from neuroendocrine stem cells in the islets of Langerhans or pancreatic ductal epithelium. Several genetic alterations which may be associated with the tumorigenicity of PanNETs have been reported. Jiao et al. [4] showed that alterations of *DAXX/ATR*, *MEN1*, and mTOR pathway genes are frequently observed in well-differentiated PanNETs. It is well known that NF-PanNETs are often accompanied by hereditary diseases including multiple endocrine neoplasm type 1 (MEN 1), von Hippel–Lindau disease, von Recklinghausen disease, and tuberous sclerosis (TS). On the other hand, poorly differentiated PanNECs are reported to have alterations in *p53*, *Rb*, and *bcl-2*, and therefore are considered to be included in a different disease group from well-differentiated PanNETs [5].

Clinical Findings

PanNENs account for about 2% of all pancreatic neoplasms, and NF-PanNETs are the most frequent PanNENs (40–60%), followed by insulinoma (~20%) and gastrinoma (~10%). In the Japanese nationwide survey [6], the estimated prevalence of PanNENs in 2010 was 2.69/100 000 with annual onset incidence of 1.27/100 000 including 65.5% of NF-PanNENs. Most NF-PanNETs are solitary, but occasionally multiple, especially in hereditary diseases. Well-differentiated NF-PanNETs grow slowly but large NF-PanNETs have the potential to metastasize to lymph nodes and/or liver. Of note, NF-PanNETs sometimes acquire hormonal production and its relevant symptoms with progression [1,2]. On the other hand, poorly differentiated NECs show quite high malignant behavior, and most

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PanNECs are found to be unresectable because of distant metastases at the time of diagnosis. The frequency of PanNEC among NF-PanNENs was 2–10%, and associated MEN 1 was observed in 4–30% of NF-PanNETs. Those distributions are different among races [6].

Symptoms

Most patients with NF-PanNENs do not have specific symptoms, and the number of patients diagnosed as having asymptomatic small NF-PanNET at the time of medical examination or during surveillance for other diseases has recently been increasing. Patients with large NF-PanNENs often present with symptoms such as abdominal pain, discomfort, distention, weight loss, nausea, or palpable mass. Involvement of the bile duct or pancreatic duct leads to jaundice, obstructive pancreatitis, or diabetes mellitus.

Diagnosis

Typical radiologic findings in well-differentiated NF-PanNETs (G1) are well-demarcated homogeneous hypoechoic lesion on ultrasonography, well-demarcated enhanced solid tumor on early phase enhanced computed tomography (CT) (Fig. 105.1a), low-intensity tumor on T1-weighted images and high-intensity lesion on T2-weighted images on magnetic resonance imaging (MRI). Large NF-PanNETs often have cystic change or calcification, which are reflected in the radiologic findings (Figure 105.1b,c). Lesions which should be discriminated from well-differentiated PanNETs because of the similarity of radiologic findings include acinar cell carcinoma, solid and pseudopapillary neoplasm, solid-type serous cystic neoplasm, metastatic pancreatic tumor from renal cell carcinoma, and accessory spleen.

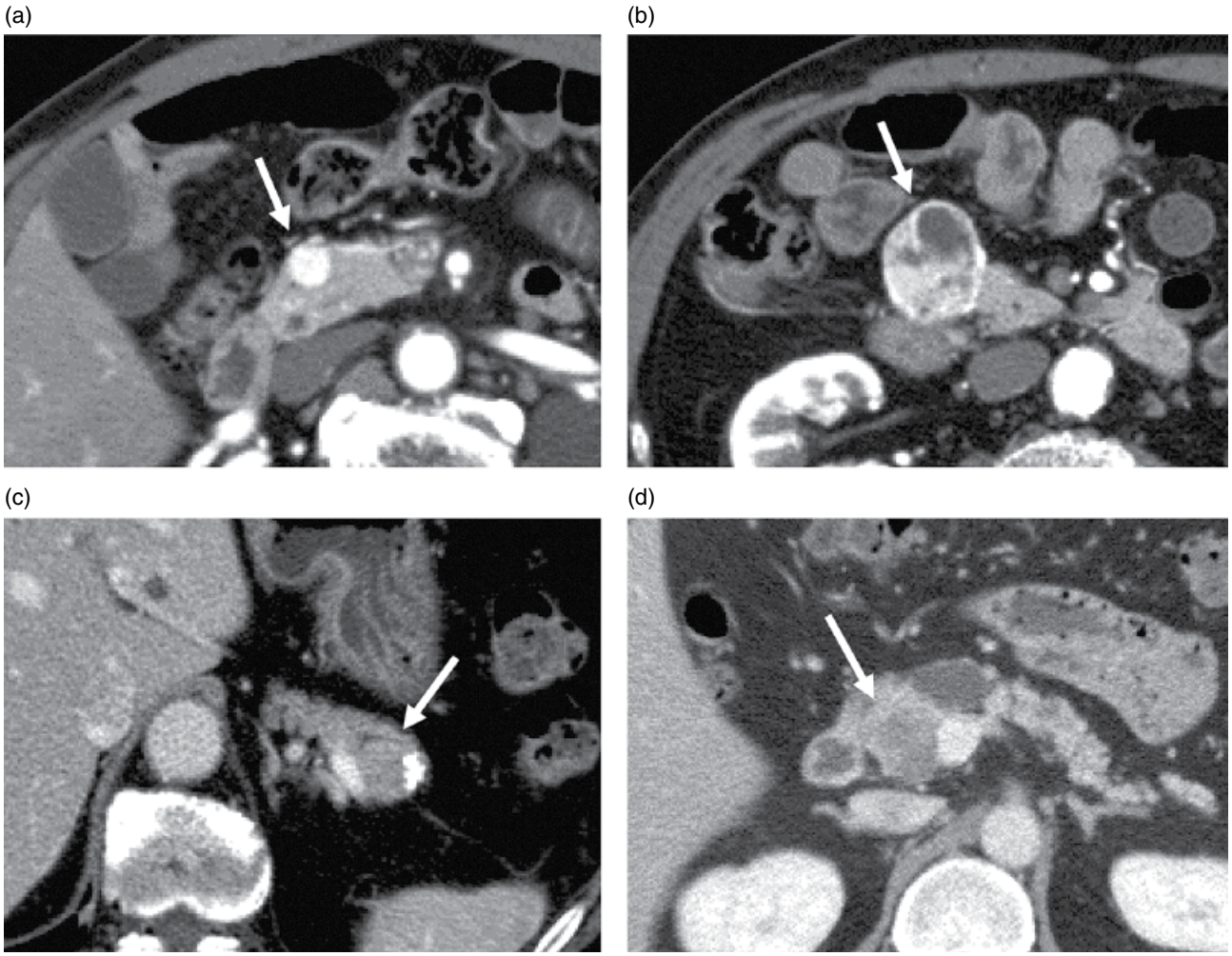


Figure 105.1 Computed tomography findings of nonfunctioning pancreatic neuroendocrine tumor. (a) Well-demarcated enhanced lesion in the pancreas head (arrow, 13 mm, G1). (b) Enhanced lesion with cystic change in the pancreas head (arrow, 35 mm, G2). (c) Lesion with calcification in the pancreas head (arrow, 23 mm, G1). (d) Low-density lesion in the pancreas head with atrophy of distal pancreas (arrow, 34 mm, NEC).

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Somatostatin receptor scintigraphy is applied for detection of metastatic lesions, and enhanced MRI is also useful to detect small hepatic metastases. Serum chromogranin A concentration is used to assess disease control during chemoradiotherapy or to detect recurrence after curative resection.

However, a PanNEC has various radiologic findings and sometimes shows an irregular low-density solid lesion on enhanced CT (Figure 105.1d), which is similar to the finding for pancreatic ductal adenocarcinoma.

For a definitive diagnosis, cytologic assessment under endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is mandatory, and histologic grading can also be evaluated if enough neoplastic cells (usually over 2000 cells) can be obtained [7].

Table 105.1 presents a brief summary of the diagnostic issues.

Table 105.1 Summary of diagnosis and treatment principles for nonfunctioning pancreatic neuroendocrine neoplasm.

1) Well-differentiated PanNET (G1–G3)
   a) Diagnosis
      Typical radiologic findings of primary lesion
         Ultrasonography; well demarcated homogeneous, hypoechoic
         Enhanced computed tomography; well-demarcated enhanced lesion in early phase
         Magnetic resonance imaging; T1-low intensity, T2-high intensity
         Other findings; cystic change, calcification, etc.
      Differential diagnosis
         Acinar cell carcinoma, solid-pseudopapillary neoplasm, solid type serous cystic neoplasm, accessary spleen, etc.
      Definitive diagnosis
         Endoscopic ultrasonography-guided fine needle aspiration
      Detection of metastatic lesion
         Systemic; computed tomography, somatostatin receptor scintigraphy
         Liver; enhanced magnetic resonance imaging
   b) Treatment
      Primary
         <2 cm
         ≥2 cm
         Tumor with asymptomatic, occasionally found by imaging, <20 mm in size, G1 and low G2, can be observed without resection based on the consideration of patient's general condition as well as expected invasiveness of the operation
         In multiple tumors of MEN 1, remove only functioning tumor and high-risk nonfunctioning tumor (>1–2 cm in diameter) to avoid total pancreatectomy
      Metastases
         Resection, if possible, or multidisciplinary treatment including debulking surgery, regional ablation therapy, systemic chemotherapy, molecular-targeted therapy, somatostatin receptor agonist, etc.
2) Poorly differentiated PanNEC
   a) Diagnosis
      Radiologic findings of primary lesion
         Ultrasonography; irregular hypoechoic
         Computed tomography; irregular low density
         Magnetic resonance imaging; T1-low intensity, T2-high intensity
      Differential diagnosis
         Pancreatic ductal adenocarcinoma, etc.
      Definitive diagnosis
         Endoscopic ultrasonography-guided fine needle aspiration
      Detection of metastatic lesion
         Computed tomography, magnetic resonance imaging, positron emission tomography
   b) Treatment
      Resectable primary
         Resection + adjuvant chemotherapy using platinum-based regimen
      Unresectable primary or metastases
         Chemotherapy using platinum-based regimen

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Treatment

Surgical Treatment for Localized Lesion

Curative resection should be considered as the first aid of treatments in all cases of localized well-differentiated NF-PanNETs [8–10]. However, National Comprehensive Cancer Network (NCCN) guidelines [8] recommend that asymptomatic well-differentiated NF-PNETs (less than 20 mm in diameter), which are occasionally found by imaging, can be observed without resection based on consideration of the patient's general condition as well as the expected invasiveness of the operation. The European Neuroendocrine Tumor Society (ENETS) guidelines [9] also include the option that NF-PanNETs with tumor size of 2 cm or less, with characteristics such as G1, low G2, asymptomatic, mainly in the head, no radiologic signs suspicious for malignancy, patient factors (personal wishes, age, comorbidities, etc.), can be observed without resection and surveyed every 6–12 months.

Surgery for localized well-differentiated NF-PanNETs ranges from enucleation, organ-preserving pancreatectomy to standard pancreatectomy with regional lymph node dissection, and surgical treatment strategy is determined based on tumor size, the invasiveness and presence of regional lymph node metastases on imaging studies. The rate of lymph node metastases in small, well-differentiated NF-PNET remains unclear and thus, sampling of the regional lymph node is always necessary even in enucleation or organ-preserving pancreatectomy for small NF-PanNETs. In several guidelines [8–10], small NF-PanNETs are considered as being those with a tumor size of less than 2 cm with no sign of invasiveness or lymph node metastasis. There is no evidence showing the benefit of neoadjuvant therapy before operation or adjuvant therapy after curative resection for well-differentiated NF-PanNETs and therefore, those adjuvant therapies are not recommended at this time.

Surgical treatment for resectable PanNEC is standard pancreatectomy with regional lymph node dissection, and adjuvant therapy using platinum-based chemotherapy in proportion to the regimen for small cell carcinoma of the lung is recommended [8].

PanNETs are clinically observed in 50–60% of MEN 1 patients, while all the autopsy cases of MEN 1 have PanNETs, although they are microlesions [11]. Most cases are multiple, and the most frequent type is NF-PanNET. Presence of PanNET is an important prognostic factor in MEN 1 [12].

Surgical treatment for multiple NF-PanNETs in MEN 1 is complicated. Several guidelines [8–10] recommend removing only functioning PanNETs and high-risk NF-PanNETs (over 1 or 2 cm in diameter) to avoid total pancreatectomy; for example, distal pancreatectomy with enucleation of the PanNETs in proximal pancreas, or pancreatoduodenectomy with enucleation of the PanNETs in distal pancreas.

Prognosis for NF-PanNENs after resection depends on histologic grade, and five-year survival rates are 80–100% in PanNET G1, 50–70% in PanNET G2, and 0–30% in PanNET G3/PanNEC [13]. Some patients experience recurrence over 10 years after operation, and therefore long-term postoperative surveillance is necessary.

Multidisciplinary Treatment for Metastatic Lesions

The most frequent site for distant metastases of PanNETs is the liver, and 70% of hepatic metastases are diagnosed as multiple lesions at the time of initial assessment [14,15]. In recurrent cases after resection, some patients experience hepatic metastasis over 10 years after curative operation, as described above. Resectable hepatic metastases without extrahepatic metastases are usually treated by operation with or without regional ablation therapies such as radiofrequency ablation and transarterial chemoembolization. Even in unresectable cases, aggressive multidisciplinary treatment including debulking surgery might lead to over 50% five-year survival rate, if over 70–90% of the lesions can be removed [14,15]. Asymptomatic and slow-growing unresectable small volume of metastatic NF-PanNETs can be observed without any treatment until signs of growth or symptoms are apparent. Liver transplantation for unresectable hepatic metastases from PanNET is not recommended because of unsatisfactory outcomes [16].

The necessity of resection of the primary lesion in cases of synchronous unresectable hepatic metastases remains controversial. One report [17] claimed that resection of the primary lesion would lead to definitive diagnosis of PanNET with accurate histologic grade as well as subsequent application of such specific therapies for hepatic metastases as transarterial chemoembolization and radiofrequency ablation. On the other hand, another report [18] showed that there was no difference in survival between patients with synchronous unresectable hepatic metastases who underwent resection of primary PanNET and those without primary resection. Due to recent advances in the technique of EUS-FNA for the definitive diagnosis of PanNET with histologic grade, and development of new drugs including molecular-targeted drugs, various types of somatostatin receptor analogue, and radionucleotide-labeled peptide targeting somatostatin receptor, resection of primary tumor is not always necessary in cases with synchronous unresectable hepatic metastases of PanNETs.

Surgical indication for extrahepatic metastases is limited, because most of these cases also have hepatic metastases, and indication depends on the status of hepatic metastases.

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Treatment principles for NF-PanNENs are summarized in Table 105.1. Medical treatments for PanNETs include chemotherapy (streptozocin, dacarbazine), molecular-targeted therapy (everolimus, sunitinib), and somatostatin receptor analogue therapy including radionucleotide therapy, and details of these therapies are described elsewhere.

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Medical and Nucleotide Treatment of Neuroendocrine Tumors of the Pancreas

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Introduction

Pancreatic neuroendocrine neoplasms (pNENs), although relatively rare, are increasingly being diagnosed following the introduction of more sensitive imaging techniques. Although a number of pNENs are capable of synthesizing and secreting biochemically active substances leading to distinct clinical syndromes (functioning tumors), the great majority are nonfunctioning [1] (Table 106.1). According to the proliferative index (PI) Ki-67, defined by immunohistochemical staining for nuclear Ki-67 protein expression, pNENs are classified into grade 1 (G1) or 2 (G2), if Ki-67 PI is ≤2% or between 3% and 20% respectively, and grade 3 (G3) if Ki-67 PI is >20%. G3 neoplasms are further subdivided into well-differentiated G3 neuroendocrine tumors (G3 NETs) or poorly differentiated G3 neuroendocrine carcinomas (G3 NECs) [2].

Surgery is the mainstay of treatment of pNENs but in recent decades there has been a considerable evolution of medical treatments that are used for locally advanced or metastatic disease not amenable to surgical resection. The goals of systemic treatment are to induce tumor shrinkage and/or prevent further tumor growth, relieve symptoms related to secretory syndromes, and increase overall survival. Treatment decisions are based on several parameters, including the extent of disease, tumor differentiation, and the presence of clinical symptoms (Table 106.2). In the past, chemotherapy has been the main therapeutic approach substantiated by a few well-controlled but mostly retrospective studies but the options for systemic therapy have continuously increased [3–5]. Long-acting somatostatin analogues (SSAs) have been used for the control of symptoms secondary to secretory syndromes as well as for tumor growth control, exhibiting mainly a stabilizing effect (1).

Recent phase III studies have introduced new therapeutic approaches and several retrospective studies have provided good-quality data on the efficacy of new and previously utilized treatments. Several international societies have established guidelines to aid pNENs management and several therapeutic algorithms have been proposed (Figure 106.1), but there are still some unresolved issues regarding the most appropriate first-line therapy and/or sequence of treatments for individual patients upon disease progression [6–8].

Somatostatin Analogues (SSAs)

Somatostatin is a neuropeptide secreted in the gastrointestinal tract and brain. It acts via interaction with five somatostatin receptor subtypes (SSTR1–5) and inhibits the secretion of various hormones and may also exert immunomodulatory, cytotoxic, and apoptotic actions [9]. SSTR2 is found predominantly in NENs of gastroenteropancreatic (GEP) origin.

Somatostatin analogues act by binding with high affinity to SSTRs and exert antisecretory and antiproliferative activity [9]. Long-acting SSA formulations such as octreotide LAR and lanreotide Autogel® are currently available and are administered once monthly.

The first evidence for the antiproliferative activity of SSAs came from the PROMID clinical trial, a randomized placebo-controlled phase III study that

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Table 106.1 Treatment of functioning pNENs according to their secretory component.

pNEN	Syndrome	Secretory component	Treatment
Gastrinoma	Zollinger–Ellison syndrome (ZES)	Gastrin	Protein pump inhibitors, H2 inhibitors, (SSAs)
Insulinoma	Endogenous hyperinsulinism	Insulin	Frequent meals, IV glucose, diazoxide, SSAs, everolimus, pasireotide
VIPoma	Verner–Morrison syndrome (WDHA)	VIP	SSAs, rarely glucocorticoids, sunitinb
Glucagonoma	Glucagonoma	Glucagon	SSAs
Somatostatinoma	Somatostatinoma	Somatostatin	SSAs
ACTHoma	ACTH	ACTH	SSAs, cabergoline, pasireotide, adrenolytic treatment
GRFoma	GRF	GRF	SSAs, pasireotide, cabergoline, pegvisomant
pNET causing carcinoid syndrome	Carcinoid syndrome	Serotonin, tachykinins	SSAs, telotristat
pNET causing hypercalcemia	PTHrP	PTHrP	SSAs, bisphosphonates, cinacalcet, calcitonin
Other rare pNETs	LH, renin, GLP-1, IGF-2, erythropoietin, CCK, enteroglucagon	Various hormones	Refer to relevant syndrome

SSAs, somatostatin analogues; VIP, vasoactive intestinal peptide; WDHA, watery diarrhea hypokalemia achlorhydria; ACTH, adrenocorticotropic hormone; GRF, growth hormone-releasing factor; PTHrP, parathyroid hormone-related peptide; LH, luteinizing hormone; GLP-1, glucagon-like peptide 1; IGF, insulin growth factor; CCK, cholecystokinin.

Table 106.2 Factors determining the therapeutic choice of NENs.

Functioning tumor Grading Extent of disease (liver or other metastases) Extent of liver involvement Tumor growth rate Somatostatin receptor scintigraphy uptake	**Somatostatin analogues** **Chemotherapy** **Molecular targeted therapy** **PRRT** **Immunotherapy** **Combination of treatments**
Patient performance status Presence of a familial syndrome Local availability	

PRRT, peptide receptor radionuclide therapy.

showed a significantly prolonged time to progression (TTP) in patients with well-differentiated locally advanced or metastatic intestinal NENs on treatment with octreotide LAR (hazard ratio [HR] 0.34; 95% confidence interval [CI] 0.20–0.59; I = 0.000072) [10]. Subsequently, the randomized placebo-controlled phase III CLARINET study demonstrated significantly increased progression-free survival (PFS) in patients with locally advanced or metastatic well-differentiated (Ki-67 <10%) GEP-NENs treated with lanreotide compared to placebo [11]. The study showed a benefit in terms of PFS with a HR of 0.58 (95% CI 0.32–1.04) and median PFS of 29.7 months for the group of pNENs [12]. The benefit in PFS was observed regardless of tumor burden. Thus, SSAs are recommended as first-line systemic treatment for tumor growth control in cases of stable or slowly progressive disease.

Although there is no established Ki-67 cut-off value, SSAs are generally recommended in patients suffering from NENs with a Ki-67 up to 10% [13]. Patients with well-differentiated pNENs who are progressing under standard doses of SSAs may benefit from above-label doses [14]. Pasireotide, a new-generation SSA with high affinity for all SSTRs except SSTR4, has been shown to be effective in patients with advanced NENs but recent studies showed no advantage of this agent compared to other SSAs [15].

Common adverse events of SSAs include abdominal pain, diarrhea, nausea, gallstone development, and glucose intolerance [9]. Pasireotide is a potent hyperglycemic agent associated with alterations of glucose metabolism in up to 25% of patients treated [15].

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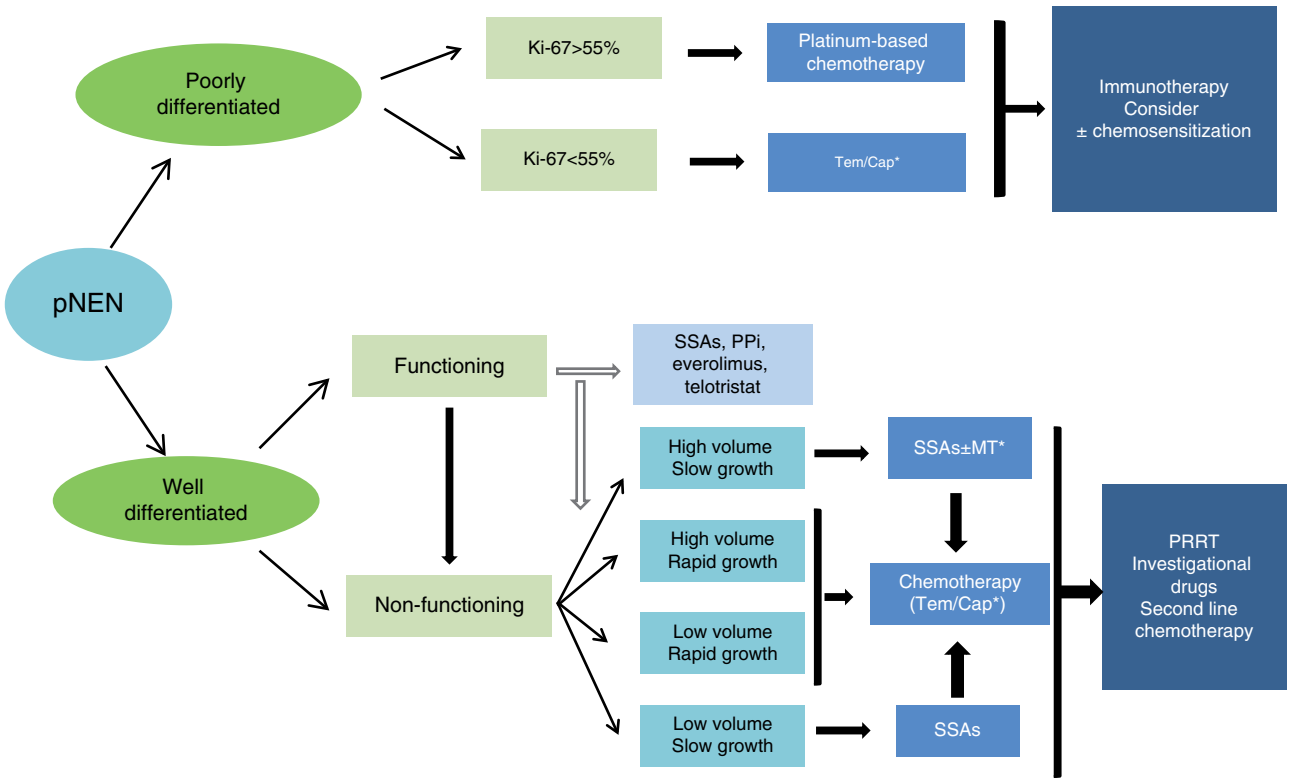


Figure 106.1 Suggested algorithm for the nonsurgical management of pNENs. MT, molecular targeted; PRRT, peptide receptor radionuclide therapy; SSAs, somatostatin analogues; Tem/Cap, temozolomide-capecitabine.

Targeted Agents

Molecular studies have revealed that two main pathways are involved in NEN growth: the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR), and drugs that target these pathways have been proved to be effective in patients with advanced GEP-NENs.

Everolimus is an mTOR inhibitor that has demonstrated antiproliferative action and is recommended as a second- or third-line treatment after failure of SSAs or other agents in well-differentiated NENs. A phase III prospective, randomized, placebo-controlled, double-blind trial (RADIANT 3) showed significant prolongation of PFS with everolimus versus placebo in patients with advanced G1 or G2 pNENs (HR 0.35; 95% CI 0.27–0.45; P <0.001). Objective responses were low (<5%) and independent of prior treatment with chemotherapy [16,17]. Common side-effects of everolimus include glucose intolerance or diabetes, stomatitis, and pneumonitis. Other inhibitors of mTOR complex-1 (mTORC1) and mTOR complex-2 (mTORC2), such as BEZ235, have been studied in patients with pNENs with disappointing results [18].

The tyrosine kinase inhibitor (TKI) sunitinib inhibits the vascular growth factor receptor (VEGFR-2 and -3), platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-kit) and is currently approved for the treatment of metastatic pNENs. The SUN11 trial, a phase III double-blind placebo-controlled study, showed a significant benefit of sunitinib over placebo with improved PFS in patients with pNENs (HR 0.32; 95% CI 0.18–0.55; P = 0.000015) [19,20]. A significantly longer PFS was observed in patients with a Ki-67 <5% while patients with nonfunctioning tumors displayed a higher response rate. However, data on the effect of sunitinib on overall survival are lacking. Common adverse events include nausea, diarrhea, fatigue, neutropenia, hypertension, hypothyroidism, and palmar-plantar erythrodysesthesia [19,20].

In recent years, other antiangiogenic agents have been tested in several trials, albeit involving a limited number of patients with pNENs. Pazopanib inhibits VEGF receptors 1, 2, and 3, and an early study has shown it has some activity in patients with pNENs [21]. Surufatinib, a small molecule inhibitor targeting VEGF receptors, fibroblast growth factor receptor 1 and colony-stimulating factor 1 receptor, showed promising antitumor effects in patients

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with advanced NENs [22]. A recent randomised, double-blind, placebo-controlled, phase III study showed significantly improved PFS with surufatinib compared to placebo (HR 0.49; 95% CI 0.32–0.76; P = 0.0011) in patients with progressive, advanced pNENs [23]. A phase II trial of capozantinib reported a median PFS of 21.8 months while the most promising response rate was reported for lenvatinib (42.3%) [5].

Bevacizumab is a monoclonal antibody against VEGF and has been tested in combination with chemotherapy (5-fluorouracil + streptozotocin) in patients with well-differentiated pNENs displaying a two-year PFS and a two-year overall survival (OS) of 88% [24]. The combination of bevacizumab with temserolimus, an mTOR inhibitor, demonstrated substantial activity with good tolerance in patients with well- and moderately differentiated pNENs [25].

Chemotherapy

In contrast to other gastrointestinal NENs that are typically chemo-resistant, well-differentiated pNENs appear to be sensitive to chemotherapy, including streptozotocin, dacarbazine, and temozolomide as well as fluoropyrimidines. However, most of the studies of chemotherapy in patients with pNENs are retrospective series or small phase II trials [5]. Streptozotocin-based chemotherapy in combination with 5-fluorouracil (5-FU) or doxorubicin has been observed to be effective in the treatment of pNENs and especially in G2 neoplasms or in those with high tumor load [4,13]. The BETTER trial showed that bevacizumab with 5-FU/streptozotocin in patients with progressive metastatic well-differentiated pNENs resulted in a PFS of 23.7 months and a two-year OS of 88% [24]. The combination of oxaliplatin with 5-FU/capecitabine in a few small phase II studies in combination with bevacizumab resulted in response rates of 30–41% [5].

Recent studies have shown that temozolomide (oral derivative of dacarbazine) as monotherapy or in combination with capecitabine (oral derivative of 5-FU) may be an effective treatment option in advanced NENs with tolerable toxicity [26,27] (Figure 106.2). In 2011, a retrospective study showed that the combination of capecitabine and temozolomide (CAPTEM) was associated with a 70% objective response rate, with a median PFS of 18 months and an OS of 92% at two years [27]. A recent phase II trial in patients with advanced pNENs who were randomized to receive CAPTEM vs monotherapy with temozolomide showed improvement in PFS from 14.4 months with temozolomide alone to 22.7 months with the combination, regardless of tumor grade [5].

The Nordic study was the first to report a higher response rate to platinum-based regimens for patients with G3 pNENs and a Ki-67 >55% (42% vs 15%), suggesting that aggressive lesions respond better to these regimens [28]. In contrast, G3 NETs have a significantly worse response to platinum-based chemotherapy than G3 NECs while results with alkylating agents are more encouraging in G3 NET patients [29].

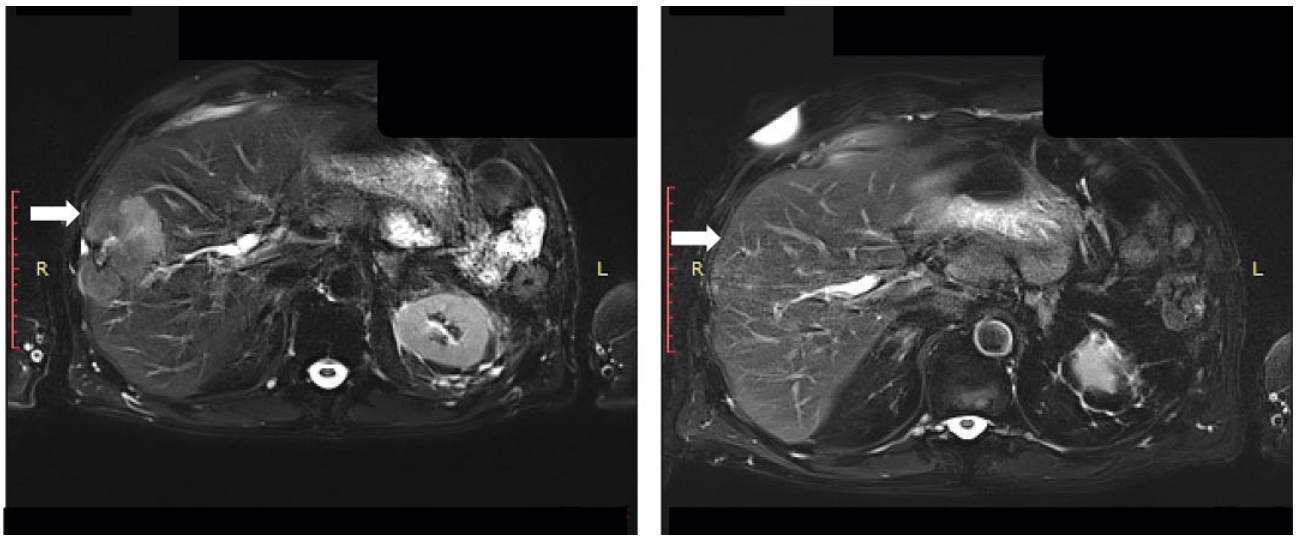


Figure 106.2 Significant liver disease response according to criteria Response Evaluation Criteria in Solid Tumors (RECIST) after one year of treatment with temozolomide-capecitabine.

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In clinical practice, systemic chemotherapy is recommended in G1 or G2 tumors with a high tumor load or displaying significant tumor progression in less than 6–12 months and in G3 NENs [6]. In G3 NECs, which frequently have a rapidly progressive clinical course, platinum-based chemotherapy is recommended as a first-line option while FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) or FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) are indicated as second-line treatment [7]. However, response rates are short-lived and eventually the majority of patients develop progressive disease.

Peptide Receptor Radionuclide Therapy (PRRT)

Peptide receptor radionuclide therapy is a plausible therapeutic option in patients with tumors expressing SSTRs, as it has demonstrated antitumor efficacy and amelioration of refractory hormone secretion syndromes. PRRT consists of a chelator (DOTA) or linker that binds on one side with a SSTR ligand (agonist or antagonist) and a therapeutic particle (yttrium-90 [90Y] or lutetium-177 [177Lu]) on the other [30]. A phase III randomized controlled trial (NETTER-1) showed that ^{177}Lu-DOTATATE was more effective than high-dose octreotide LAR (60 mg) and was associated with significant prolongation of PFS and symptomatic improvement in patients with advanced progressive SSTR-positive intestinal NENs [31]. Unfortunately, there are no randomized phase III studies investigating the efficacy of PRRT in patients with pNENs, but retrospective series and phase II studies have reported a relatively high response rate (24–54%) as well as prolonged PFS and OS.

Brabander et al. investigated the efficacy of PRRT in patients with SSTR-positive NENs, including 197 patients with pNENs. They observed a high response rate (60.9%) and long median PFS (30.5 months) and median OS (70.8 months) that were even more favorable in patients with pNENs that displayed progressive disease at baseline [32].

PRRT is considered an established treatment for G1/G2 NENs while there is promising emerging evidence supporting their effectiveness in patients with G3 disease and positive somatostatin receptor imaging (SRI) [33]. Recent studies have reported high response rates, disease response rates, PFS, and OS. Until further evidence is available, PRRT should be considered for all NET G3 cases and NEC cases with a Ki-67 21–55% with high uptake on SRI. PRRT for NEC with a Ki-67 >55% should only be considered in highly selected patents and used with caution [33].

It has been recently observed that patients with negative fluorodeoxyglucose PET imaging (FDG-PET/CT) displayed better response rates to treatment with PPRT compared with patients with positive FDG-PET/CT [34]. Thus, a scintigraphic assessment estimating both SSTR expression and glucose metabolism may be suggested in order to identify patients with more aggressive FDG-positive NENs, particularly in the context of G3 tumors, as these patients may benefit from combination of PRRT with capecitabine [33,35].

Immunotherapy

Immune checkpoint inhibitors have been shown to be effective in various cancer types such as melanoma and lung carcinoma as antibodies against programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) enhance T-cell antitumor activity. Recent studies have reported PDL-1 expression in gastroenteropancreatic NENs whereas a significant correlation between PDL-1 expression and tumor grade has been observed [36]. Unfortunately, recent studies on immunotherapy with checkpoint inhibitors in pNENs have produced equivocal results. Pembrolizumab and spartalizumab have been tested in phase I and II trials involving patients with well- and poorly differentiated pNENs, albeit reporting significantly low response rates [37,38].

Management of Secretory Syndromes

A significant number of pNENs secrete biologically active substances that result in the development of functional syndromes. The management of patients with secretory symptoms should aim primarily at reducing the tumor load either with radical resection or with debulking techniques. However, pre- and perioperative medical treatment is usually necessary while it may also be required in a palliative setting [39,40]. When surgery or the application of other cytoreductive techniques fail to control symptoms, medical treatment is introduced aiming at controlling tumor mass and secretory syndrome. Treatment of common and relatively rare secretory syndromes secondary to functioning pNENs is shown in Table 106.1.

Long-acting SSAs (octreotide LAR and lanreotide Autogel) are considered the most effective option for secretory syndrome control in patients with functioning tumors, albeit without substantial effect on tumor load [41]. Above-label doses of SSAs may be required in secretory syndromes refractory to standard doses [42].

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Patients with SSA refractory syndromes may benefit from dose escalation or increased frequency of administration. Supplemental doses of short-acting octreotide may also provide an additive effect in such cases [6,40]. In cases of insulinoma, SSAs should be used with caution as worsening of hypoglycemia may be observed due to inhibition of counterregulatory hormones [43]. Furthermore, treatment with continuous intravenous infusion of octreotide is required in patients with carcinoid syndrome before and during any kind of intervention in order to prevent carcinoid crisis [40]. SSAs can also be used for the treatment of other rare syndromes secondary to the secretion of VIP, glucagon and ectopic hormonal secretion that is occasionally encountered in patients with pNENs.

Recently, the safety and efficacy of PRRT were investigated in 34 patients with metastatic functioning pNENs (G1–G2), including insulinomas, VIPomas, gastrinomas, and glucagonomas [44]. The treatment resulted in partial or complete response in 59% of patients, disease control in 78%, and reduction of symptoms in more than 80%. While the treatment was safe, the authors recommended considering prevention of hormonal crises, including high-dose proton pump inhibitors for those with gastrinoma, fluids, antidiarrheal medications, and short-acting octreotide for VIPomas, and glucose infusion or short-acting octreotide for insulinomas [44].

In patients suffering from insulinoma, the primary treatment target is to avoid hypoglycemic episodes. Frequent small-volume meals enriched in long-acting carbohydrates are suggested while in some cases, especially in metastatic tumors, continuous feeding via a nasogastric or nasoduodenal tube may be required [39]. Diazoxide decreases insulin secretion through inhibition of adenosine triphosphate (ATP)-sensitive potassium channels and has been shown to be effective in approximately 60% of cases. It has been observed to be efficacious in controlling hypoglycemia, in doses 50–300 mg/day (maximum dose up to 600 mg/day), but it is associated with significant adverse events such as hirsutism, edema, and renal impairment [45,46]. In addition, everolimus has been shown to be effective in controlling hypoglycemia in cases of metastatic insulinomas while there are some reports regarding the hyperglycemic action of glucocorticoids [46–48]. Pasireotide, that has been observed to be associated with high glucose levels, could also be an additional option although it has not been specifically evaluated [15].

In patients with Zollinger–Ellison syndrome, treatment with high dose of a proton pump inhibitor (PPI) is recommended to reduce the acid hypersecretion. PPIs can also be administered intravenously in the acute state while add-on treatment with histamine-2 receptor blockers or antacids may also be required [39]. Long-term treatment with PPIs has been shown to be safe, with potential side-effects including PPI-induced achlorhydria that may lead to B12 deficiency and an increased incidence of bone fractures [6].

In some rare cases, pNENs are associated with carcinoid syndrome. In patients inadequately controlled with SSAs, treatment with telotristat etiprate, an oral inhibitor of the enzyme tryptophan hydroxylase, has been shown to result in significant clinical and biochemical control [49]. Recent phase III studies have shown that addition of telotristat in the treatment of patients inadequately controlled with SSAs is associated with significant reduction in the number of bowel movements and 5-hydroxyindoleacetic acid (5-HIAA) levels while a long-term benefit in weight maintenance has also been observed [50,51].

The first step in the treatment of a patient with a VIPoma is to correct the fluid and electrolyte deficits while in some cases intravenous resuscitation with potassium and bicarbonate may be required. In addition to treatment with SSAs and PRRT, case series have reported a symptomatic response rate of 33–100% in patients with VIPoma treated with sunitinib, probably unrelated to its antitumor effect [52,53].

Rare syndromes related to the unique ability of these tumors to synthesize and secrete compounds that traditionally originate from different tissues, leading to the so-called paraneoplastic syndromes, necessitate the administration of additional, more specific treatment [54].

Future Perspectives

The systemic treatment of patients with pNENs is complex and challenging due to the significant heterogeneity of these tumors, while their relatively low incidence makes research efforts difficult. As our understanding of the molecular basis has advanced, several clinical trials have been conducted to investigate the different biologic behavior and response to treatments between well- and poorly differentiated G3 pNENs. Novel agents that target specific genetic and protein regulators of neoplasms have been investigated in multiple studies. A biomarker-based approach is currently under evaluation in an attempt to inform clinicians regarding tumor prognosis and to facilitate the individualized management of patients with pNENs [55]. Genetic and epigenetic alterations, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), histone modifications and miRNAs, are being investigated as prognostic factors and predictors of response to treatment.

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While monotherapy has already been shown to be effective, there are multiple ongoing trials investigating the efficacy and safety of potential combinations. The efficacy of combination of SSA with targeted agents or SSA with chemotherapy remains to be determined. In addition, the role of PRRT in patients with pNENs as well as in those with G2 or G3 neoplasms should be further investigated. A phase III randomized study (NETTER-2) investigating the efficacy and safety of PRRT in patients with advanced G2 or G3 GEP-NENs is currently ongoing.

Another issue that needs to be addressed is the sequential use of therapeutic options available for NENs. A recent retrospective study, comparing different sequences of treatments in patients with well-differentiated NENs who received first-line treatment with SSA, observed no significant difference in PFS between patients who received high-dose SSA, everolimus, chemotherapy or PRRT [56]. However, prospective studies are required to further clarify this issue.

Conclusion

Treatment of pNENs has evolved over the last decade and has become extremely complex following the introduction of newer therapeutic agents and the accumulation of good-quality information regarding the efficacy and safety of several therapies. Current therapeutic strategies aim to offer an individualized approach that is based on discussion in a multidisciplinary context, not only at diagnosis but also during different lines of treatment. Research regarding different therapeutic choices, in combination or sequentially, in the treatment of patients with advanced pNENs is required. In addition, there is a clear need for the development of specific biomarkers that could help in selecting patients for individualized treatment. Although several relevant societies have proposed therapeutic algorithms based on the findings of recent studies and acquired cumulative experience, there are still some unresolved issues to be addressed from prospective multicenter studies.

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Interventional Radiology in the Treatment of Pancreatic Neuroendocrine Tumors

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Type of Interventional Radiology Treatment

In 2017, the World Health Organization classified pancreatic neuroendocrine neoplasms (PanNENs) into well-differentiated pancreatic neuroendocrine tumors (PNETs) and poorly differentiated neuroendocrine carcinoma (PanNEC) [1]. PanNEC is not indicated for interventional radiological therapy because tumor progression is rapid and often causes multiorgan metastases. On the other hand, interventional radiologic treatments can be performed in PanNETs. The reasons for this preference are that PanNETs show morphologic well-demarcated lesions and are relatively slow growing, even at metastatic sites, and over 90% of the blood supply to metastatic lesions in the liver is reported to be provided by the hepatic artery [2] (Figure 107.1). Therefore, as is the case for hepatocellular carcinomas, transarterial embolization (TAE), transarterial chemoembolization (TACE), and radiofrequency ablation (RFA) are applied for metastatic PanNETs in the liver. Microwave coagulation therapy, laser interstitial thermotherapy, and cryotherapy have recently been incorporated as potential advances in the various effective treatment options for unresectable PanNETs.

Liver metastases from PanNETs are morphologically classified into three patterns according to the European Neuroendocrine Tumor Society (ENETS) guidelines [3]: simple (unilobar or limited), complex (bilobar), and diffuse pattern. Simple and complex patterns without extrahepatic metastases are usually treated by curative resection, while diffuse pattern is treated by multidisciplinary treatment including systemic medication and surgical debulking with regional ablation therapies such as TAE/TACE and RFA. Owing to recent advances in surgical techniques and the development of systemic medication using anticancer agents, molecular targeted drugs, and peptide receptor analogues, the roles of TAE/TACE and RFA have been limited to providing relief of the hormonal symptoms caused by rapid growth of the tumor or the adjuvant therapy during or after operation [3–9].

TAE/TACE

TAE/TACE are used in the multidisciplinary treatment for unresectable liver metastases from PanNETs (Table 107.1). Therefore, the effects of TAE/TACE alone on survival remain unclear; however, TAE/TACE are reported to provide a decrease of 50–90% of the symptoms caused by hormonal hypersecretion, with a prolonged effect of 6–53 months and a time to progression of 10–19 months [2]. The reported five-year survival rate of TAE/TACE ranges widely from 0% to 80%, because the conditions, such as the range of tumor spread, timing of the TAE/TACE during multidisciplinary treatment, and other treatments subsequently performed after TAE/TACE, are different among the reports [2].

In TAE, histoacryl, in conjugation with lipiodol, gel forms particles with or without lipiodol, polyvinyl alcohol foam, and microspheres using glass or resin, which are used as embolic agents [2]. Several chemotherapeutic drugs, such as doxorubicin, streptozocin, dacarbazine, adriamycin, cisplatin, and mitomycin C, are used in conjugation with lipiodol during TACE [2,7,8]. Drug-eluting beads (DEB) preloaded with doxorubicin have been used as a drug delivery device with a pharmacokinetic benefit in a novel TACE technique, usually defined as DEB-TACE [8].

A recent trend in transarterial technique is radioembolization using a radioconjugated somatostatin analogue.

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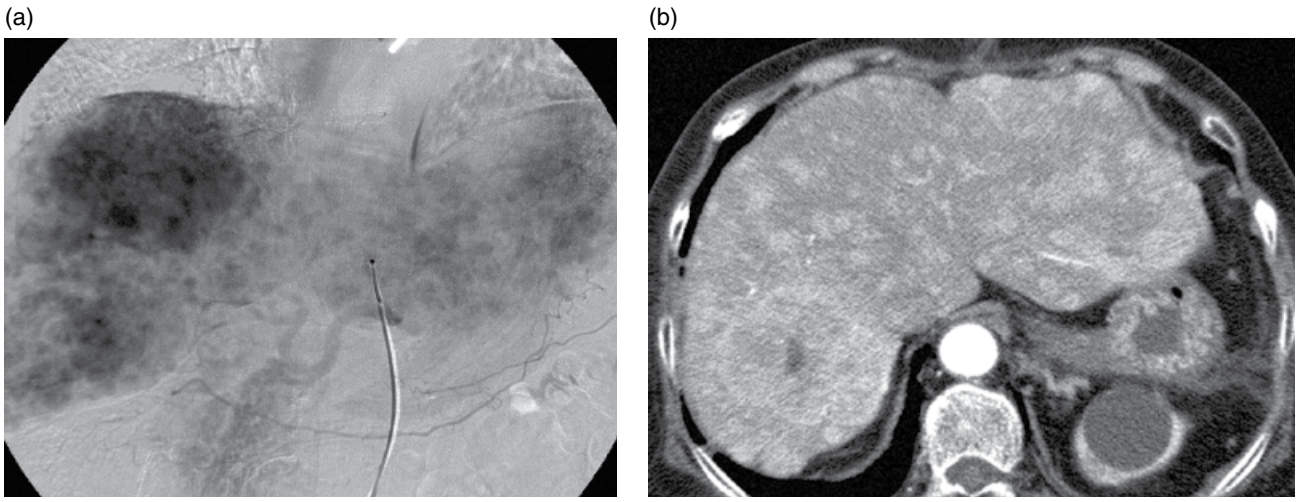


Figure 107.1 Staining of hepatic metastases during angiography. Results of tumor staining during angiography from the common hepatic artery (a) and computed tomography (b) in patients with multiple hepatic metastases from nonfunctioning pancreatic neuroendocrine tumor.

Table 107.1 Treatment indications for TAE/TACE of liver metastasis.

Guidelines	Treatment indication
ENETS	Functional PanNET
	Unresectable lesions with metastases in the liver or mostly in the liver
NCCN	Functional PanNET (unresectable and poor hormone control due to drug treatment)
	Well-differentiated PanNET with a large amount of intrahepatic tumor
NANETS	Unresectable and poor hormone control due to drug treatment

ENETS, European Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network; NANETS, North American Neuroendocrine Tumor Society; PanNET: pancreatic neuroendocrine tumor.

Selective internal radiation therapy (SIRT) is a novel treatment option in which radioactive microspheres containing β-ray source yttrium-90 (^{90}Y) are injected into the hepatic artery under fluoroscopy and directly irradiated from inside the tissue [7–9]. Radioembolization using ^{90}Y-lanreotide provides a radiologic response of 22.5–63% and median survival times of 22–70 months [7]. The regional concentration of chemotherapeutic drugs by TACE is reported to be 10–20 times higher than that by systemic chemotherapy; however, the additional effect of chemotherapeutic drugs on TAE alone remains unclear [2]. Repeat TAE/TACE would lead to the disruption of the arterial endothelium and then accelerate collateral formation, resulting in difficulty in future TAE/TACE.

Morbidity and mortality after TAE/TACE are reported to be 0–28% and 0–5.6%, respectively [2]. Complications in relation to TAE/TACE include hepatic abscess, hepatic dysfunction (sometimes hepatic failure arising from infarction), pleural effusion, gastric ulcer, and so forth. Many patients experience post-TAE/TACE syndrome symptoms, including transient fever elevation, leukocytosis, and increase in hepatic enzyme, most of which are observed within several days after TAE/TACE. Regional chronic infection in the biliary tree is a risk factor for hepatic abscess after TAE/TACE because the biliary system has a blood supply exclusively from a hepatic artery, and TAE/TACE would lead to biliary ischemia. Therefore, this technique should be avoided in patients who have a history of biliary intervention, including after pancreatoduodenectomy or endoscopic sphincterotomy. In addition, patients who have portal neoplastic thrombus or hepatic ascites are also contraindicated for TAE/TACE because of the high risk of post-TAE/TACE hepatic failure.

RFA

RFA can be performed during open surgery as well as laparoscopic operation, or by computed tomography or ultrasound-guided percutaneous techniques (Table 107.2). A previous report [10] demonstrated that RFA alone for hepatic metastases from well-differentiated PanNET can provide a favorable prognosis comparable to hepatic resection; however, the indicated cases were limited to patients who had a relatively small size and small number of metastatic lesions. At present, RFA is being performed

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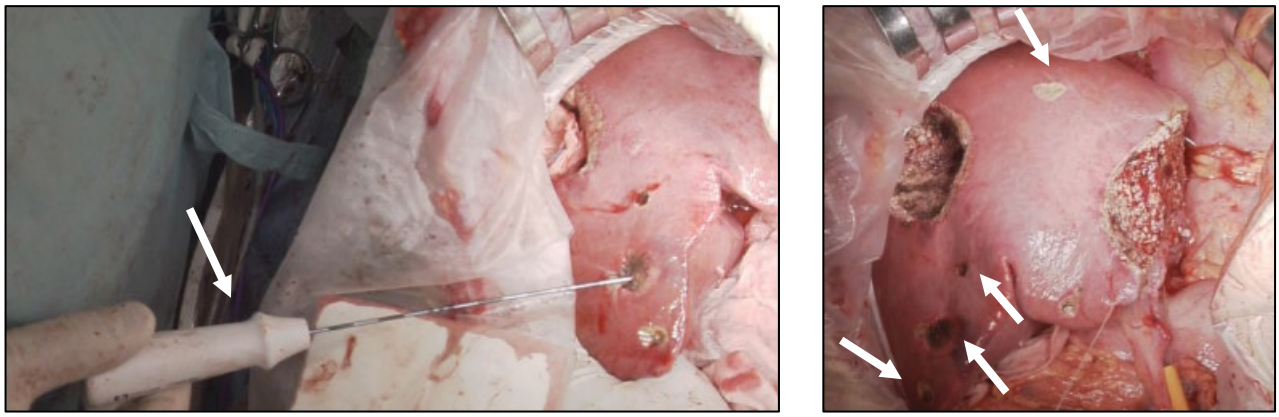


Figure 107.2 Surgical debulking using radiofrequency ablation for hepatic metastases from pancreatic neuroendocrine tumor. (a) Radiofrequency ablation using a tip device (arrow). (b) Completion of the debulking operation. Arrows indicate the trace of the tip device for radiofrequency ablation.

Table 107.2 Treatment indication of RFA for liver metastasis.

Guidelines	Treatment indication
ENETS	Unresectable liver metastasis that is localized or bilobed lesions used in combination with hepatectomy
NCCN	Liver metastasis (size 3 cm or less and four lesions or fewer)
NANETS	More useful than hepatectomy and TAE/TACE, performed in combination with resection and cryoablation

ENETS, European Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network; NANETS, North American Neuroendocrine Tumor Society; TAE/TACE, transarterial embolization/transarterial chemoembolization.

for persistent viable lesions as an adjuvant therapy during or after hepatic resection, or after TAE/TACE [3–9] (Figure 107.2). Adverse events related to RFA include pneumothorax, hepatic abscess, perforation of the gastrointestinal tract, skin burn, and so forth; however, major and fatal complications are rarely observed [7]. RFA for patients who have a history of biliary intervention should be avoided because of the same reason described above for TAE/TACE, where there is a risk of fatal hepatic abscess.

Use of RFA for primary PanNETs has been reported. An Italian group [11] reported their experience with 10 patients, with a mean tumor diameter of 16 mm (range 9–29 mm). All the lesions were completely ablated by the percutaneous route in seven patients, under laparotomy in two, and under laparoscopy in one. Mild pancreatitis occurred in three patients, all of whom were cured within ~2 days. No recurrence was observed during the median surveillance period of 30 months (range 12–60 months). Furthermore, a French group [12] reported transgastrointestinal endoscopic ultrasound-guided RFA ablation (EUS-RFA) for 14 PanNETs in 12 patients, with a mean tumor size of 13.1 mm (range 10–20 mm). All the lesions were safely ablated by this technique.

Although this intervention can be applicable for relatively small-sized primary PanNETs in patients who are in generally poor condition, further investigation using a larger study population and with long-term surveillance is needed to determine the adequacy of this procedure.

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Enucleation of Benign, Neuroendocrine Tumors of the Pancreas

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Introduction

The history of pancreatic surgery is closely connected to pancreatic neuroendocrine tumors (PanNETs), namely surgery for malignant and benign insulinoma [1,2]. Although not evidence based at the time, enucleation used to be preferred over resection because the endocrine tumor was almost always cured and the patient developed few and mostly minor surgical complications [3].

Some 90 years of surgical experience with small, clinically benign PanNETs later, the important role of enucleation is still uncontroversial. However, the growing number of pancreatic incidentalomas, unearthed by advanced imaging techniques [4–10], has multiplied the challenge of managing these tumors appropriately. Risk stratification, using proliferation markers such as frequency of mitosis and the Ki-67 index in the tumor [11–14], informs clinical treatment plans such that the therapy selected is commensurate with the risk profile of the tumor at hand. Interventions range from expectant observation in the absence of hormone excess to enucleation, and ultimately to pancreatic resection.

Observation Versus Surgery for Small Sporadic, Benign-Appearing, Nonfunctioning Pancreatic Neuroendocrine Tumors

Incidental small, nonfunctioning PanNETs feature less aggressive growth patterns on histopathology compared with symptomatic PanNETs [5]. Primary tumor size, reflecting a biological continuum, positively correlates with tumor grade [15], Ki-67 index [16], and the presence of lymph node and distant metastases [16–18]. The rate of lymph node metastases in nonfunctioning PanNETs smaller than 1 cm and up to 2 cm is estimated at 6.5% and 11.5% respectively. Therefore, these small tumors should not necessarily be considered indolent neoplasia [19]

For PanNETs smaller than 2 cm, disease-related mortality in most studies was close to zero [16,18–19]. Without surgical intervention, 13% [20] and 16% [16] of these sporadic nonfunctioning PanNET enlarged by more than 20%, yielding an estimated tumor growth of 0.12 mm per year [20]. In carefully selected groups of patients with nonfunctioning PanNETs who were managed without surgery, no disease progression was seen after 18 [20], 27 [21], and even 283 months [16]. Intriguingly, analysis of more than 2000 patients with nonfunctioning PanNETs revealed a survival benefit after resection of 1–2 cm (hazard ratio [HR] 0.37) and >2 cm (HR 0.3) large tumors but not after resection of tumors smaller than 1 cm (HR 2.81) [22].

Provided that there is no clinical evidence of metastases and tumor growth, sporadic, incidentally detected nonfunctioning PanNETs smaller than 15 mm may be candidates for expectant observation.

Preoperative Imaging and Assessment of Proliferative Tumor Activity

In patients with small PanNETs, preoperative imaging using endoscopic ultrasonography [23–26], cross-sectional (computed tomography [CT]; magnetic resonance imaging [MRI]) or functional (octreoscan; [^{18}F] fluoro-2-deoxy-d-glucose positron emission tomography [FDG-PET]/CT) imaging [27–31] informs the approach to the surgical target (laparoscopic versus conventional open surgery) and the method of tumor

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clearance (enucleation versus pancreatic resection). Dual tracer scans based on ^{68}Ga-DOTATOC and ^{18F}FDG PET improve preoperative risk assessment further and should be considered for preoperative work-up [30,31].

Unlike nonfunctioning PanNETs, some functioning tumors, specifically very small insulinomas, may evade standard imaging. In this scenario, selective arterial stimulation is indicated to narrow down the location of the hormone-producing pancreatic tumor [32]. Small tumors residing in the anterior pancreatic head and the pancreatic body and tail usually qualify for enucleation unless they are situated deep down inside the pancreas and involve the main pancreatic duct (Table 108.1; Figs 108.1, 108.2, and 108.3). Conversely, deep-seated pancreatic tumors and tumors adherent to, or invading, the main pancreatic duct (see Figs 108.1 and 108.3) necessitate pancreatic resection, with partial or complete resection of the pancreatic head, body, or tail depending on the situation. Of note, preoperative imaging, whatever technique is being used, cannot exclude tumor involvement of the main pancreatic duct. Therefore, it is crucial in this setting that intraoperative ultrasonography be used to identify the pancreatic duct and to rule out multifocal lesions before deciding on whether to embark on enucleation or pancreatic resection [33].

Preoperative risk stratification is performed by endoscopic ultrasound-guided fine needle aspiration cytology to establish the diagnosis and allow tumor grading, supported by Ki-67 immunocytology to determine the proliferative tumor activity [33–36]. To make that determination correctly, the cytopathologist must be sufficiently experienced and cognizant of the methodologic limitations [34]. There is also a paucity of data about the prognostic significance of preoperative grading and Ki-67 immunocytology for small pancreatic tumors so that the benefits of enucleation versus pancreatic resection based on these findings remain unclear.

Table 108.1 Indications for enucleation of PanNET.

Small nonfunctioning PanNET 1–2 cm, or insulinomas up to 2 cm in greatest dimension and:
• benign appearing and low grade, based on standard and functional imaging, and, if performed, Ki-67 immunocytology
• without suspicious lymph node enlargement or distant metastases
• without wide and deep involvement of the pancreas
• without attachment to the main pancreatic duct on intraoperative ultrasonography.
Enucleation can be performed as a stand-alone procedure or in combination with pancreatic resection for multiple MEN 1-associated PanNET.
For PanNET located in the posterior head of the pancreas, both enucleation and head dorsal pancreatectomy may be considered.
Pancreatic gastrinomas should be treated preferentially by standard pancreatic resection irrespective of size because as many as 80–90% may be malignant and node positive.

(a)



(b)



Figure 108.1 Adherence of a pancreatic body insulinoma (asterisk) to the main pancreatic duct (arrow) (a) that was laparoscopically resected, instead of enucleated, because of this fact (b).

Surgical Technique of Enucleation

Enucleation is the surgical technique of choice for small, benign-appearing or low-grade functioning and nonfunctioning PanNETs without clinical evidence of metastases or involvement of the main pancreatic duct [37–47]. Unless the tumor is situated in the posterior part of the pancreatic head [48,49], enucleation of tumors from the head, body, and tail of the pancreas is technically feasible. The key advantage of enucleation is reduced surgical trauma, with better postoperative

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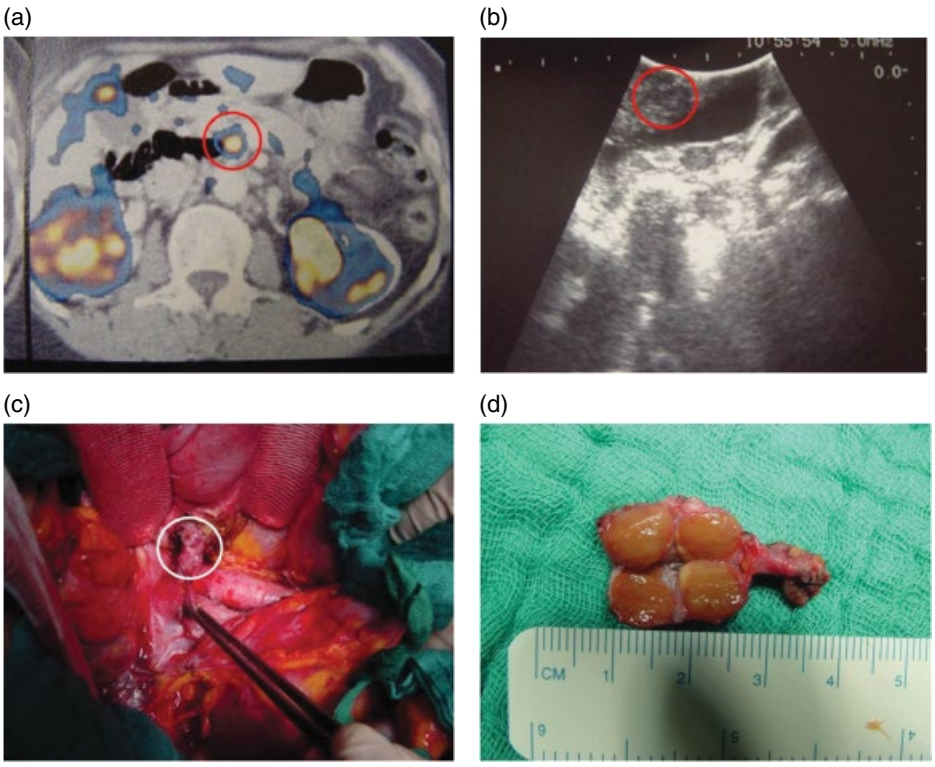


Figure 108.2 Enucleation of a multiple endocrine neoplasia type 1 (MEN 1)-associated insulinoma (encircled) in the uncinate process of the pancreas enucleated via open relaparotomy. (a) Preoperative ^{18}F-DOPA PET/CT; (b) intraoperative ultrasonography; (c) intraoperative view showing tumor enucleation; (d) surgical specimen.

endocrine and exocrine pancreatic function. Major disadvantages include the considerable risk of pancreatic fistula and the fairly low risk of late recurrence and metastases if pancreatic tumors should turn out to be malignant and no lymph node dissection was carried out at the time [49,50].

Enucleation of the PanNET is performed after ultrasonographic verification that the main pancreatic duct courses more than 2 mm away from the pancreatic tumor. There is curretnly inconclusive evidence as to whether preoperative stenting of the main pancreatic duct can enable deep pancreatic enucleation of larger tumors without jeopardizing surgical outcome [51].

Particular care must be taken to dissect the pancreatic parenchyma around the tumor capsule meticulously, without opening it or resecting adjacent pancreatic tissue (Figs 108.2 and 108.3). Great emphasis is laid on closing small pancreatic ducts and vessels using fine sutures or clips. Upon confirmation that the surgical margins of the enucleated tumor specimen are clear on frozen section, the pancreatic capsule is closed using atraumatic absorbable single or running 5-0 or 6-0 sutures. Surgical drains are routinely placed and subsequently removed depending on the amount of, and the enzyme concentrations in, the fluid drained. When the main pancreatic duct has been inadvertently opened, it may be safer not to attempt to over-sew the leak but to convert the planned enucleation into a segmental (pancreatic body) or distal (pancreatic tail) resection or fashion a Roux-en-Y jejunal loop onto the pancreatic defect to drain the leak [47].

Laparoscopic and robot-assisted techniques have become more popular in recent years and may evolve into a new routine for enucleation and distal pancreatectomy (Fig. 108.4) [52]. The placement of the port depends on the preoperative location of the tumor within the pancreas. Generally, a 12 mm supraumbilical port enables inspection of most lesions. Commonly energy devices are used for dissection. However, great care should be taken to heed the principles of open enucleation: careful identification of tumor margins and parenchyma-sparing dissection.

Short- and Long-Term Outcomes After Enucleation

Pancreatic enucleation is associated with a considerable rate of postoperative morbidity (48.1%) and Clavien–Dindo grade >3 complications (16%) [50]. A systematic

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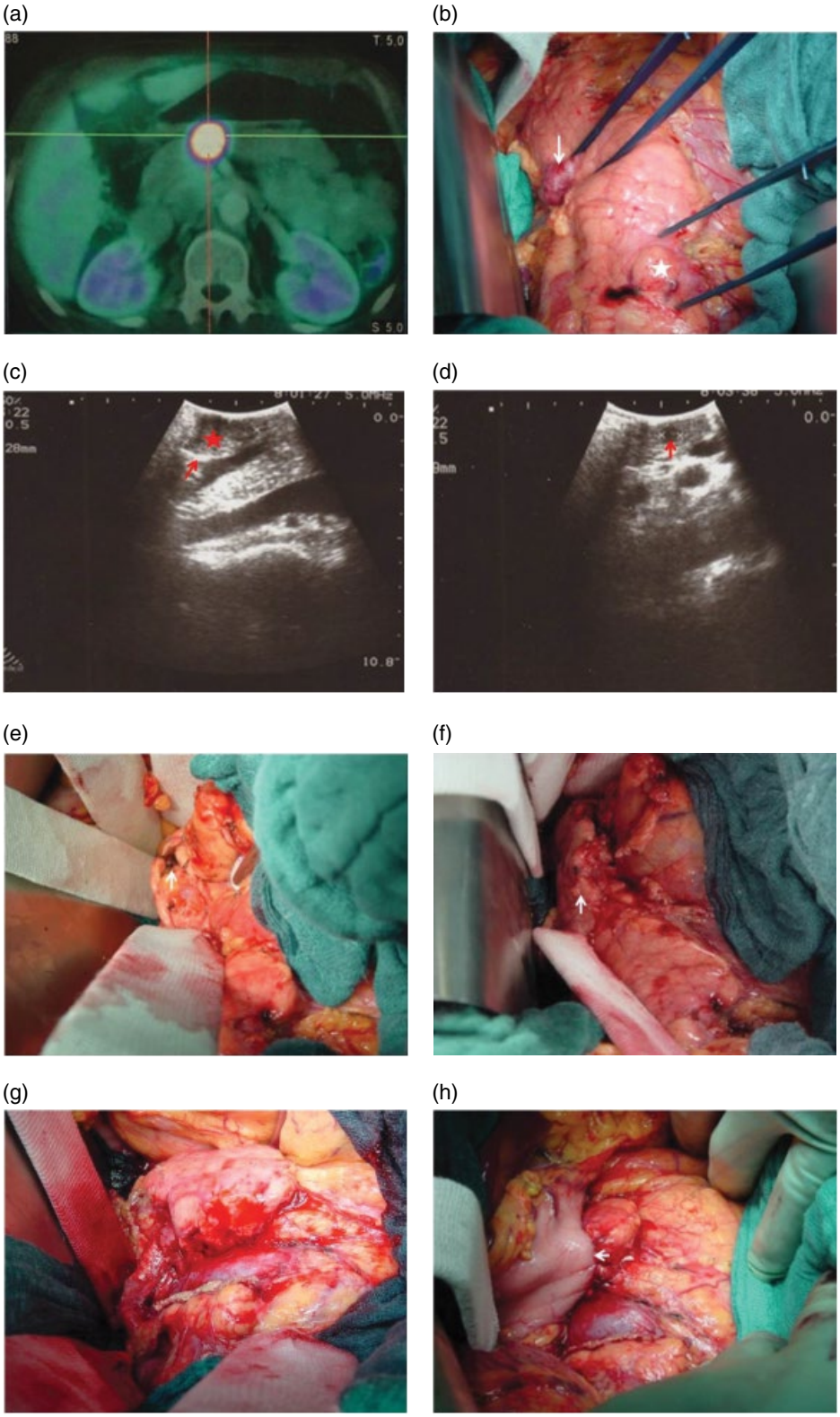


Figure 108.3 Combined pancreatic tail enucleation and central pancreatectomy for multiple MEN 1-associated nonfunctioning neuroendocrine pancreatic tumors. (a) Preoperative [^{68}Ga]DOTA-NOC (DOTA-Nal-octreotide) PET/CT showing a PanNET in the body of the pancreas adjoining the posterior pancreatic vascular axis; (b) intraoperative view picturing a PanNET at the body (asterisk) and another PanNET at the tail of the pancreas (arrow); (c) intraoperative ultrasonography revealing close proximity of the 25 mm pancreatic body PanNET (asterisk) to the mesenterico-portal vein and the main pancreatic duct (arrow); (d) intraoperative ultrasonography delineating the 6 mm PanNET in the pancreatic tail (arrow); (e) intraoperative situs of the pancreatic tail after enucleation (arrow); (f) intraoperative view of the closed pancreatic defect (arrow); (g) intraoperative situs after central pancreatectomy; (h) intraoperative view of the pancreas reconstructed by pancreatogastrostomy (arrow).

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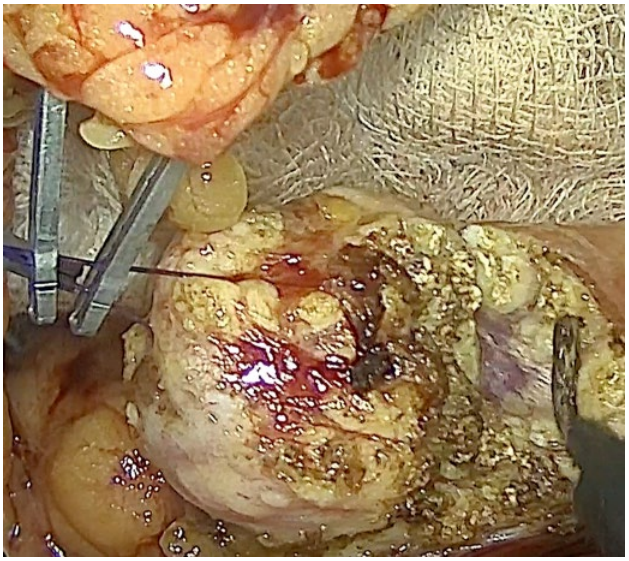


Figure 108.4 Laparoscopic enucleation of a 10 mm large, nonfunctioning neuroendocrine pancreatic tumor with a Ki-67 index of 3%. A transtumoral single stitch suture is used for traction to keep the line of resection close to the tumor capsule.

review and metaanalysis of enucleation versus standard pancreatic resection for small, mainly (69%) neuroendocrine tumors found that enucleation was superior to standard pancreatic resection, leading to shorter operations (P <0.001) with fewer blood loss incidents (P <0.001) [53]. In addition, enucleation was inferior regarding the overall fistula rate (33% versus 20%) but comparable in the length of hospitalization, postoperative mortality, and percentage of reoperation [53]. Other recent studies confirmed this observation [46,50,54]. Although the incidence of grade B/C pancreatic fistula was slightly higher after enucleation than after standard pancreatic resection (24.5% vs 14.0%), long-term outcome remained essentially the same [54]. Major contributors to postoperative pancreatic fistula included deep enucleations [39] and enucleation of PanNETs from the head and uncinate process of the pancreas [37,38], but not surgical (laparoscopic versus open) approach [39].

With respect to long-term oncologic outcome, enucleation was not inferior to standard pancreatic resection when the tumor was low grade, surgical margins were clear on definitive histopathology, and locoregional or distant metastases were absent [49,50,53,54]. After enucleation of <2 cm nonfunctioning PanNETs, late recurrences and metastases were found in 8% of patients [55].

The need to dissect regional lymph nodes in addition to clearing these tumors from the pancreas has sparked a lot of debate [56–59] because lymph node metastasis may have a negative prognostic impact on survival [54,57–59]. Among others, tumor size ≥2 cm, proximal location, and Ki-67 ≥3% are risk factors that predict LN positivity. However, lymph node metastases can be present in up to 25% of patients with nonfunctioning PanNETs, even in the absence of one or more of these risk factors [19,56,59]. Importantly, a recent muticenter study yielded comparable recurrence-free survival between node-positive and node-negative patients after removal of less than seven lymph nodes during distal pancreatoduodenectomy [59]. Preoperative identification of involved lymph nodes continues to be challenging [59], and concomitant lymph node dissection can drive up surgical morbidity.

Balancing the benefits against the risks, it becomes immediately apparent that the recommendation for or against lymph node dissection must be individualized considering the circumstances of each case. There is evidence to suggest that patients with small non-grade 1 tumors and clinically suspicious lymph nodes [19,58,59] benefit more from standard pancreatic resection and lymph node dissection than from enucleation alone. Otherwise, enucleation, preserving more pancreatic parenchyma, caused fewer endocrine (1% versus 11%) and exocrine (0% versus 25%) pancreatic failures than standard pancreatic resection [53].

Outcome After Laparoscopic Enucleation

The technical feasibility of laparoscopic and robot-assisted enucleation of PanNETs, alone or in conjunction with lymph node dissection, is well established, and both procedures are widely used [46,50,60–66]. In spite of this, prospective randomized controlled trials comparing laparoscopic with open enucleation have not been performed. Retrospective studies hint at a higher risk of pancreatic fistula after laparoscopic enucleation than laparoscopic resection without compromising overall outcome [54]. Enucleations of tumors from the pancreatic head are associated with more pancreatic leaks than left-sided enucleations [63], regardless of whether laparoscopic or conventional open enucleation has been carried out [65]. There is a dire need for more research, especially randomized controlled clinical trials, to clarify long-term oncologic and functional outcome (a) after open enucleation versus conventional pancreatic resection, and (b) after laparoscopic versus open pancreatic surgery.

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Duodenum-Preserving Pancreatic Head Resection or Local Extirpation of Neuroendocrine Tumors of the Pancreas Larger than 2 cm

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Background

An analysis of 35618 cases in the US Surveillance, Epidemiology, and End Results (SEER) database [1] revealed that the median age of onset for neuroendocrine neoplasms of the pancreas (PanNENs) ("neuroendocrine tumors" [NET] in the original paper) was 60 years; lesions were localized in the pancreas ("local") for 14% of patients, regional lesions ("regional") for 22% of patients, and distant metastasis ("distant") for 64% of patients. Regarding prognosis, the median survival time of localized cases was 136 months, whereas those of regional and distant cases were low, at 77 and 24 months, respectively. A 2017 analysis of the SEER database [2] reported that the total number of cases with neuroendocrine neoplasms (NENs) (NETs in the original paper) had greatly increased, with a particularly prominent increase in the number of localized and grade 1 (well-differentiated) cases. Considering the median survival time of PanNEN cases, localized cases had a survival of 230–240 months, regional cases had a survival of slightly less than 100 months, and distant cases had a survival of 20–30 months. Additionally, the extended survival times of localized and regional cases were reported. It is thought that early detection and treatment (surgical resection) of NENs led to improved diagnosis.

Imaging diagnosis is extremely important for diagnosing the progress of PanNENs and determining indications for resection. Dynamic computed tomography (CT), dynamic magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and fine needle aspiration using EUS (EUS-FNA) are widely used for diagnosing the primary lesion. Thorough investigation of the presence of distant metastasis is also necessary, and dynamic MRI using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is useful for diagnosing the number of localized liver metastases. Furthermore, somatostatin receptor scintigraphy (SRS) is excellent for the detection of extrahepatic metastases, such as bone metastasis, and fluorodeoxyglucose-positron emission tomography (FDG-PET) has also been reported to be useful for detecting the distant metastases of NETs, or NECs with high Ki-67 index values [3,4]. Additionally, ^{68}Ga-DOTATOC (gallium-68-DOTA [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid] TOC [tri-octreotide])-positron emission tomography (PET)/CT has better image resolution than SRS and can favorably extract small lymph node or liver metastases, making it useful for detecting distant metastases [5,6]

Indications for surgical resection are determined based on these types of diagnostic imaging; however, for localized and regional PanNENs, resection is indicated for both functioning and nonfunctioning tumors, excluding a few cases. Among hereditary diseases, cases with multiple PanNENs with multiple endocrine neoplasia (MEN) type 1 complications are allowed to undergo follow-up observations until the tumor diameter reaches 2 cm (in the case of a nonfunctioning tumor) due to the young age of onset, and with the objective of avoiding total pancreatectomy.

The theme of this chapter is the surgical treatment of PanNETs over 2 cm; therefore, the main subject will be nonfunctioning PanNETs (well-differentiated grade 1–2), with descriptions provided regarding the treatment policy for small PanNETs.

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Surgical Indication for Small Neuroendocrine Tumors of the Pancreas

The number of patients diagnosed with small, asymptomatic, nonfunctioning PanNETs around 20 mm increased along with the number of EUS and EUS-FNA cases. In response, it was debated whether all cases should be indicated for resection. In fact, investigating the follow-up observations of nonfunctioning PanNETs with sizes at or below 10 mm [7], 15 mm [8], or 20 mm [9] revealed only slight tumor growth, and there were no cases of lymph node or distant metastasis. Follow-up observations were first conducted on these cases, and it was reported that resection should be considered according to the increase in tumor diameter. Meanwhile, investigations that actively conducted pancreatectomy, including lymphadenectomy, reported that lymph node metastasis was observed at a certain frequency—even in PanNETs with a small tumor diameter [10,11]—warning against careless follow-up observations [12].

The National Comprehensive Cancer Network (NCCN) guidelines [13] indicate that even with a tumor diameter of 1–2 cm, there is a risk of lymph node metastasis; thus, they generally recommend enucleation with regional lymphadenectomy, or resection with regional lymphadenectomy. However, PanNETs that can undergo follow-up observations, i.e., those with tumor diameter <2 cm, low grade, incidental discovery, nonfunctional type, were divided between 12 weeks to 12 months, 1–10 years, and 10 years onwards according to resected cases. The European Neuroendocrine Tumor Society (ENETS) guidelines also indicate that when a major pancreatic resection is needed, follow-up observations are also allowed for asymptomatic, sporadic, nonfunctioning PanNETs smaller than 2 cm if minimal change is observed [14–17].

Local Extirpation of the Pancreas (Tumor Enucleation) and Parenchyma-sparing Local Resection

Pancreaticoduodenectomy (PD), a standard procedure for PanNETs of the pancreatic head, poses the risk of organ damage [18–22]; additionally, there is a risk of diabetes mellitus onset after distal pancreatectomy (DP), which is a standard procedure for PanNETs of the pancreatic tail [23]. Considering these risks, tumor enucleation and parenchyma-sparing local resection are useful options with respect to preserving organ function. The NCCN guidelines [13] state that tumor enucleation without lymphadenectomy, or parenchyma-sparing local resection (spleen-preserving DP, etc.), may be considered for insulinomas or nonfunctioning PanNETs smaller than 1 cm that are believed to have low risk of lymph node metastasis. However, as previously mentioned, it is important to fully recognize reports of positive cases of lymph node metastasis, even for nonfunctioning PanNETs smaller than 1 cm. The procedure should therefore be determined after sampling lymph nodes around the tumor during surgery, and confirming the absence of metastasis with rapid histology.

Furthermore, there are methods for tumor enucleation or parenchyma-sparing local resection where the endoscopic pancreatic duct stent is placed before surgery to prevent damage to the main pancreatic duct [24]. However, it has been reported that the risk of grade B+C postoperative pancreatic fistulas increases, and cases must be carefully selected [25].

Surgical Treatment of Neuroendocrine Tumors of the Pancreas Larger than 2 cm

The frequency of lymph node metastasis usually increases for tumors exceeding 2 cm; thus, standard pancreatectomy with regional lymphadenectomy (e.g., PD or DP/splenectomy) is recommended [13,17]. However, there are no data demonstrating that prophylactic lymphadenectomy improves the prognosis for PanNETs, and it is unlikely that lymphadenectomy procedures equivalent to regional lymphadenectomy for pancreatic ductal adenocarcinomas (PDAC) are uniformly conducted across all PanNETs larger than 2 cm in clinical practice.

It is currently believed that resection is conducted without excess or deficiency and includes the section suspected of metastasis via imaging. The objective of surgical resection is R0 resection, and it is thought that for the pancreatic head, avoiding pancreaticoduodenectomy accompanying multiorgan resection and selecting a procedure that preserves as much of the organs as possible—as long as radical cure is not impaired—will lead to improved quality of life in the patient. In that respect, duodenum-preserving total or subtotal pancreatic head resection (DPPHR), which can easily be combined with local lymphadenectomy in functional or nonfunctional PanNETs, including lymph nodes along the common hepatic artery, right of the portal vein/superior mesenteric vein and in the mesoduodenum up to the main trunk of the inferior pancreaticoduodenal artery, is thought to be a useful option regarding the frequency of postoperative complications and the preservation of pancreatic endocrine and exocrine function [20–22].

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Duodenum-preserving Total or Partial Pancreatic Head Resection of Neuroendocrine Tumors of the Pancreas Larger than 2 cm

DPPHR comprises methods that include either complete or partial resection of the pancreatic head (Figure 109.1). Complete resection of the pancreatic head can be divided between methods that preserve or resect the common bile duct. Cases of common bile duct resection require reconstruction of the duodenum or jejunum and bile duct, in addition to pancreatic reconstruction (Figure 109.2). Cases of partial resection require pancreatic reconstruction of both the caudal pancreas and residual pancreatic head, including the common bile duct.

Three cases are described that underwent DPPHR for PanNETs with a tumor diameter over 2 cm; all cases underwent DPPHR with total resection of the pancreatic head. Case 1 describes a 40-year-old man with a nonfunctioning PanNET in the pancreatic head measuring 25 mm; after sampling the lymph nodes along the anterior pancreaticoduodenal vessels and confirming metastasis negativity, gallbladder/bile duct-preserving DPPHR was conducted (Figure 109.3). Pancreatic reconstruction was conducted by pancreaticojejunostomy, there were no early postoperative complications, and pathologic examination revealed PanNET G1. To date, the patient has survived for 14 years without recurrence, and no decreases in pancreatic endocrine and exocrine function were observed.

Case 2 describes a 50-year-old woman with a nonfunctioning PanNET in the pancreatic head measuring 23 mm; after sampling the lymph nodes along the anterior pancreaticoduodenal vessels and confirming metastasis negativity, DPPHR with cholecystectomy and bile duct resection was conducted (Figure 109.4). Bile duct reconstruction was conducted using biliary duodenal anastomosis, and pancreatic reconstruction was conducted using pancreaticojejunostomy; there were no early postoperative complications, and pathologic examinations revealed PanNET G1. To date, the patient has survived for 19 years without recurrence, and no decreases in pancreatic endocrine or exocrine functions were observed.

Case 3 describes a 60-year-old woman with a nonfunctioning PanNET adjacent to the superior mesenteric vein, measuring 30 mm from the lower part of the pancreatic head to the pancreatic uncinate. After sampling the lymph nodes along the superior mesenteric vein and artery near the tumor and confirming metastasis negativity, gallbladder/bile duct-preserving DPPHR was conducted (Figure 109.5). Pancreatic reconstruction was conducted via pancreaticojejunostomy, and there were no early postoperative complications. Pathologic examinations indicated PanNET G2 (Ki-67 index >3% [<5%]). Metastasis to the lymph nodes along the superior mesenteric vein and artery was observed eight years and two months later, and lymphadenectomy was conducted (Figure 109.6). Three years and one month later (11 years and three months after the initial surgery), multiple lymph node metastases were observed around the superior mesenteric artery, as well as around the stomach and aorta; drug treatment was therefore conducted.

DPPHR is excellent at preserving organ function, including pancreatic endocrine and exocrine function. However, since lymphadenectomy is insufficient for PanNETs over 2 cm, there is a need to carefully select cases, and indications are currently thought to be limited. The ENETS guidelines [17] indicate reduction surgery only when there are favorable conditions for maintaining

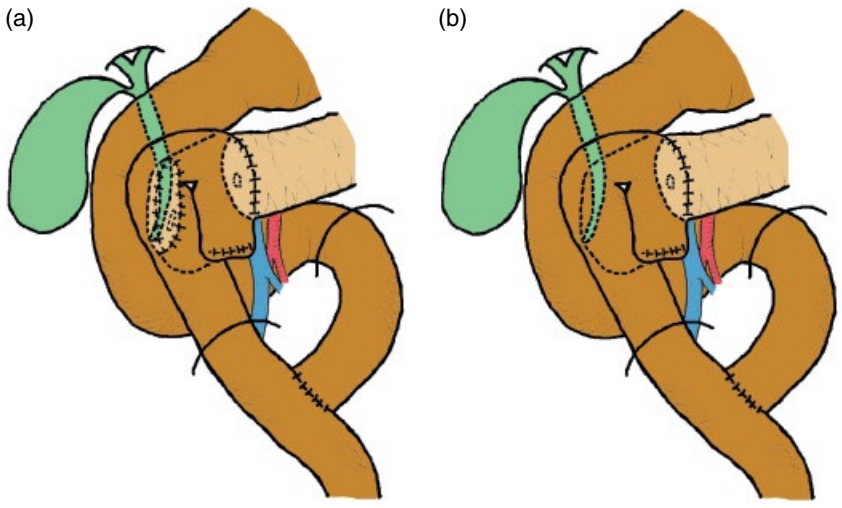


Figure 109.1 (a) Duodenum-preserving total pancreatic head resection. (b) Duodenum-preserving partial pancreatic head resection.

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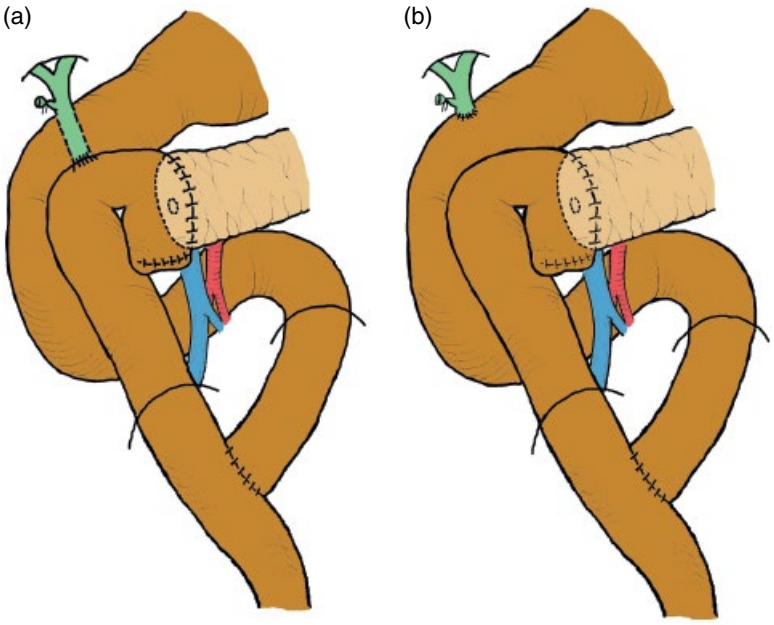


Figure 109.2 Biliary reconstruction after duodenum-preserving pancreatic head resection of the common bile duct. (a) Choledochoduodenstomy. (b) Choledochojejunostomy.

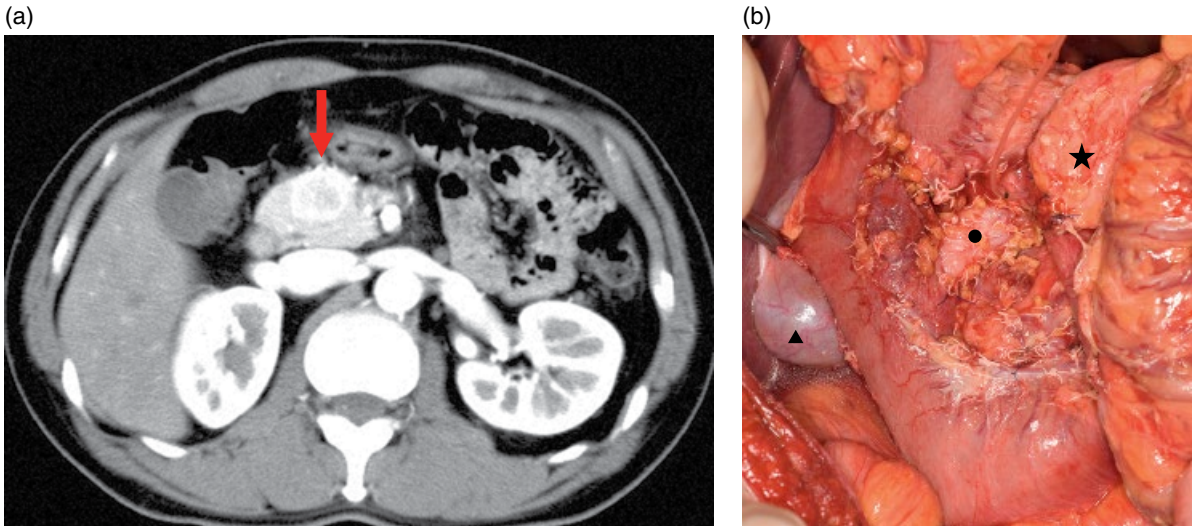


Figure 109.3 Duodenum-preserving pancreatic head resection (DPPHR) for nonfunctioning neuroendocrine tumors of the pancreas measuring 25 mm in the pancreatic head. (a) Preoperative computed tomography (arterial phase). (b) Intraoperative view showing DPPHR with preservation of the gallbladder and common bile duct. ★ remnant pancreas, ● common bile duct, ▲ gallbladder.

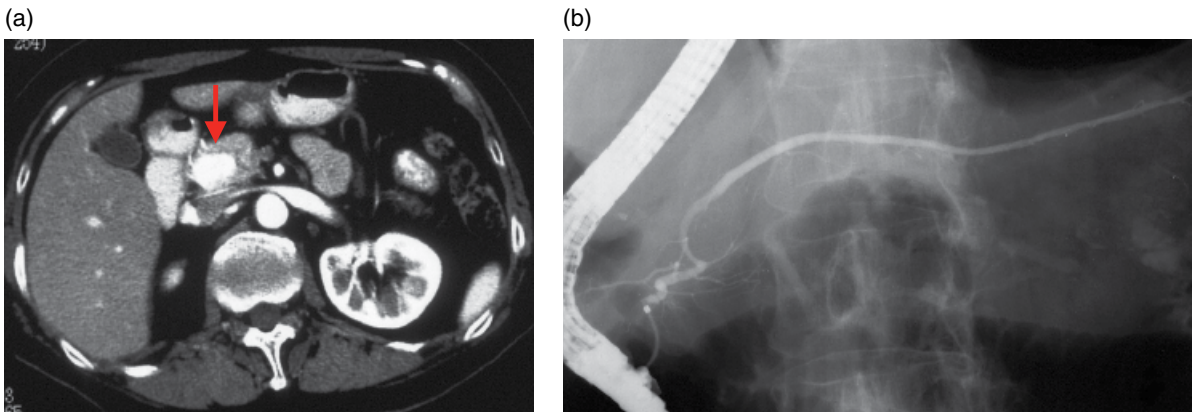


Figure 109.4 Duodenum-preserving pancreatic head resection (DPPHR) for nonfunctioning neuroendocrine tumors of the pancreas measuring 23 mm in the pancreatic head. (a) Preoperative computed tomography (arterial phase). (b) Preoperative endoscopic retrograde pancreatography.

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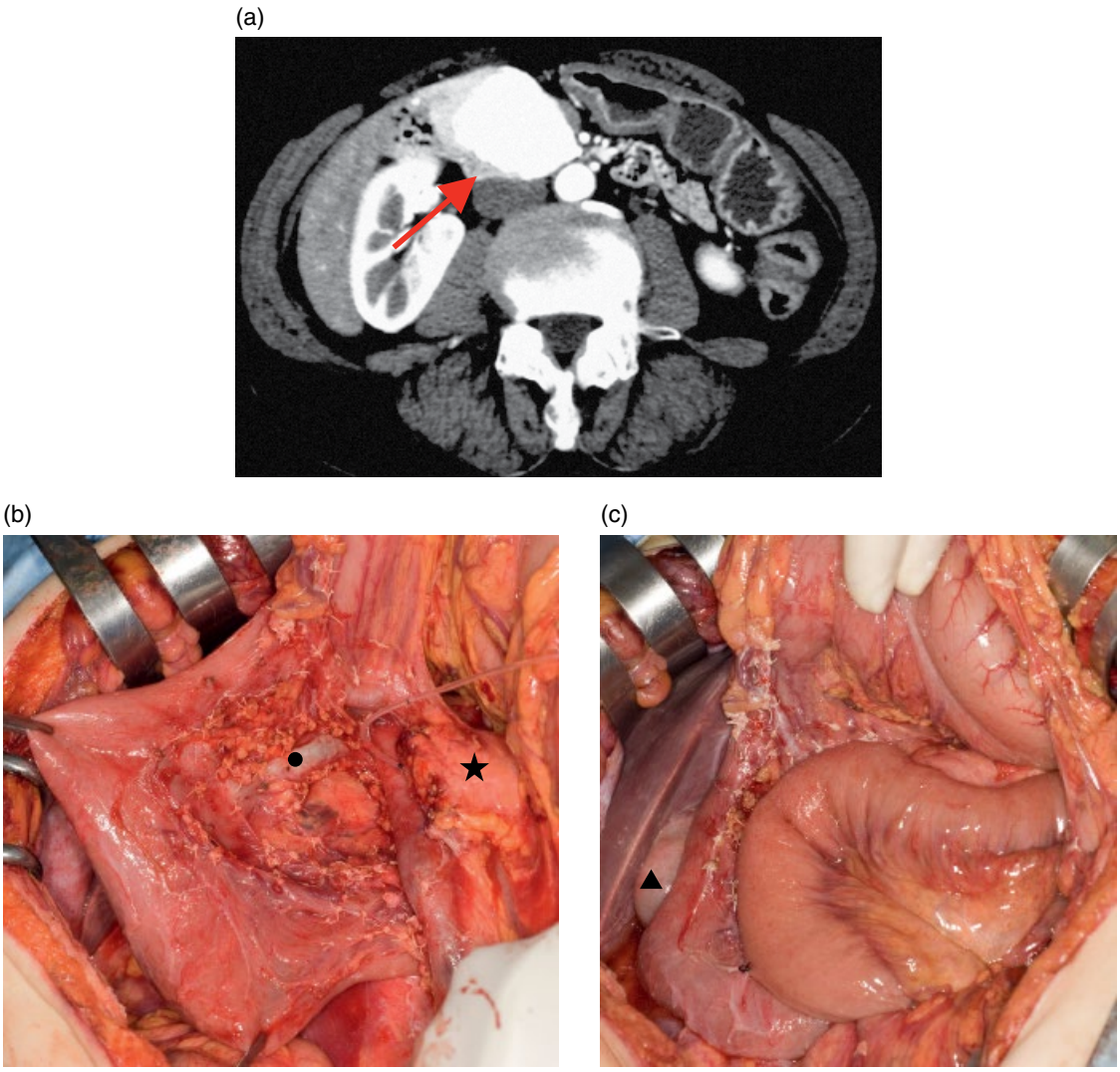


Figure 109.5 Duodenum-preserving pancreatic head resection (DPPHR) for nonfunctioning neuroendocrine tumors of the pancreas measuring 30 mm near the superior mesenteric vein from the lower part of the pancreatic head to the pancreatic uncinate. (a) Preoperative computed tomography (arterial phase). (b) Intraoperative view showing DPPHR with preservation of the gallbladder and common bile duct. (c) After pancreatic reconstruction (pancreaticojejunostomy). ★ remnant pancreas, ● common bile duct, ▲ gallbladder.

organ function; enucleation/local resection at surgery remains possible in many patients with PanNETs >2 cm, with pancreaticoduodenectomy reserved for selected cases. Factors other than tumor diameter need to be investigated to identify conditions where local extirpation or DPPHR for PanNETs over 2 cm may be indicated.

An investigation of the recurrence and survival of patients with nonfunctioning PanNETs following curative resection revealed that those with a Ki-67 index of 0–5% had a significantly more unfavorable recurrence rate within five years than patients with an index value of 6–20%. Multivariate analysis demonstrated that tumor diameter (>41 mm), lymph node metastasis, and Ki-67 index (>5%) were independent predictors of recurrence within five years [26]. Fujimori et al. also reported that patients with a Ki-67 index of less than 3% had a less favorable overall survival than patients with index values of 3–5%, 5.1–10%, 10.1–20%, and over 20% [27].

Therefore, it is believed that for PanNETs over 2 cm, DPPHR may be considered under the following conditions: Ki-67 index less than 3% and at least under 5% during preoperative EUS-FNA; lymph node metastasis not suspected on diagnostic imaging; no metastasis during sampling of lymph nodes near tumor during surgery; tumor diameter exceeds 2 cm, but only slightly and up to 25 mm; and organ preservation is expected. Furthermore, it may be possible to indicate DPPHR in

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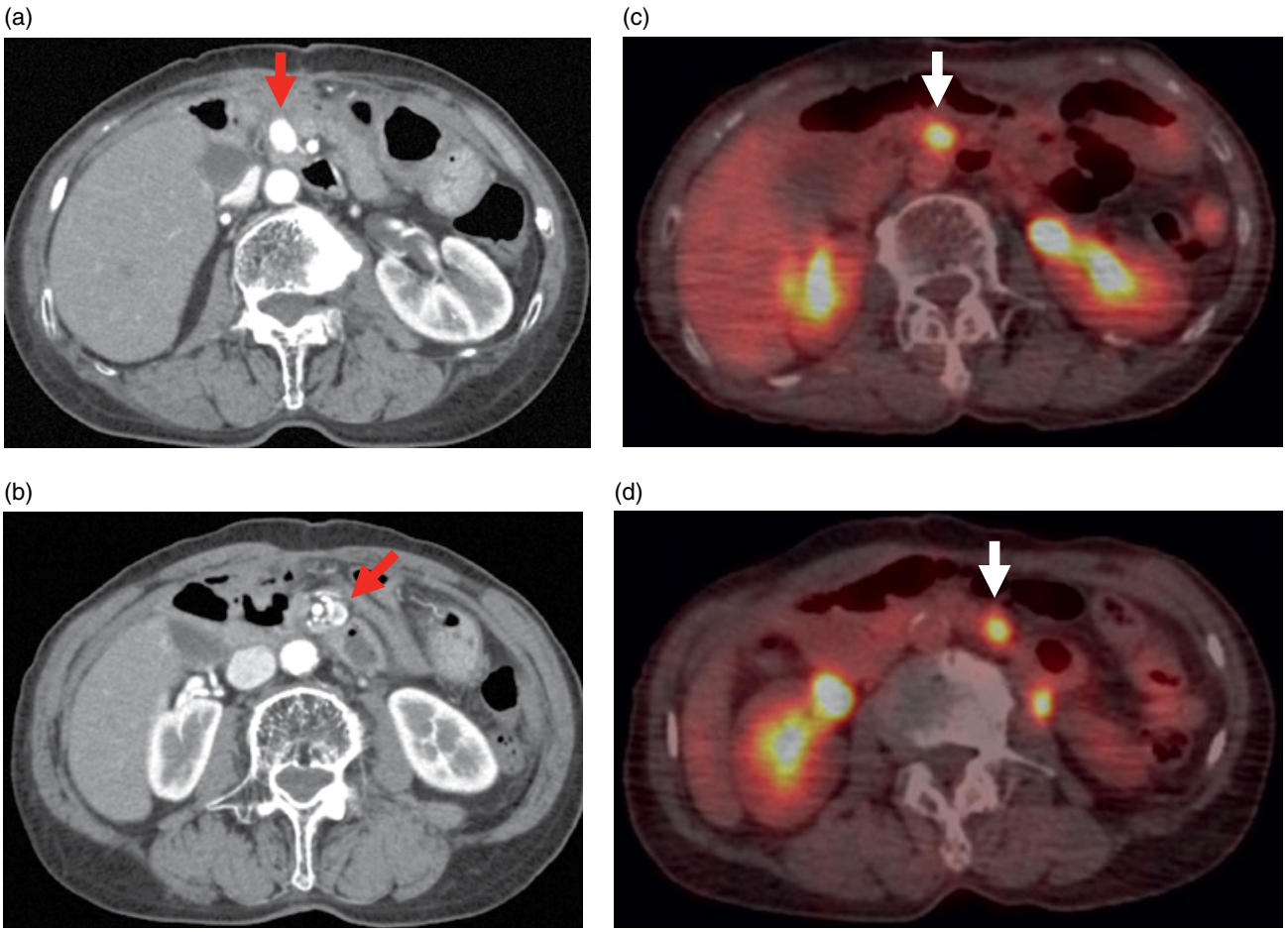


Figure 109.6 Lymph node metastases along the superior mesenteric vein and artery eight years and two months after duodenum-preserving pancreatic head resection. (a,b) Computed tomography (arterial phase). (c,d) FDG-PET/CT.

cases where multiple PanNETs are complicated with MEN 1, with maximum lesions exceeding 2 cm in the pancreatic head, and in cases of insulinomas—which are often benign—where the tumor larger than 2 cm is near the main pancreatic duct in the pancreatic head [13,17,28,29]. Nevertheless, in the Ki-67 index test, the concordance rate between EUS-FNA specimens and surgically resected specimens is typically around 72–74%. Therefore, including cases where the number of collected tumor cells is small or the tumor diameter is large may result in underestimation due to intratumoral heterogeneity; thus, a judgment must be made considering these factors [30–33].

Conclusion

DPPHR or local extirpation for PanNETs larger than 2 cm is thought to be limited regarding its indications due to the risk of lymph node metastasis. The following conditions are considered surgical options: Ki-67 index of 3–5% with EUS-FNA, no lymph node metastasis suspected with diagnostic imaging, no metastasis observed with sampling of lymph nodes near the tumor, tumor diameter of up to 25 mm, multiple PanNETs complicated with MEN 1 in the pancreatic head for the maximum lesion, insulinomas near the main pancreatic duct of the pancreatic head, and when the benefits of organ preservation can be expected.

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Individualized Surgery for Nonfunctional Pancreatic Neuroendocrine Tumors (NF-pNET) <2 cm: Indication, Surgical Principles, and Long-term Outcome

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Introduction

Pancreatic neuroendocrine tumors (pNETs) are rare neoplasms with an incidence of around 0.8/100 000 persons/year [1]. Nonfunctional pNETs (NF-pNETs) represent around 90% of all pNETs. They present clinical, radiologic, and molecular heterogeneity. Their origin can be sporadic or embedded in a genetic syndrome, mainly multiple endocrine neoplasia type 1 (MEN 1). They can be discovered as a localized stage or as metastatic disease. Nevertheless, NF-pNETs are more and more frequently diagnosed with a small size (<2 cm) and as incidentaloma. Their incidence over the last decades has been constantly increasing, mainly due to improvement in and wide diffusion of cross-sectional diagnostic imaging techniques, and some have reported an increased incidence of 710.4% in the last 22 years [2]. Consequently, most medical practitioners will be confronted with this type of neoplasm in their career.

Given the low-aggressive nature of NF-pNETs <2 cm, several management modalities can be discussed, depending on a delicate benefit–risk balance that remains debated. In this chapter, we will try to present all elements involved in the decision of surgical management of small NF-pNETs <2 cm, including indication, surgical principles, and long-term outcome, limiting our chapter to sporadic tumors.

Surgical Indications: The Controversy!

Surgical indication for NF-pNETs mainly depends on the oncologic risk of nodal and systemic dissemination, which remains one of the most important prognostic factors for pNETs [3]. Several studies have demonstrated the relationship between tumor size and aggressiveness of pNETs [4] and there is a well-documented relationship between NF-pNETs size and lymph node (LN) dissemination. Unlike NF-pNETs >2 cm, for which surgical indication is more consensual because of the significant risk of LN and distant metastases, the surgical indication for NF-pNETs <2 cm remains controversial. Indeed, given the low aggressiveness of these tumors, an active surveillance strategy can be discussed and should be balanced with the morbidity and functional consequences of pancreatic surgery.

Why Not Operate on a NF-pNET <2 cm?

Firstly, the risk of lymph node involvement in NF-pNETs <2 cm is considered to be relatively low in various studies and estimated at around 10%. Indeed, in a large and recent metaanalysis concerning 13 374 patients operated on for pNETs, the rate of LN involvement was around 11% for these small NF-pNETs <2 cm [5]. Furthermore, this risk of LN involvement can be even lower in selected patients considered to be at low risk: (i) with a tumor of 2 cm or smaller on preoperative imaging, (ii) with no bile or pancreatic duct dilation, (iii) being asymptomatic, (iv) with no enlarged lymph node or distant metastasis in imaging studies, and (v) WHO 2017 grade 1 [4,6]. In addition, the morbidity and mortality of pancreatic surgery are far from negligible. A study of the French national database of more than 22 000 patients undergoing pancreatic resection found that the overall postoperative mortality was 8.1% [7]. Additionally, postoperative morbidity was over 50% in the German ISGPS-based metaanalysis [8]. Thus, given the high morbidity and mortality of pancreatectomy, an initially nonsurgical

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strategy seems acceptable for selected patients at very low risk of LN involvement.

Additionally, the natural history of NF-pNETs <2 cm has been investigated and on follow-up of 34 months (still too short), neither tumor progression nor LN dissemination was observed [9]. Furthermore, the idea of operating on small and well-differentiated NF-pNETs, especially in young patients, to avoid the risk of tumor progression is nuanced by several data in the literature which suggest that there is no correlation between age and tumor aggressiveness [10]. According to these same authors, there is therefore an overtreatment of these tumors in young patients.

For all these reasons, a "watch and wait" strategy has been proposed and validated by the National Comprehensive Cancer Network (NCCN), the European Neuroendocrine Tumor Society (ENETS), and the European Society for Medical Oncology (ESMO) [11,12] for asymptomatic NF-pNETs <2 cm, grade 1 with neither signs of radiologic progression nor suspicion of LN involvement and distant metastases.

Why Operate on a NF-pNET <2 cm?

Nevertheless, this active surveillance strategy is still debated in the literature, with contradictory results. Indeed, in a SEER national database study of 263 NF-pNETs <2 cm [2], the rates of extrapancreatic extension, LN involvement, and distant metastases were ultimately higher, respectively 17.9%, 27.3%, and 9.1%. In addition, the five-year overall survival (OS) for these tumors was 85%. In a recent study of the national NCDB database, a multivariate analysis showed that patients with NF-pNETs of 1–2 cm had a better OS after surgery than those without surgery (hazard ratio [HR] 0.55; P <0.001) [13]. Similar results were found in the study by Sharpe et al. that concerned 380 patients with pNET <2 cm, in whom the risk of all-cause mortality was increased in the non-operated group compared to the operated group in multivariate analysis (HR 2.8; P = 0.0103) [14].

However, although the idea of an aggressive surgical strategy for small NF-pNETs is supported by several authors, the 2 cm cut-off is also debated. In a multicenter retrospective study, Dong et al. demonstrated that patients with small NF-pNETs had a higher risk of LN metastasis for tumor size 1.5–2 cm vs <1.5 cm (17.9% vs 8.7%; P = 0.015). They suggest the need to operate on patients with small NF-pNETs by performing systematic LN dissection for tumors over 1.5 cm [15]. In another multicenter retrospective study, a cut-off of 1.7 cm has also been proposed to predict the risk of malignancy with a sensitivity and specificity respectively of 92% and 75% [16].

In a recent systematic review and metaanalysis by Ricci et al. [17], even if the malignancy rate in sporadic and small pancreatic neuroendocrine neoplasms was lower than in large ones, for the authors this difference did not justify a "watch and wait" policy. They also pointed out several methodologic problems with the studies evaluating the "watch and wait" strategy, notably the retrospective nature of these studies with their inherent bias and the insufficient follow-up given the long life expectancy of these patients which prevents us from fully appreciating the true natural history of small NF-pNETs.

Moreover, in a recent study comparing the use of surgery and active surveillance in a population of asymptomatic NF-pNETs <2 cm, it was found that in clinical practice many parameters are taken into account in the decision to perform surgery in addition to those issued by international recommendations. These included patient preferences (32%), strong positivity at ^{18}FDG-PET/CT-scan (21.5%), young age of the patient (14.5%), and cytologically determined grade 2 tumors (14.5%) [18].

Finally, this conflicting literature highlights the difficulty in correctly standardizing the management of patients with NF-pNETs <2 cm and correctly distinguishing those who should be operated on from those who could be watched. It is also important to remember that any decision on the indication for surgery must take into account the patient's background and comorbidities and the type of surgery to be performed: pancreaticoduodenectomy vs distal pancreatectomy vs parenchyma-sparing pancreatectomy.

Summary

It remains to be determined whether NF-pNETs with "indolent" or "aggressive" behavior (since they cannot formally be called "benign" and "malignant") have a different, genetically unrelated carcinogenesis or if their progression follows the "adenoma–carcinoma sequence" and how to truly differentiate them [19]. What should be retained from this controversy is that if surgical resection is being considered for NF-pNETs <2 cm, a "watch and wait" strategy could be proposed in selected patients (i) with no bile or pancreatic duct dilation, (ii) who are asymptomatic, (iii) with no enlarged lymph node or distant metastases in imaging studies, (iv) WHO 2017 grade 1, (v) positive SRS imaging and negative ^{18}FDG-PET/CT-scan, (vi) candidate for pancreaticoduodenectomy, and/or (vii) with significant comorbidity. The most consensual cut-off is set at 2 cm.

A synthetic management algorithm is proposed to highlight the crucial elements involved in the discussion (Figure 110.1), and the factors that need to be taken into account are summarized in Table 110.1. Finally, there is no debate about the need to operate on patients with symptomatic NF-pNETs <2 cm or with suspected lymph node involvement. A prospective observational study,

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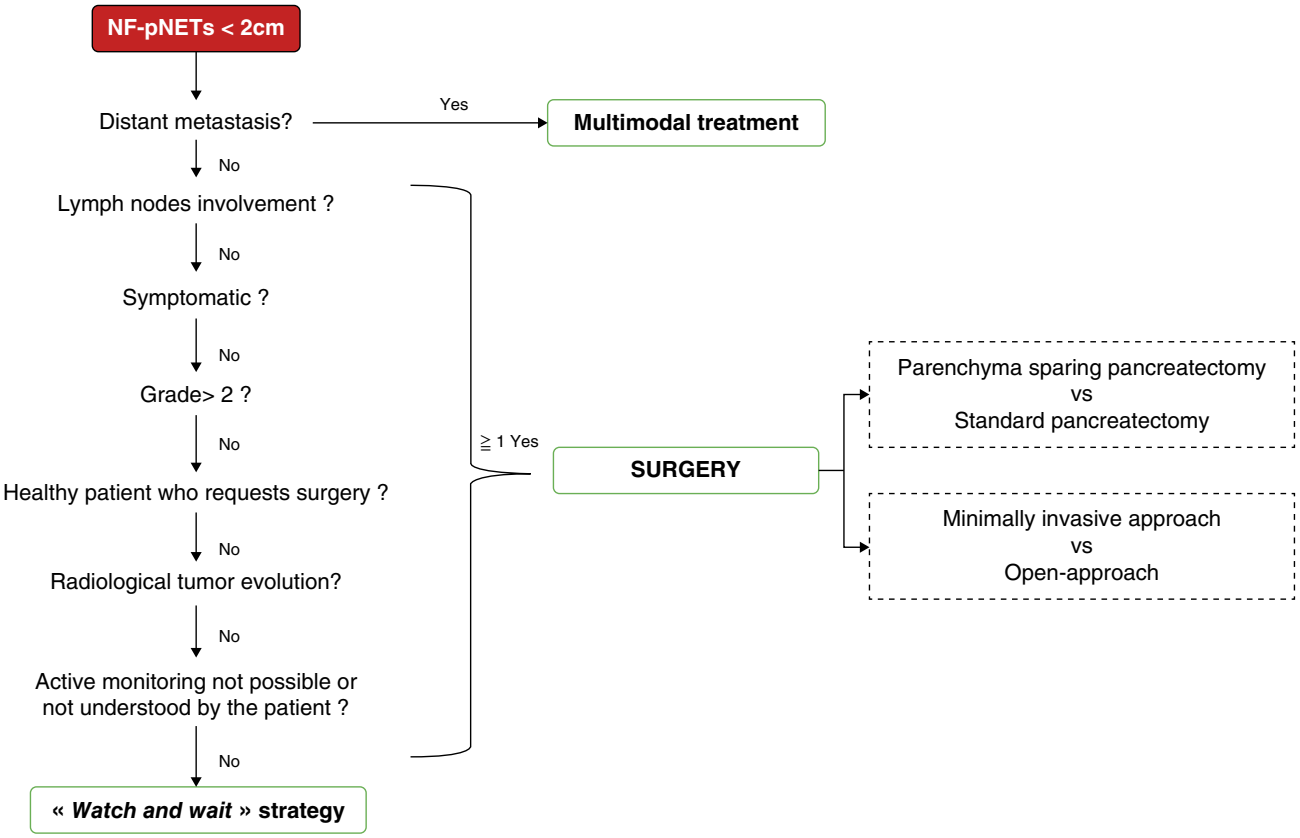


Figure 110.1 Algorithm for the therapeutic management of NF-pNETs <2 cm.

Table 110.1 Summary of the main arguments for the surgical approach and surveillance strategy for asymptomatic and well-differentiated NF-pNETs.

Why NOT operate on NF-pNETs <2 cm?	Why operate on NF-pNETs <2 cm?
High morbidity and mortality rates after pancreatectomy	Avoids excessive radiation from surveillance (especially in the young population)
Very low aggressiveness of these tumors according to retrospective studies	Definitive histologic evidence and better tumor staging (notably nodal involvement)
Low risk of lymph node involvement (<10%)	Benefit in terms of overall survival
Apparently, no relationship between age, disease duration, and tumor aggressiveness	The long-term natural history of these tumors is not well known
No clear argument in the literature to support a typical sequence: dysplasia–adenoma–carcinoma	

No ranking was made according to the importance of each argument.

the ASPEN study, is currently under way to better understand the natural history of asymptomatic NF-pNETS <2 cm and to provide more precision on the place of the "watch and wait" strategy [20].

Surgical Management

When surgery has been chosen for specific patients and tumors, the remaining questions are: when and how to operate?

Where Should Patients Be Operated On?

There is no doubt that the management of pNETs requires significant expertise. There is a consensus on the need to treat these patients in expert centers and this is particularly the case for pancreatic surgery in which the relationship between the volume of activity and postoperative outcomes has been extensively confirmed in the literature. For example, in the metaanalysis of Hata et al. involving 58 023 patients who underwent

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pancreaticoduodenectomy, the postoperative mortality rate was significantly higher in low-volume centers than in high-volume centers (odds ratio [OR] 2.37; 95% confidence interval [CI] 1.95–2.88) [21]. In addition, in a retrospective study of 899 patients managed for gastroenteropancreatic neuroendocrine tumors, results showed a lower survival rate for patients treated in a low-volume hospital (HR 0.63; 95% CI 0.4–0.9) [22]. Lastly, the definition of a high-volume center is not consensual and varies between studies, but a reasonable threshold of >20–25 procedures per year seems acceptable [7,23].

What Kind of Surgery?

Choice Between Standard and Parenchyma-sparing Pancreatectomy

Pancreatic surgery can be divided into standard pancreatectomy (SP) and parenchyma-sparing pancreatectomy (PSP). SP includes pancreaticoduodenectomy (PD) for tumor localized in the head of the pancreas and distal pancreatectomy (DP) for tumor localized in the body and tail. Both allow resection with satisfactory oncologic criteria, i.e., lateral and deep margins while ensuring extensive lymphadenectomy. Nevertheless, they lead on the one hand to the resection of a significant part of the healthy pancreatic parenchyma, responsible for frequent endocrine and exocrine pancreatic insufficiencies in the long term, and on the other hand to significant morbidity and mortality in the short term [7,24].

Parenchyma-sparing pancreatectomy is a more conservative surgical approach that involves targeted resection of the tumor to minimize the sacrifice of pancreatic parenchyma. It includes central pancreatectomy (CP) for tumor localized on the isthmus, and enucleation, regardless of the location on the pancreatic gland, but usually in the head as an alternative to pancreaticoduodenectomy. Because of this more targeted resection, this approach avoids pancreatic insufficiency in the long term, but does not allow for formal lymph node dissection, but at best a peritumoral "cherry picking." It is therefore generally indicated for benign or low malignant potential tumors. In addition, CP has a high complication rate, notably postoperative pancreatic fistula (POPF) due to the existence of a pancreatic stump and a pancreatico-digestive anastomosis [25].

Finally, enucleation has usually a lower complication rate than the other pancreatectomies but can only be performed for tumors located more than 2–3 mm distant from the main pancreatic duct to avoid damage which would lead to a significant risk of POPF and the need to convert the surgery to a SP [26].

We therefore acknowledge that each of these techniques has advantages and disadvantages, summarized in Table 110.2, and which form the basis of

Table 110.2 Characteristics of the different pancreatectomy techniques.

		Pancreaticoduodenectomy [27–29]	Distal pancreatectomy [30–33]	Enucleation [26,30]	Central pancreatectomy [25,30]
Complications	Mortality[a]	3–5%	2%	1%	3–5%
	Overall morbidity	50%	30–50%	40–50%	60–70%
	POPF (grade B + C)[b]	20%	20–30%	20–40%	40%
	Endocrine pancreatic insufficiency [34]	10–20%	20–35%	<7%	2–5%
	Exocrine pancreatic insufficiency [35]	50–60%	10–30%	<3%	4–10%
Advantages		LND Bulk resection[c]	LND Bulk resection[c]	No pancreatic insufficiency	No pancreatic insufficiency
Disadvantage		Pancreatic insufficiencies Functional problems Bilio-digestive anastomosis[d]	Pancreatic insufficiencies Functional problems	No LND Only superficial tumor Risk of positive margins	No LND Many postoperative complications Risk of positive margins

[a] These numbers are for the expert centers. Mortality is more like 9.2% and 6.2% for PD and PD respectively outside expert centers [7].
[b] According to ISGPS 2017.
[c] Also allows the resection of other possibly associated pNETs in the same resection piece.
[d] Contraindicates certain therapies like arterial embolization in the context of liver neuroendocrine metastases [36].
LND, lymph node dissection; POPF, postoperative pancreatic fistula.

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the discussion on the type of surgery indicated for NF-pNETs <2 cm.

Once a surgical indication has been decided, SP can technically be performed for all nonmetastatic NF-pNETs <2 cm. This is indicated when there is a doubt about preoperative LN invasion. Kasai et al. have proposed a preoperative risk stratification of lymph nodes metastasis for NF-pNETs based on tumor size, <50% cystic component and dilation of the main pancreatic duct to predict malignant potential and determine the necessity of LN dissection [37]. In DP, splenic preservation is possible if the tumor or metastatic LN does not invade the spleen or hilum, ideally with vessel resection (Warshaw procedure) to ensure adequate LN dissection.

Moreover, as discussed above, NF-pNETs <2 cm have a low risk of LN dissemination. It is therefore legitimate to propose a PSP when a surgical indication is considered [38], all the more if the patient is young and in good health, in whom the interest of avoiding long-term pancreatic insufficiency seems essential. However, in symptomatic NF-pNETs <2 cm, the feasibility of PSP (including enucleation) should be rediscussed according to the suspected risk of LN invasion.

There is some debate about the number of LN required on the resection specimen in the case where SP has been decided. According to studies, the number varies between 11 and 13, but by analogy with pancreatic adenocarcinoma, the most commonly accepted cut-off point is 12 LN removed [39]. Nevertheless, at least a lymph node picking should be done to assess N status.

Which Approach?

A minimally invasive approach (including laparoscopy and robot-assisted) has become the standard of care for many surgical procedures [40,41], reducing intraoperative blood loss, length of hospital stay and postoperative pain while ensuring a satisfactory oncologic outcome [42]. Nevertheless, its place in pancreatic surgery is not consensual [43].

In the case of PD, the laparoscopic approach is nowadays not recommended in routine practice. Indeed, a randomized controlled trial comparing laparoscopic vs open approach for PD was stopped prematurely because of excess mortality (10% vs 2%) [28]. In addition, some studies report on the robotic-assisted approach to PD and its value in performing anastomoses due to the three-dimensional vision and degrees of instrument mobility in all planes [29]. However, no recommendation has been defined yet to validate this approach in PD. This consideration can be extended to the central pancreatectomy that requires a pancreatic anastomosis.

In the case of DP, several trials, including randomized ones, report on the laparoscopic approach with satisfactory short-term results: shorter length of hospital stay, fewer severe complications, faster functional recovery, and less postoperative pain [32,33,43]. The laparoscopic approach seems to have at least equivalent results to the open approach in enucleation cases [30]. Systematic metaanalyses have produced encouraging results on the use of laparoscopy for pNETs [44] with a benefit of short-term postoperative outcomes. For these reasons, the ENETS recommendations consider that a minimally invasive approach could be proposed for DP, ensuring that the oncologic criteria are scrupulously respected (resection margins and quality of LN dissection if performed) [38]. This can be extended to enucleation that does not require a pancreatic anastomosis.

The Place of Surgery for NF-pNETs <2 cm in the Metastatic Context

The management of NF-pNETs <2 cm in the context of metastases can reasonably be done by analogy with publications evaluating the management of pNETs in the same context. The risk of metastasis at the time of diagnosis of NF-pNETs <2 cm is low in the literature, of the order of 9–10% of cases, and the preferred location is the liver as for all other pNETs [2]. Extrahepatic location is a contraindication to surgical resection due to the poor prognosis of these tumors [45]. The same applies to G3 pNETs with liver metastases for which the risk of recurrence is considered too high [38,46].

The management of NF-pNETs with synchronous metastases is conditioned by the resectability of the hepatic lesions. For patients with G1 or G2 NF-pNETs with resectable liver metastases, radical resection appears to be associated with increased disease-free survival, especially if it is a single metastasis (five-year disease-free survival: 100% for single metastasis and 51% for diffuse liver metastases) [47]. For patients with non-resectable liver metastases, primary resection of NF-pNETs seems controversial. In the case of a primary tumor located in the head of the pancreas, palliative resection of the pancreas employing PD seems unreasonable given the need to perform a biliary-digestive anastomosis which would contraindicate several medical therapies, notably chemoembolization [36]. In this case, and only if there is a local complication related to the tumor, other alternatives should be proposed (endoscopic drainage, gastroduodenal bypass, etc.) [46]. Nevertheless, for some patients with NF-pNETs G1 and G2 with tumor localized in the body or tail of the pancreas, resection of the primary tumor would appear to improve survival [38,46,48].

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Long-term Outcomes and Follow-up

In the retrospective study of Assi et al. based on 2004 nonmetastatic well-differentiated NF-pNETs from the NCDB database, complete surgical resection provides a five-year OS rate of nearly 100%, 92%, and 89% for NF-pNETs <1 cm, 1–2 cm, and >2 cm respectively [49]. These OS rates are higher than in older studies (around 70% at five years), a difference that may be attributed to the initial presentation of these tumors which are diagnosed earlier. For small NF-pNETs, there does not appear to be any difference in OS between PSP and SP. Nevertheless, it cannot be denied that tumors resected by PSP had a more favorable clinical presentation, which obliges us to remain cautious about the interpretation of these results.

Moreover, in a recent metaanalysis, based on 2754 NF-pNETs operated on, the rate of disease recurrence was 21%, but this includes lesions over 2 cm. It was correlated with nodal metastases, tumor grade G2–3, microvascular invasion, and perineural invasion. However, no relationship was found between T stage, resection margins status, and disease recurrence. A scoring system has also been proposed to predict the rate of disease recurrence [50]. This would make it possible to better select patients at risk in order to offer personalized follow-up.

Long-term outcomes according to the type of surgery are mainly determined by the rate of endocrine and exocrine pancreatic insufficiencies (see Table 110.2). Thus, exocrine pancreatic insufficiency is maximal after pancreaticoduodenectomy (up to 60%) but almost absent after enucleation. It is an often misdiagnosed complication with a significant impact on quality of life [35]. The treatment is simple and based on supplementation with pancreatic enzyme. Regarding endocrine pancreatic insufficiency, there is a higher proportion of *de novo* diabetes after SP and especially after distal pancreatectomy (around 30%). This might be explained quite simply by the preferential distribution of β-cells and islets of Langerhans (responsible for insulin secretion) in the tail of the pancreas [51]. In a recent retrospective study of 268 patients operated on for pNETs (including 261 NF-pNETs) [34], the rate of postoperative diabetes (*de novo* or worsening of preexisting diabetes) was 21% and 7% for SP and PSP respectively. The authors demonstrated by multivariate analysis that postoperative diabetes was associated with a significant risk of tumor recurrence, independent of main prognostic factors and type of pancreatic surgery. This result is explained by the fact that diabetes mellitus has a known prooncogenic effect on some cancers, including pancreatic and gastrointestinal cancers [52].

Patients operated on for pNETs need long-term follow-up with clinical and biological (chromogranin A) checks and CT scan usually every six months. It is also reasonable to suggest that initially positive somatostatin receptor imaging (notably ^{68}Ga-DOTATOC PET/CT-scan) can be performed at baseline, and then every two years or in any doubtful situation. This prolonged follow-up is necessary because most recurrences occur after 5–10 years [11,38,46].

Conclusion

The management of pNETs and more specifically of small NF-pNETs (<2 cm) is particularly complex. It requires a multidisciplinary evaluation within expert centers with surgeons, gastroenterologists, oncologists, geneticists, radiologists, and pathologists. For NF-pNETs <2 cm, two options can be considered: a "watch and wait" strategy or a surgical resection. The choice between SP with LN dissection and PSP depends on the characteristics of the tumor, the presence of preoperative LN invasion, and the patient's condition. The laparoscopic approach is commonly accepted and encouraged except for PD. In selected patients, it is possible to propose a "watch and wait" strategy, but it is important to remember that long-term data are still lacking for this strategy.

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111

Surgical Treatment of Endocrine Tumors: Major Oncologic Resection

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Introduction

Over the past two decades, pancreatic neuroendocrine tumors (PanNET) in general, not just small tumors <2 cm in greatest dimension, have become more frequent worldwide [1–8]. Among large PanNET, 90% of tumors are nonfunctioning [2], and about 40% have spread to distant organs at the time of diagnosis [8]. Whereas patient age is by and large comparable in patients with small and large sporadic tumors, greater primary tumor size correlates positively with lymph node and distant metastases, lower histopathologic grading, and extrapancreatic extension [1,5–9] Although resection of the primary tumor, even when metastases are present, may prolong survival, the considerable morbidity inherent in major pancreatic resection limits the net benefit of extended surgery for locally advanced and metastasized PanNET [10–13].

Clinical Work-up of Advanced PanNET for Major Oncologic Resection

Unlike functional PanNETs that present with signs and symptoms of hormone excess, such as insulinoma, gastrinoma, and the rare glucagonoma, vasoactive intestinal peptide-releasing tumor (VIPoma), or somatostatinoma, nonfunctioning PanNETs manifest with symptoms caused by tumor expansion, invasion, or metastatic disease. Nonfunctioning PanNETs often reside in the pancreatic head, mimicking pancreatic adenocarcinoma, and compress adjacent organs, giving rise to jaundice, abdominal pain, weight loss, nausea and vomiting, back pain, and occasionally pancreatitis [2]. About 10% of PanNETs are inherited in the context of multiple endocrine neoplasia type 1 (MEN 1), von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and the tuberous sclerosis complex (TSC). Patients with hereditary PanNET typically are younger than patients with sporadic PanNET, have multiple lesions scattered throughout the pancreas, and often yield a positive family history. MEN 1-associated PanNET often comprises functioning and nonfunctioning tumors [14,15], necessitating more customized treatment plans than are required for solitary sporadic PanNET (Fig. 111.1) [16,17].

Diagnosis and extent of PanNET are established by cross-sectional (computed tomography [CT]; magnetic resonance imaging [MRI]) [18–20] and functional imaging (somatostatin receptor scintigraphy) in conjunction with [^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) [21,22] and percutaneous or endoscopic ultrasound (EUS)-guided biopsy [23–26]. Because treatment concepts for metastatic exocrine and endocrine cancers differ tremendously, biopsy of the primary tumor or its metastasis takes center stage in differentiating pancreatic adenocarcinoma from PanNET. Clinical staging and grading of the PanNET afford stratification of patients into prognostic subgroups and facilitate individualized treatment concepts [27–29]. Ki-67 immunocytology, using World Health Organization (WHO)-defined categories of 0–3% (grade 1), 3–20% (grade 2), and >20% (grade 3) [30], helps estimate the patient's risk of recurrence and survival [3,7,31–33].

The separation of neuroendocrine cancers (NECs) from highly proliferative, well-differentiated NETs prompted calls for biomarkers that distinguish NECs

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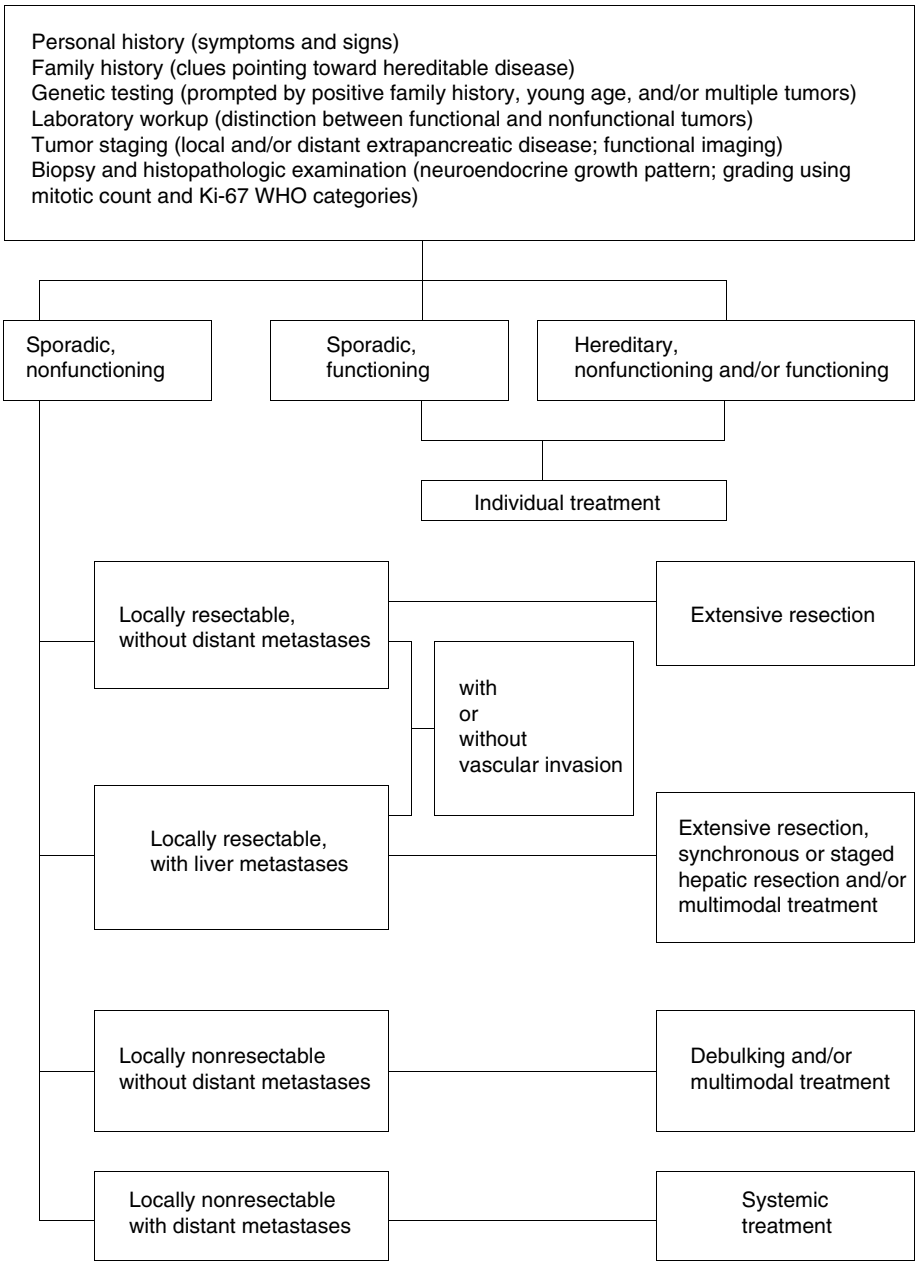


Figure 111.1 Algorithm for clinical work-up and surgical treatment of advanced PanNET.

from G3 NETs because the latter, unlike the former, typically qualify for major oncologic resection [30]. For WHO grades 1, 2, and 3, five-year overall survival has been estimated at 77%, 63%, and 20%, respectively [8]. With a Ki-67 score of <2%, the likelihood is remote that the cancer extends beyond the pancreas, invades great vessels, is metastatic, or will recur [3,31]. Most studies support the notion that poor tumor differentiation, WHO grade 3, and distant metastases are closely connected to PanNET-specific mortality [31,34–39].

Surgical Approach to Locally Advanced Nonfunctioning PanNET Without Clinical Evidence of Distant Metastases

Based on preoperative imaging and intraoperative exploration, locally advanced nonfunctioning PanNETs are defined as large tumors frequently invading parapancreatic organs such as the stomach, spleen, colon, kidney, or adrenal gland, and/or great vessels, namely the mesentericoportal vein, superior mesenteric artery, or celiac

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trunk. Lymph node metastases may evade imaging [40,41] but if clinically apparent, often herald systemic disease. As positive lymph nodes have been identified as a risk factor for early recurrence [42], regional lymph node dissection has become an integral element of surgery for advanced disease.

Given the unavailability of equally effective nonsurgical treatment options, resection of a locally advanced nonfunctioning PanNET at institutions experienced in pancreatic surgery is the method of choice [11–13,32,40]. Provided that clear surgical margins are achievable, resection of neighboring organs and great vessels seems worthwhile [39,40]. Multivisceral resection of advanced (pT3/pT4) PanNETs frequently includes the spleen (>70%) but also major vessels (17%), stomach (4%), bowel (2%), and kidney (2%) [11]. Retrospective data suggest that complication rates after multivisceral resection are comparable to those after standard surgery [43]. Resection of the mesentericoportal axis is almost always feasible (Fig. 111.2) and requires only rarely the use of an autologous vein, or prosthetic material for reconstruction [44–50]. Although it has been shown not to increase surgical morbidity in patients with PanNET, macrovascular venous invasion is associated with significantly worse median overall survival (60 vs 149 months) [51].

Conversely, arterial resection and reconstruction (Figs 111.3, 111.4, and 111.5) are much more complex [52–56] and entail incremental surgical morbidity and mortality [57,58]. The decision to embark on resection of great arteries needs to be pondered carefully, taking into account patient age and comorbidity, stage and grade of the PanNET, extent of tumor invasion of the artery (celiac/hepatic artery and/or superior mesenteric artery without or with invasion of the mesentericoportal vein), and the condition of the artery itself (presence or absence of arteriosclerosis). However, systematic clinical

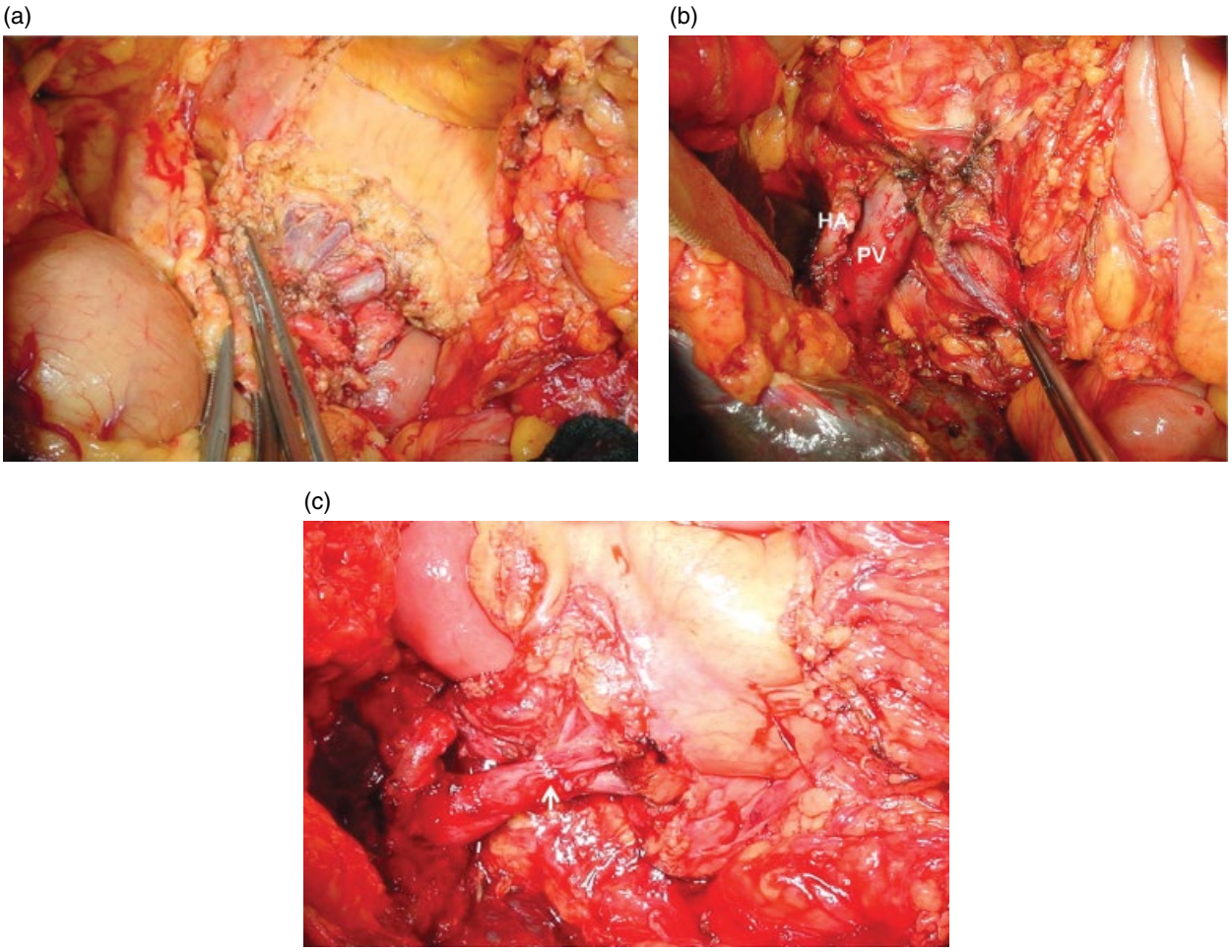


Figure 111.2 Neuroendocrine carcinoma of the pancreatic uncinate process invading the mesentericoportal vein. (a) Infrapancreatic clamping of the superior mesenteric vein; (b) dissection of the portal vein (PV) and hepatic artery (HA); (c) end-to-end anastomosis of the mesentericoportal vein (arrow).

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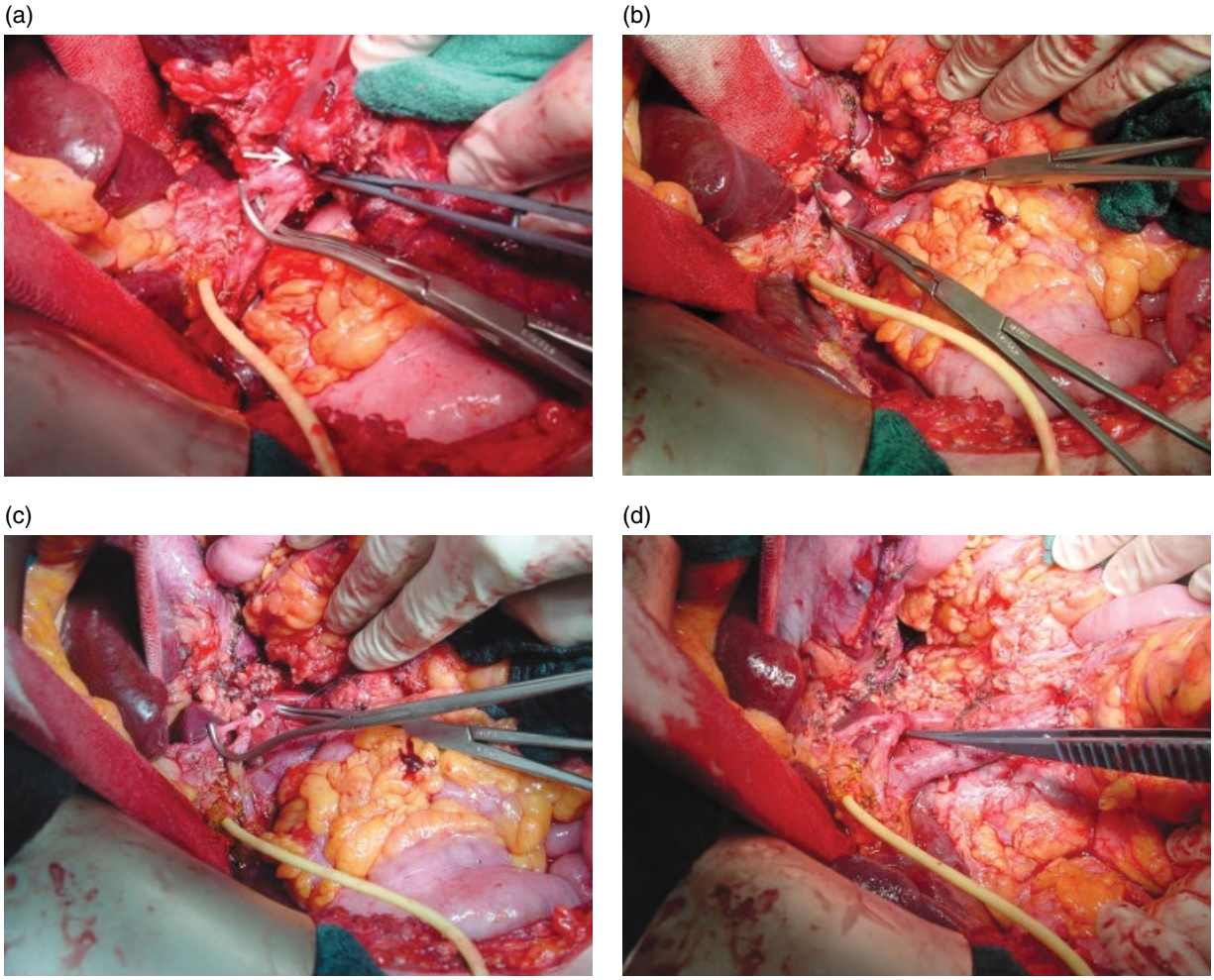


Figure 111.3 Neuroendocrine carcinoma of the pancreatic head invading the hepatic artery. (a) Operative view of the invaded hepatic artery (arrow); (b–d) resection of the invaded hepatic artery segment and reconstruction by end-to-end anastomosis.

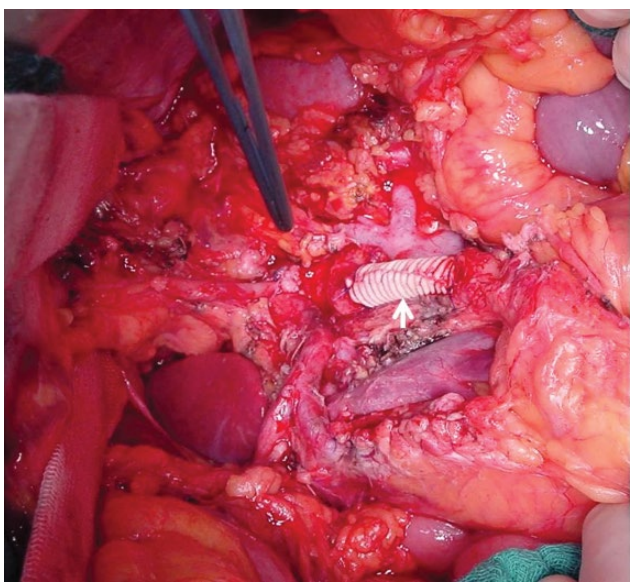


Figure 111.4 Neuroendocrine carcinoma of the pancreatic body invading the superior mesenteric artery: operative situs after resection and prosthetic reconstruction (arrow).

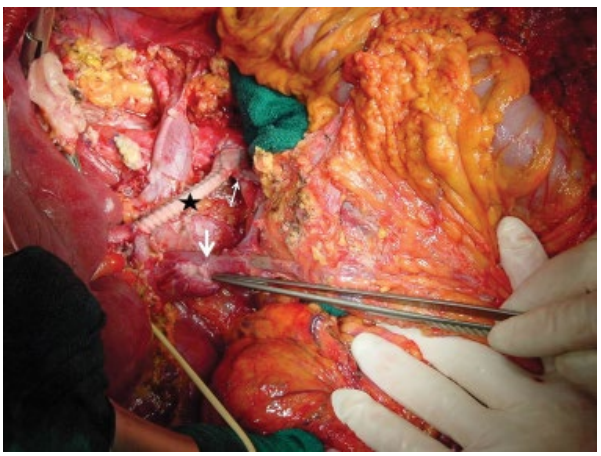


Figure 111.5 Neuroendocrine carcinoma of the pancreatic body encroaching onto the pancreatic head and tail and invading the superior mesenteric artery, superior mesenteric vein, and hepatic artery: operative situs after total pancreatectomy, three-vessel resection, end-to-end-reconstruction of the superior mesenteric vein (thick arrow) and arterial reconstruction using a Y-shaped prosthesis connecting the hepatic (asterisk) and superior mesenteric (thin arrow) arteries with the aorta.

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outcome studies after resection and reconstruction of one, two, or more major vessels invaded by PanNET (see Fig. 111.5) are unavailable because of the rarity of the condition [52,54].

In the absence of evidence-based information, best judgment should be exercised to determine, on a highly selective basis, whether to resect major arteries invaded by nonfunctioning locally advanced PanNET. Importantly, recent data indicate that pancreatic surgery for large PanNET does not improve cancer-specific survival in patients aged 80 or older, nor in patients aged 70 or older who harbored small (<20 mm) primary tumors [59].

A number of studies have explored the effectiveness of neoadjuvant therapies for locally advanced and metastatic PanNETs [60]. These treatments included various combinations of capecitabine/temozolomide or streptozotocin/5-fluorouracil, which produced partial responses and tumor shrinkage [61–63]. Other studies that evaluated the feasibility of neoadjuvant peptide receptor therapy significantly reduced tumor size and enabled resection of previously unresectable primary tumors in up to one-quarter of patients [64,65].

To clarify resectability, the greatest tumor extension outside the pancreas needs to be explored first. For invasion of the mesentericoportal axis below the pancreas, the infrapancreatic/infracolonic approach (Fig. 111.6) is a natural choice. When major branches of the superior mesenteric vein are invaded, complete resection of the tumor is unfeasible and should not be attempted. Major arteries invaded by tumor, such as the superior mesenteric or hepatic artery, are best resected toward the end of pancreatic surgery to allow immediate arterial reconstruction, keeping ischemia time to a minimum. Arterial reconstruction is accomplished directly, or with the use of autologous or prosthetic material. Resection of the splenic vein alone does not warrant reconstruction [66]. In one study, segmental portal hypertension was not associated with increased mortality or severe morbidity after surgery for advanced PanNET [67].

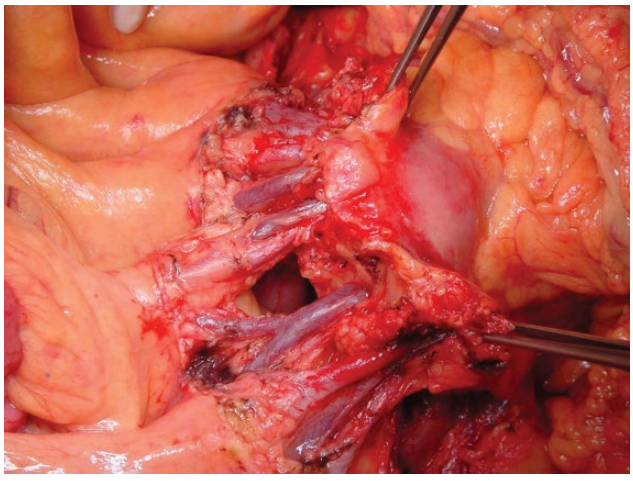


Figure 111.6 Infracolonic dissection of the superior mesenteric vein and its branches, fenestrating the transverse mesocolon to gain access to a locally advanced PanNET of the pancreatic head.

Locally Advanced Nonfunctioning PanNET with Clinical Evidence of Distant Metastases

Larger primary PanNET are often associated not only with invasion of adjacent organs and major vessels and more frequent lymph node metastasis, but also with liver metastases [7]. Extensive surgery for locally advanced PanNETs with liver metastases, even though it may prolong survival, is controversial regardless of whether the metastases are resectable or not [68–73]. Clinically, PanNETs present in more than 50% of patients with liver metastases as the only systemic manifestation, which are unresectable in 80% of patients [68].

For locally advanced PanNETs without or with liver metastasis alone, or with liver metastasis as only one manifestation of systemic disease, there are no systematic outcome studies regarding the benefit of resection of the primary tumor so that the role of surgery remains to be defined for a wide range of clinical settings: symptomatic versus asymptomatic PanNET, with or without liver or other remote resectable or unresectable metastases; number and size of liver metastases; location of the primary tumor within the pancreas (head versus body or tail); and tumor grade and differentiation.

In light of the current literature, and subject to interdisciplinary consensus taking into account the circumstances of the case, it may be reasonable to suggest the following courses of action.

- For patients with *locally advanced PanNETs with resectable liver metastases*, resection of the primary tumor should be considered, especially when the tumor is symptomatic [39]. The issue of whether liver resection should take place in the same surgical session or whether a staged approach should rather be pursued depends on the extent of resection and the patient's condition [69,71]. A recent metaanalysis found that liver resection improved symptom relief and survival compared with nonsurgical therapy [72].
- Patients with *unresectable liver metastases of locally advanced PanNETs* also may benefit from resection of the primary tumor. In a single-center study of

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43 patients with PanNET and unresectable liver metastasis, the five-year disease-specific survival was 82% in the operative group compared with 50% in the nonsurgical group (P = 0.027). On multivariate analysis, not only removal of the primary tumor but also younger patient age, a lower Ki-67 index, and a liver tumor burden <25% were associated with better disease-specific survival [68].

- Patients with *locally advanced PanNET and liver metastases as only one manifestation of systemic disease* are candidates for surgery only in exceptional circumstances, even when the liver metastases should be resectable. In these highly selected patients, the limited clinical effects of resection need to be carefully balanced with the benefits of nonsurgical treatment options [39,74,75].

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112

The Management of Insulinoma

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Introduction

Insulinoma is the most common functional neuroendocrine neoplasm (NEN) [1–5]. As symptoms of hyperinsulinemic hypoglycemia are varied and nonspecific, diagnosis of insulinoma is sometimes difficult. Therefore, a cautious diagnostic approach is taken to detect the presence of insulinoma and localize the tumors [1,2,5]. Most insulinomas are benign, and surgical resection can bring about complete cure. However, in incurable cases, hormonal symptoms are difficult to control, requiring multidisciplinary therapy tailored to each patient [1,3–5].

Clinical Features of Insulinomas

Insulinoma is a very rare disease, developing in 1–32 individuals per 1 million population a year [1–4]. Insulinoma presents characteristically in the fifth decade of life, and has a predilection for women (41% male and 59% female) [2,4]. Among functional NENs, insulinomas occur most frequently. Over 99% of insulinomas occur in the pancreas [1–3]. The majority of these tumors are sporadic, solitary, and small in size (≤2.0 cm) [2,4]; 4–12% of cases are associated with multiple endocrine neoplasia type 1 (ME1), and ME1-associated insulinomas are often multiple [6–9]. About 90% of insulinoma are benign, and surgical resection can bring about complete cure [1–3,6]. The remaining 10% are malignant insulinomas with distant metastasis at the time of diagnosis; the five-year relative survival rate is 55.6% [1,3,10,11].

Hypoglycemic symptoms in insulinomas are divided into two major categories: neuroglycopenic symptoms, such as confusion, visual changes, amnesia, and coma; and adrenergic symptoms, such as sweating, weakness, and tremors (Table 112.1) [4,9,12,13]. Hypoglycemic symptoms occur most frequently in the fasting state but they may occur in both fasting and postprandial state in 18–21% of patients, and only postprandial in 6% [1,13].

The classic diagnosis of insulinoma is via Whipple's triad (presence of hypoglycemic symptoms, blood glucose level under 50 mg/dL at the time of symptom onset, improvement of symptoms after glucose intake) [1,2,4,5]. Although insulinoma is the most frequent cause of adult hypoglycemia, there are other various hypoglycemia-causing diseases that require differentiation, and therefore cautious diagnosis is important [2,4,7–9].

Diagnosis of Insulinomas

When excessive endogenous insulin secretion is observed during hypoglycemia, insulinoma should be suspected [1,4,5,11,14]. When spontaneous hypoglycemia is observed, blood is drawn to measure plasma glucose (PG), serum levels of immunoreactive insulin (IRI), proinsulin, C-peptide, and β-hydroxybutyrate (BHOB) [13–19]. According to the United States Endocrine Society Clinical Practice Guideline, the diagnosis of insulinoma is confirmed by hypoglycemic symptoms and the following six diagnostic criteria [1]: (i) plasma glucose levels ≤3.0 mmol/L (≤50 mg/dL), (ii) insulin levels ≥3.0 μU/mL (≥18 pmol/L), (iii) C-peptide levels ≥0.6 ng/mL (0.2 nmol/L), (iv) proinsulin levels ≥5.0 pmol/L, (v) BHOB levels ≤2.7 mmol/L, and (vi) an increase in plasma glucose 1.4 mmol/L (≥25 mg/dL) after IV glucagon. When spontaneous hypoglycemia is not

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Table 112.1 Clinical symptoms and frequencies in patients with insulinoma.

Symptoms	Frequency (%)
Neuroglycopenic symptoms	
Confusion	67–80
Visual changes	42–59
Amnesia or coma	47
Altered consciousness	16–38
Seizures	16–17
Headache	7
Adrenergic symptoms	
Sweating	30–69
Weakness	28–56
Tremors	12–24
Hyperphasia	14
Palpitations	5–12
Anxiety	12
Obesity	<50

Data adapted from references Adapted from [6,23].

observed, the following tolerance tests are conducted to induce hypoglycemia, and the above parameters are measured.

Fasting Test (Table 112.2)

The 72-hour fasting test is the gold standard for the diagnosis of insulinoma [1–5,7,9,13,20]. In recent years, various insulin surrogates have become measurable, and some reports have indicated that the fasting period can be shortened to 48 hours [17,21]. For the fasting test, a patient needs to be hospitalized for blood collection every 4–8 hours under close medical supervision, for measurement of PG, IRI, proinsulin, and C-peptide [1,2,18–21]. PG ≤45 mg/dL with hypoglycemic symptoms is considered as a positive response. Positive results are obtained within 12 hours in 33–42.5%, within 24 hours in 65–66.9%, within 48 hours in 93–94.5%, and within 72 hours in 98.4–99% [17,20]. As hypoglycemic symptoms are often unnoticeable in patients with insulinoma, those symptoms should not be overlooked [17,22]. After the fasting test, serum levels of BHOB and free fatty acid are measured as supplementary data [15–17,21].

In rare insulinoma cases, positive results are not produced in the fasting test, and insulin is excessively secreted in response to glucagon or glucose loading, according to previous reports [21,23,24]. After the fasting test, glucagon 1.0 mg is intravenously injected, and PG is measured at 10, 20, and 30 minutes.

Table 112.2 Fasting test instructions.

1) Meal is eaten at 18:00, and the fasting test is started.
   - Medication is minimized, and unnecessary medicines are suspended.
   - No-calorie decaffeinated drinks can be taken.
   - The patient is instructed to engage in daily activities.
2) Blood is drawn every 6 hours.
   - Blood tests include plasma glucose (PG), immunoreactive insulin and C-peptide.
   - After PG is lowered to 60 mg/dL or below, blood is drawn every 1–2 hours.
3) Judgment is made as to whether the fasting test should be terminated.
   - PG ≤45 mg/dL and emergence of hypoglycemic symptoms are taken as a positive result for the fasting test, and the test is terminated.
   - When the result is negative, the test is terminated at 72 hours.
   - As PG ≤45 mg/dL may occur during fasting in healthy people (females in particular), the test should not be terminated only with PG decrease.
   - Even if PG ≤45 mg/dL is not achieved, the test can be terminated if hypoglycemic symptoms are severe. In such cases, the succeeding blood tests are carried out.
4) The following blood examinations are conducted at the end of the fasting test.
   - β-hydroxybutyrate and free fatty acid are measured.
   - Glucagon 1.0 mg is intravenously injected, and PG measurements are taken at 10, 20, and 30 minutes.
   - ΔPG = PG(max)−PG (baseline) is calculated to determine the response to glucagon.

   When insulin autoantibody syndrome is suspected, antiinsulin antibody and antiinsulin receptor antibody levels are measured.
5) Blood glucose level is promptly corrected after the test.

When ΔPG, defined as the difference between the maximum and baseline levels, is ≥25 mg/dL, insulinoma may be considered [1,15,21].

Mixed Meal Tolerance Test

Some insulinoma patients present with hypoglycemic symptoms only in the postprandial state [1,13]. Furthermore, it is important to differentiate noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) from insulinoma. As hypoglycemia often occurs after meal intake in NIPHS, it is important to carry out a mixed meal tolerance test [18,25]. In this test, fasting starts the night before the test, and the mixed meal tolerance test begins at breakfast. The meal consists of the items that are likely to induce hypoglycemia, or a commercially available mixed meal is used. Since reactive hypoglycemia often occurs over five hours after meal intake, observation is continued until five hours after the start of test [18,26].

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Localization of Insulinomas

In typical cases of insulinoma, the tumor is well vascularized and has a well-defined border. Its image is most enhanced in the arterial phase in dynamic CT imaging (Fig. 112.1) [27,28]. On magnetic resonance imaging (MRI), insulinomas generally show low signal intensity on fat-suppressed T1-weighted images and high signal intensity on T2-weighted images [27,28]. As the size of the insulinoma is small (under 2.0 cm) in 80%, and MEN 1-associated insulinoma often occurs at multiple sites, it is difficult to identify all tumors with conventional imaging [1,7–9,29]. The sensitivities of dynamic computed tomography (CT) and MRI are 45–63% and 54–85%, respectively [28–30]. The diagnostic ability of these tests is not sufficient, so these modalities are combined with

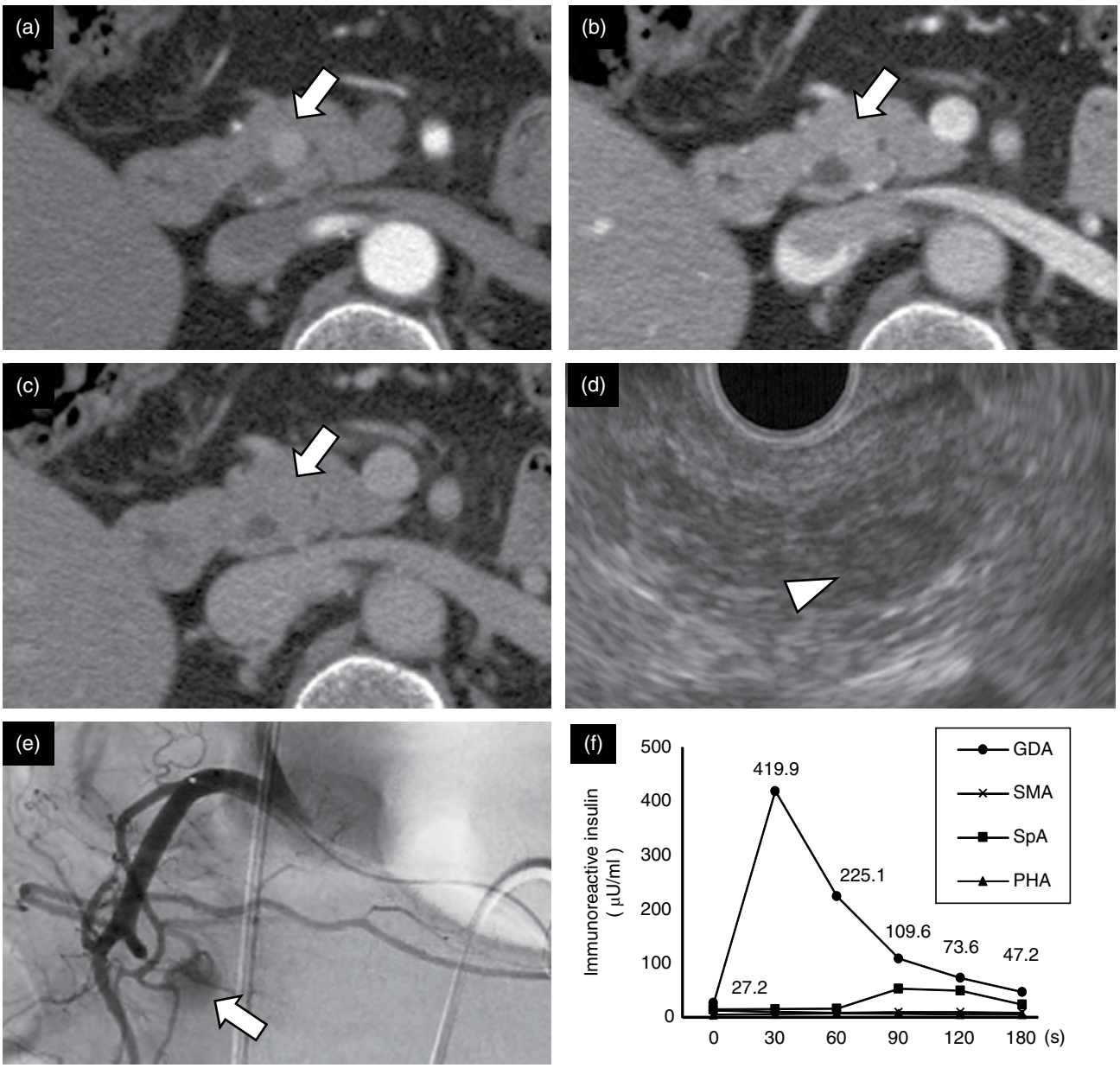


Figure 112.1 A 68-year-old woman with insulinoma at the pancreatic head. Abdominal CT imaging (a–c) shows an oval lesion with regular margins and well-defined borders, which is most enhanced in the early phase. The lesion cannot be identified in the portal phase/late phase (arrow). (d) EUS shows an oval hypoechoic mass with regular margins and well-defined borders (arrowhead). In the SACI test (e,f), a tumor is shown by gastroduodenal artery imaging, and the insulin level is markedly stepped up by GDA. The tumor localization by SACI test coincided with imaging findings.

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endoscopic ultrasonography (EUS), selective arterial calcium injection (SACI) test, and molecular imaging [1–4,14].

Endoscopic Ultrasonography

On EUS, insulinoma appears as an oval hypoechoic mass with a well-defined border; on color/power Doppler, it appears as a hypervascular pattern (see Fig. 112.1) [29,31,32]. Due to its high sensitivity (80–94%), EUS is more useful for localization of tumors, compared with CT or MRI [2,29,31,32]. EUS is especially effective for detection of small insulinomas, and when the size of the insulinoma is 12 mm or smaller, EUS is significantly superior to CT imaging [31].

Selective Arterial Calcium Injection (SACI) Test

The SACI test is useful when a tumor cannot be confirmed by other modalities (occult insulinoma) [1,5,33,34]. It is also useful in identifying insulinomas from among multiple pancreatic tumor masses in a MEN 1-associated case. For abdominal arterial angiography, calcium gluconate (0.025 mEq/kg) is injected from the feeding artery for each pancreatic region (gastroduodenal artery, superior mesenteric artery, splenic artery, etc.), and then IRI in hepatic venous blood is measured. Based on the increase in IRI, the location of insulinoma is determined (see Fig. 112.1) [33,34]. IRI is measured at baseline, 30, 60, 90, and 120 seconds, and a twofold or higher increase in IRI over baseline is considered positive. Sensitivity of SACI test for insulinoma is 82.2–100% and it produces excellent results [33,34].

Molecular Imaging (Scintigraphy, SPECT, PET/CT)

As the proliferative ability of insulinoma is low, ^{18}F-FDG PET/CT imaging of insulinomas is disappointing [1,30,35]. While ^{68}Ga-DOTATOC PET/CT, ^{111}In-pentetreotide scintigraphy, and SPECT are carried out for somatostatin receptor imaging, the expression rate of somatostatin receptor 2a is low in benign insulinomas, with a low positivity rate and sensitivity below 50% [29,30,35]. Meanwhile, the glucose-like peptide 1 (GLP-1) receptor is known to be highly expressed in more than 90% of insulinoma cases. Therefore, GLP-1 receptor imaging is considered useful[29,30,35-37].

To improve imaging of insulinomas, radiolabeled GLP-1R analogues for SPECT/CT imaging, such as ^{111}In-DOTA-exendin-4, ^{111}In-DTPA-exendin-4, and ^{99m}Tc-HYNIC-exendin-4, have been developed and evaluated in patients [29]. In recent reports, GLP-1 receptor SPECT/CT had 95–100% sensitivity [29]. In patients with occult insulinoma, ^{68}Ga-DOTA-exendin-4 PET/CT is superior to ^{111}In-DOTA-exendin-4 SPECT/CT [36].

Treatment of Insulinomas

Treatment of insulinomas can be divided into two categories: treatment of symptomatic hypoglycemia caused by excessive insulin secretion, and treatment of the tumor itself. Therefore, in treating insulinomas, hormone symptoms should be well controlled, while the tumor is simultaneously treated [1,3,5].

Treatment of Symptomatic Hypoglycemia

Firstly, small, frequent meals or oral/intravenous glucose supplementation is given [1,3,38]. As for medical therapy, diazoxide (50–300 mg/day, increasing up to 600 mg/day) is most useful [1,3,9]. Diazoxide directly acts on pancreatic β-cells, suppressing insulin secretion and thus improving hypoglycemic symptoms. Several days are required for stabilizing blood glucose, while edema, weight increase, deterioration of renal function, and hirsutism may occur as adverse reactions [1,3,4,13]. Other drugs such as glucocorticoids and glucagon injections are effective, according to some reports [3,13].

Somatostatin analogues, such as octreotide, pasireotide, and lanreotide, were effective for improving hypoglycemic symptoms in 35–50% of insulinoma cases [1,3,5]. The effects of somatostatin analogues depend upon the expression of somatostatin receptor subtypes 2, 3, and 5. Therefore, in cases of no or low expression of somatostatin receptor, hypoglycemia may be exacerbated by inhibiting the secretion of competitive hormones, such as glucagon [1,3,38,39].

In malignant insulinoma, the mTOR inhibitor everolimus is effective for control of excessive insulin secretion and hypoglycemic symptoms [40,41].

Treatment of Resectable Insulinoma (Surgical Treatment)

Surgical resection is a radical treatment for insulinoma [1,3,5,42]. Surgical procedures differ depending upon the size and number of tumors, the tumor location, and whether MEN 1 is present or not [1–5]. Blind resection is not recommended for the occult insulinoma that cannot be preoperatively localized [2,43–45]. In general, enucleation is possible if the insulinoma is 2 cm or smaller and its distance from the main pancreatic duct is about 2–3 mm. In the case of damage to the main pancreatic duct, pancreatic partial excision, segmental resection, pancreaticoduodenectomy or distal pancreatectomy is carried out [43–45]. In patients with ineligibility for or refusal of surgery, several studies have demonstrated the safety and efficacy of endoscopic ultrasound-guided radiofrequency ablation [1,46].

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Treatment of Unresectable Insulinoma

The therapeutic objectives in unresectable insulinoma cases are hormone symptom control and prolongation of prognosis [3,9,14,38]. Systemic chemotherapy for well-differentiated NEN (NET G1/G2) generally consists of a combination of streptozotocin and doxorubicin or fluorouracil. In recent years, dacarbazine- or temozolomide-based chemotherapy has also been used as the standard chemotherapy for insulinoma [14,38,47]. In 6–70% of well-differentiated NEN patients (insulinoma included), improvement of hormone symptoms or objective tumor response was demonstrated [38]. Among molecular target drugs, everolimus is considered effective against hormone oversecretion, and its antitumor effect has also been shown [40,41,48].

If medical therapy cannot sufficiently control hormone symptoms, tumor debulking surgery is sometimes conducted even in unresectable cases, targeting the removal of at least 90% of the tumor volume, with the objective of alleviating the symptoms [2,47,49].

Other therapies for unresectable NENs, including insulinoma, are liver-directed therapies (embolization, chemoembolization, radiofrequency ablation), laser-induced thermotherapy (LITT), selective internal radiotherapy (SIRT) using ^{90}Yttrium microspheres, peptide receptor radiotherapy (PRRT) with 177-Lutetium labeled somatostatin analogues, as well as liver transplant; alleviation of hormonal symptoms and improvement of prognosis have been reported [1,3,48–54].

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Evidence of Medical and Surgical Treatment of Gastrinoma

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Treatment Strategy

The goals of gastrinoma treatment are to manage gastric acid hypersecretion and to remove the risk of distant metastasis and ultimately death of the patient by resecting tumors that are usually malignant.

Treatment for gastrinoma has changed significantly since the syndrome was originally described in 1955 [1]. Initially, most patients developed severe symptoms and underwent emergency surgery for complications such as massive hemorrhage or perforation. Partial gastrectomy with or without vagotomy was insufficient so total gastrectomy became the standard operation for patients with gastrinoma [2].

The development of effective antisecretory drugs has drastically changed the management of gastrinoma [3]. In most patients, gastric acid hypersecretion can be controlled with antisecretory agents such as H_2-receptor antagonists and proton pump inhibitors. Because those agents are so effective, surgery for the control of gastric acid hypersecretion such as total gastrectomy is no longer required.

About 60% of gastrinomas are malignant and are the major cause of death during long-term follow-up, although they are relatively slow growing. Now, the roles of surgery are to remove the responsible tumor or tumors and prevent tumor progression and ultimately death.

Along with the increasing recognition of the duodenum as the most common site for gastrinomas, and with improved localization methods, at least 50% of patients with sporadic gastrinoma can be cured by tumor resection [1,4]. Therefore, an aggressive approach to tumor localization is strongly recommended in selecting patients for operative treatment.

Tumor Localization

Before surgical treatment, tumor localization studies are required in all patients with gastrinomas. Imaging techniques such as computed tomography (CT), ultrasonography (US), endoscopic ultrasonography (EUS), and intraoperative ultrasonography (IOU) have been useful for the localization of most neuroendocrine tumors greater than 2 cm in diameter [5]. However, imaging techniques have difficulty in visualizing neuroendocrine tumors smaller than 5 mm [5]. As gastrinoma shows characteristic symptoms even when smaller than 5 mm, the selective arterial secretagogue injection (SASI) test is useful for preoperative localization of gastrinoma leading to curative resection surgery [6–8]. Somatostatin receptor scintigraphy (SRS) and positron emission tomography (PET) with [68]Ga-DOTATOC are indispensable for localization of ectopic gastrinoma and the metastatic lesions of gastrinoma throughout the body [9,10].

Selective Arterial Secretagogue Injection Test with Secretin or Calcium

The SASl test was first described for localization of gastrinoma, and has gradually proved useful for the localization of other symptomatic pancreatic neuroendocrine tumors (panNETs) [6–8,11]. At the time of abdominal arteriography, secretagogue is injected into the splenic artery, gastroduodenal artery, and superior mesenteric artery (Fig. 113.1). Then 2 mL blood samples are drawn from the hepatic vein through a catheter inserted via the femoral vein before and at 20, 40, and 60 seconds after the injection of secretagogue to detect the change in gastrin levels in hepatic venous blood. When the rise in gastrin levels at

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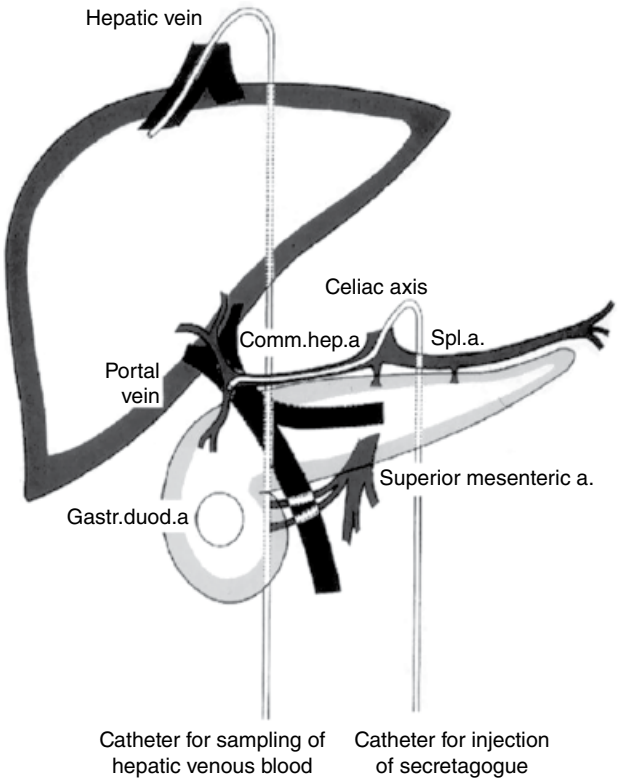


Figure 113.1 The selective arterial secretagogue injection test. Results of the selective arterial secretagogue injection (SASI) test in a patient with Zollinger–Ellison syndrome. In this patient, serum immunoreactive gastrin at 40 s after the injection of 30 units of secretin rose only after injection into the gastroduodenal artery. Hence it was diagnosed that the gastrioma(s) was located in the upper part of the pancreas and/or the duodenum. Gastr.duod.a, gastroduodenar artery; Spl.a., splenic artery; Superior mesenteric a., superior mesenteric artery.

40 seconds after injection is significantly higher than the measurement errors, the artery is diagnosed as a feeding artery of gastrinoma. Functioning gastrinoma is then located in the feeding area of the identified feeding artery.

More precise localization is possible by injecting secretagogue into a branch of the identified artery. Both the sensitivity and specificity of the SASI test for gastrinoma have been shown to be more than 90% [7].

In addition to secretin, which has been the first choice for injecting secretagogue for SASI, calcium gluconate solution is clinically used [12,13]. Unlike the response to secretin, the response to calcium gluconate is relatively slow; the SASI test by calcium gluconate is as useful as secretin in localizing gastrinoma if it is not detected by diagnostic imaging.

Somatostatin Receptor Scintigraphy

Somatostatin receptor scintigraphy can visualize PanNETs larger than 2 cm in diameter in the body, and has contributed to the staging of PanNETs [14–16]. SRS can visualize 100% of gastrinomas larger than 3 cm in diameter, but only 20% of gastrinomas are smaller than 5 mm and 30% are smaller than 1 cm [15]. SRS visualized 73% of gastrinomas, depending on the extent of the presence, the differences in subtypes of somatostatin receptors and the size of the tumor [16]. For the localization of ectopic gastrinoma, SRS is indispensable [17].

Intraoperative Ultrasonography

Intraoperative ultrasonography is useful in estimating the character of a tumor and in measuring the distance between gastrinoma and the main pancreatic duct. In addition, the form and size of the gastrinoma can be measured more accurately with IOU than any other preoperative imaging technique [18].

Surgery

Surgery for gastrinoma needs a thorough exploration and careful technique. The omentum is widely opened, and the entire pancreas from head to tail is mobilized. This allows careful bimanual palpation of the gland.

Intraoperative ultrasonography should be performed in any patient undergoing exploration for gastrinoma to identify tumors that are difficult to palpate. It may also detect signs suggestive of malignancy in addition to the relationship of the tumor to the main pancreatic duct and major blood vessels.

IOU is not particularly useful in identifying duodenal wall gastrinomas; however, intraoperative endoscopy with transillumination of the duodenum is capable of locating duodenal wall gastrinomas.

The most accurate method of detecting duodenal wall gastrinomas is duodenotomy with careful palpation, a technique employed by experienced surgeons during surgical exploration for gastrinoma. Duodenotomy has been shown to increase the gastrinoma detection rate to 98% compared with 76% without duodenotomy, and also the short-term cure rate (65% versus 44%) and long-term cure rate (52% versus 26%) [19].

Because primary duodenal gastrinomas are associated with lymph node metastases in 60% of patients, a more aggressive lymph node dissection has been recommended. Major vascular involvement is not a contraindication to attempting a resection. A study of 273 patients showed that 46 (17%) had evidence of major vascular involvement on preoperative imaging, and 42 of these 46 patients underwent successful resection [20].

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The use of endoscopic and/or laparoscopic approaches for the management of neuroendocrine tumors, including gastrinomas, has been reported in small numbers of patients. However, the role for such an approach in patients with gastrinomas appears to be limited owing to a variety of technical issues, including the multiplicity of lesions, the small size of duodenal tumors, the frequent presence of lymph node metastases, and the presence of critical structures in the usual gastrinoma location in the pancreatic head region. These difficulties tend to favor an open surgical approach.

Treatment of Hepatic Metastases

A very aggressive management approach has been advocated for advanced and metastatic gastrinomas because of the poor outcome of patients and the overall disappointing results with systemic therapy. It was reported that aggressive resectional procedures were associated with no operative deaths and a five-year actuarial survival of 80% in 20 patients with locally advanced and metastatic neuroendocrine tumors, including 10 gastrinomas [21]. Another study in 85 patients with liver metastases suggested that chemoembolization may be preferred unless a curative resection is possible or 90% of the tumor volume can be removed [22]. Bilobar disease and patients with more than 75% liver involvement were least likely to benefit from surgery.

The role of liver transplantation in patients with liver metastasis remains controversial. The UNOS database showed that 150 liver transplantations were carried out for patients with liver metastasis from neuroendocrine tumors out of 87 280 performed. Among them, 11 cases of gastrinoma (7.3%) were included. Overall survival rates were similar to those for patients who underwent transplantation for hepatocellular carcinoma [23].

Other liver-directed therapies include chemoembolization, radioembolization, and percutaneous radiofrequency ablation. These therapies continue to play a role in the management of neuroendrocrine tumors metastatic to the liver, including gastrinomas. In general, transarterial chemoembolization (TACE) has been shown to be a relatively safe procedure with improvements in symptom control, time to progression, and survival.

Systemic Chemotherapy

Streptozocin appears to be the most active single agent in patients with metastatic gastrinoma, with objective response rates reported in up to 50% of patients [24]. There is no evidence that the addition of 5-fluorouracil (5FU) with or without doxorubicin improves the outcome compared with streptozocin alone [24].

A study using a combination of 5FU, cisplatin, and streptozocin for metastatic or locally advanced neuroendocrine tumors of a variety of sites in 79 patients showed that the overall results are not superior to those with streptozocin alone [25].

Octreotide, either alone or combined with interferon, appears to have a role in the management of patients. The development of a long-acting somatostatin analogue has greatly facilitated management, and it is effective in reducing symptoms.

A randomized multiinstitutional double-blind placebo-controlled trial studying the vascular endothelial growth factor (VEGF) inhibitor sunitinib was reported in 171 advanced well-differentiated neuroendocrine tumors, including 19 patients with gastrinoma. Progression-free survival (PFS) was 11.4 months in the sunitinib group compared with 5.5 months in the placebo group. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. Nine deaths were reported in the sunitinib group (10%) versus 21 in the placebo group (25%).

The use of mTOR inhibitors, either alone or combined with octreotide therapy, has recently been studied in patients with pancreatic neuroendocrine tumors. The RADIANT 1 trial, a multinational phase II study, studied the efficacy of everolimus alone and in combination with octreotide in patients with metastatic PanNET who had progressed on chemotherapy [26]. Treatment with everolimus alone resulted in stable disease in 67.8% of patients and partial response in 9.6%. Combination therapy with everolimus and octreotide LAR resulted in stable disease in 80% of patients and partial response in 4.4%.

In the RADIANT III trial, 410 patients with radiologic progression of disease were randomized to everolimus l0 mg daily or usual therapy, which could include somatostatin [27]. The median PPS was 11 months with everolimus compared with 4.6 months with usual therapy. The proportion of patients alive and progression free at 18 months was 34% with everolimus compared with 9% with placebo.

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Rare Neuroendocrine Tumors of Pancreas: Management and Evidence of Surgical Treatment

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Introduction

As pancreatic neuroendocrine tumors (PanNET) are rarely encountered in hospitals, standardization of diagnosis and/or treatment strategy has not progressed until recently. However, recent advances in localization techniques, such as the selective arterial secretagogue injection (SASI) test and somatostatin receptor scintigraphy (SRS), have promoted curative resection surgery of PanNETs [1,2]. As the number of resections has rapidly increased, a few important characteristic pathologic features of PanNETs have been revealed year by year.

PanNETs include both those associated with a functional syndrome (functional PanNET) and those associated with no distinct clinical syndrome (nonfunctional PanNET) [3–6]. Nonfunctional PanNETs are the most common but they do not usually produce specific symptoms and are therefore considered clinically to be nonfunctional tumors, but they produce and frequently even secrete small amounts of pancreatic polypeptide, chromogranin A, neuron-specific enolase, calcitonin, neurotensin, and other peptides [4,5,7–9]. Gastrinoma and insulinoma are the two most common functional PanNETs, but there are also various kinds of rare functional PanNET [3–6], including glucagonomas, vasoactive intestinal peptide-releasing tumors (VIPomas) (Verner–Morrison syndrome, pancreatic cholera, watery diarrhea, hypokalemia, and achlorhydria [WDHA] syndrome) and somatostatinomas (Table 114.1) [3-7,9]. Each of the established rare PanNET syndromes is associated with a distinct clinical syndrome reflecting the actions of the secreted excess hormone. Cholecystokinin (CCK)-releasing tumors (CCKoma) and secretin-releasing tumors (secretinoma) are further rare neuroendocrine neoplasms of which entities are being recognized [10,11].

Clinical Features

Gastrinoma, insulinoma, and nonfunctional PanNETs represent over 90% and other rare PanNETs less than 10% of all PanNETs [4,7]. Rare but well-known PanNETs include glucagonomas, VIPomas, and somatostatinomas whose syndromes are established. Rare and lesser known tumors include PanNETs that secrete CCK, secretin, calcitonin, renin, luteinizing hormone, erythropoietin, and insulin-like growth factor II whose status is unclear as to whether they represent a specific syndrome because of the small numbers of cases (see Table 114.1) [3–5,7,9–13].

The majority of patients with rare PanNETs have liver metastases at initial diagnosis (40–90%). Somatostatinomas can occur in the pancreas or upper small intestine; however, duodenal somatostatinomas are rarely associated with a functional clinical syndrome [4,12,14]. In addition to somatostatinomas, a number of other rare PanNETs also occur in extrapancreatic locations (see Table 114.1).

The average age at diagnosis is 50–55 years, with equal gender distribution. Patients with malignant tumors may present with mixed syndromes or tumors may change clinically over time. The most frequent familial condition associated with rare PanNETs is multiple endocrine neoplasia type 1 (MEN 1). Glucagonomas occur in 3% of MEN 1 patients, VIPomas in 3%, and GRHomas (secreting growth hormone-releasing hormone) and somatostatinomas in less than 1% [15,16]. Somatostatinomas are seen in up to

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Table 114.1 Rare pancreatic neuroendocrine tumors (PanNET) Adapted from [3,5,7].

Name	Biologically active peptide(s) secreted	Estimated incidence (new cases/10^6 population/year)	Tumor location	Malignant (%)	Associated with MEN 1 (%)	Main symptoms/signs
Glucagonoma	Glucagon	0.01–0.1	Pancreas (100%)	50–80	1–20	Rash (67–90%); glucose intolerance (38–87%); weight loss (66–96%)
VIPoma	Vasoactive intestinal peptide (VIP)	0.05–0.2	Pancreas (90%, adult); other (10%, neural, adrenal, periganglionic)	40–70	6	Watery diarrhea (90–100%); hypokalemic (80–100%); dehydration (83%)
Somatostatinoma	Somatostatin	Rare	Pancreas (55%); duodenum/jejunum (44%)	>70	45	Diabetes mellitus (63–90%); cholelithiases (65–90%); diarrhea (35–90%)
CCKoma	Cholecystokinin	Rare	Pancreas	Unknown	Unknown	Nonwatery diarrhea; weight loss; gallbladder disease; duodenal ulcer disease; low plasma levels of gastrin
Secretinoma	Secretin	Rare	Pancreas	Unknown	Unknown	Watery diarrhea; dilated gallbladders; dilute bile; low plasma levels of VIP
GRHoma	Growth hormone-releasing hormone	unknown	Pancreas (30%); lung (54%); jejunum (7%); other (13%)	>60	16	Acromegaly (100%)
ACTHoma	ACTH	Rare	Pancreas (4–16% all ectopic Cushing)	>95	rare	Cushing syndrome (100%)
PanNET causing carcinoidsyndrome	(Serotonin; tachykinin)	Rare	Pancreas (<1% all carcinoids)	60–88	rare	Carcinoid syndrome
PanNET causing hypercalcemia (PTHrp-oma)	PTHrp; others unknown	Rare	Pancreas (rare cause of hypercalcemia)	84	rare	Abdominal pain due to hepatic metastases, symptoms due tohypercalcemia
PanNET secreting calcitonin	Calcitonin	Rare	Pancreas (rare cause of hypercalcitonemia)	>80	16	Diarrhea (50%)
PanNET secreting renin	Renin	Rare	Pancreas	Unknown	no	Hypertension
PanNET secreting luteinizing hormone	Luteinizing hormone	Rare	Pancreas	Unknown	no	Anovulation, virilization(female), reduced libido (male)
PanNET secreting erythropoietin	Erythropoietin	Rare	Pancreas	100	no	Polycythemia
PanNET secreting insulin-like growth factor II	Insulin-like growth factor II	Rare	Pancreas	Unknown	no	Hypoglycemia

ACTH, adrenocorticotrophic hormone; MEN, multiple endocrine neoplasia.

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l0% of patients with von Recklinghausen disease (neurofibromatosis type 1) but in almost all cases they are not associated with a functional syndrome [7,14,15].

Prognosis and Survival

Most rare PanNETs present with metastatic disease and patient survival time is determined by growth of the tumor rather than the hormone excess state. Five-year survival for the group with advanced disease is 29–45% [3,4,6,7]. All the survival or prognostic data on the individual rare PanNETs come from retrospective studies and their results are often included in noninsulinoma or nongastrinoma series that include nonfunctional PanNETs. These studies demonstrated tumor Ki-67 index ≥62%, presence of lymph node metastasis, presence of cytokeratin-19 staining, and various molecular features that were associated with a poor prognosis [4,17].

Diagnosis

Rare PanNETs characteristically present with symptoms of the specific hormone excess state, and in most cases present late in the disease course when advanced disease is already present [4,6,7]. In a few patients with a rare PanNET, a second functional syndrome may develop over time. Therefore, the diagnosis of all rare PanNETs requires demonstration of an inappropriate elevation of the specific serum hormones combined with clinical and/or laboratory evidence of oversecretion of the appropriate hormone [3–5,18,19]. The diagnosis of functional rare PanNET requires clinical evidence of hormonal overexpression and is not based solely on immunohistochemical results [3–5,18,19].

General markers such as serum chromogranin A also support the presence of a neuroendocrine tumor, and may be helpful for monitoring during the disease's course [3,5,19,20].

All biochemical tests should be performed at first visit. PanNETs causing Cushing syndrome should be suspected from the clinical examination and history, and the diagnosis established by performing 24-hour urinary cortisol determinations, midnight plasma or salivary cortisol assessments, and dexamethasone suppression tests as needed [9,19].

Theoretically, pancreatic cells that produce any kind of hormones can become neoplasms. As we do not have methods of measuring serum concentration of the candidate responsible hormone, that is, a specific antibody, we cannot diagnose that the tumor is the hormone-producing neoplasm which causes the unique symptoms. In this sense, the existence of CCKoma has been suspected and a case was reported with extremely elevated plasma cholecystokinin level and permanently low plasma gastrin level [10]. The CCKoma symptoms include persistent nonwatery diarrhea and weight loss combined with more specific symptoms of gallbladder disease and duodenal ulcer disease.

Similarly, Zollinger et al. postulated the existence of secretin-releasing tumor five decades ago based on the characteristic clinical symptoms such as watery diarrhea, hypokalemia and achlorhydria without hypergastrinemia [21]. Recently, thorough laboratory work has been done on the same specimen from half a century ago, leading to the conclusion that the tumor was almost certainly a secretinoma [11]. However, as there was no measurement of plasma secretin, which is the *sine qua non* to establish a hormone as potentially causing a clinical syndrome, the diagnosis must be tentative.

Tumor Localization

Tumor localization studies are important in all patients with rare PanNETs. They are necessary to determine whether surgical resection is indicated, to localize the primary tumor, to determine the extent of the disease and whether metastatic disease to the liver or distant sites is present, and to assess changes in tumor extent with treatments. All aspects of their management require knowledge of tumor extent. It is important to know that the majority of all pancreatic functional tumors except insulinomas are malignant. Accurate localization of the tumor can result in complete surgical resection with cure of PanNET (10–40%).

Numerous localization studies have been recommended, including conventional imaging studies (computed tomography [CT], magnetic resonance imaging [MRI], ultrasonography [US]), selective angiography, SASI test, SRS, and endoscopic ultrasonography (EUS), in addition to various intraoperative localization methods including intraoperative ultrasonography (IOU).

Most prospective studies show that the sensitivity of conventional imaging studies for localizing the primary tumor is 10–50%, angiography 20–50%, and SRS 30–70% [22]. The use of SRS changes management in 15–45% of patients with PanNETs. For SRS and all conventional studies, tumor size is an important variable and tumors smaller than 1 cm are missed in 50% or more cases. The combined use of multidetector CT (MDCT) scanning or MRI and SRS is always recommended. Conventional imaging studies suggesting vascular or tissue invasion may provide important information on whether surgical resection is contraindicated.

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If measurement of target hormone is easily accessible, the SASI test is the most reliable approach for tumor localization. This test was first described for localization of gastrinoma, and has gradually proved useful for localization of other functional PanNETs [2,23–25]. At the time of abdominal arteriography, secretagogue is injected into the splenic artery, the gastroduodenal artery, and superior mesenteric artery. Then 2 mL blood samples are drawn from the hepatic vein through a catheter inserted via the femoral vein, before and 20, 40, and 60 seconds after the injection of secretagogue to detect the change in hormone levels in hepatic venous blood. When the rise in hormone levels at 40 seconds after injection is significantly higher than the measurement errors, the artery is diagnosed as a feeding artery of the tumor. Functioning tumor is then located in the feeding area of the identified feeding artery.

Functional localization studies are not limited by tumor size but are somewhat invasive. Prospective studies of the metastatic liver disease from a malignant PanNET showed that CT and US could detect their presence in 30–80% of patients with metastases, MRI and angiography in 50–85%, and SRS in 70–95% [26]. IOU should be routinely used to assess and identify PanNETs [27].

Endoscopic US is particularly sensitive for PanNETs but its ability to detect small duodenal tumors is controversial. Hence, EUS is not universally recommended as a first-line procedure in the investigation of rare PanNETs. It may be used in circumstances where MDCT, MRI, and SRS are inconclusive, especially preoperatively. However, in patients with rare PanNETs presenting with lymph node metastasis, EUS is rarely necessary. It may be helpful in patients with large or aggressive tumors to more clearly define tumor involvement where surgery is considered.

Insufficient data are available to recommend positron emission tomography (PET)/CT methods on a routine basis; their use remains investigational and availability is limited. If results with the earlier recommended imaging methods are unclear or negative in a patient with rare PanNET, ^{68}Ga-labeled somatostatin analogue PET should be considered with performance by an experienced center.

A number of studies have demonstrated that PET, especially with ^{68}Ga-labeled somatostatin analogues (DOTA-TOC [DOTA-Tyr-octreotide], DOTA-TATE [DOTA-Tyr-octreotate], DOTA-NOC [DOTA-naloctreotide]) when combined with CT ([^{68}Ga] DOTATOC PET/CT, for example), has high specificity and is more sensitive than SRS or other modalities [28–31]. At present, it is not available in many centers and its exact place in the localization algorithm has not been clearly defined.

Standard PET with [^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) is not efficient in detecting well-differentiated tumors but may have some value in the detection of aggressive, poorly differentiated pancreatic neuroendocrine carcinomas [7]. Other examinations that may be useful are [^{18}F]DOPA-PET or [^{11}C]-5-HTP-PET if available and costs are affordable.

Surgical Treatment

The best treatment for rare PanNET is curative surgical resection. This needs to be performed before liver metastasis develops. Indications for surgery depend on clinical symptom control, tumor size, location, extent, malignancy, and metastatic spread [3,4,7,27,32].

Curative surgery should be indicated whenever possible, even in the presence of metastatic disease, including resectable metastatic disease to the liver and when the patient can tolerate the surgery [3,4,7,27,32]. The types of surgery include pancreaticoduodenectomy, distal pancreatectomy, tumor enucleation, and enucleation in combination with resection, depending on the location of the primary tumor.

Curative surgery is always recommended following optimal symptomatic control of the clinical syndrome by medical treatment. Owing to the usually large size of the tumor and the high prevalence of lymph node metastasis in rare PanNETs, curative surgery should include pancreatic resection with lymph node dissection through laparotomy. In the case of localized lymph node metastasis or more extensive disease spread, surgery should also be considered if at least 90% of the gross tumor can be resectable.

Laparoscopic resection is currently not recommended because lymphadenectomy and careful inspection for invasion and metastases are needed [7]. Surgery for lymph node metastasis may be performed during treatment of the primary tumor. Cytoreductive surgery should be considered when the metastatic disease is localized or more than 90% of the tumor load can be resected, which may help to improve hormonal control and perhaps extend survival.

Another indication for surgery is an emergency of life-threatening severe symptoms. Emergency pancreatic resection is sometimes necessary for glucagonoma associated with paraneoplastic syndromes such as severe necrolytic migratory erythema or VIPoma with profuse watery diarrhea or renal failure. When the symptoms are caused by the primary pancreatic tumor, pancreatectomy is necessary although the surgery is invasive to patients [33]. On the other hand, if the symptoms are caused by metastatic tumors of the liver, transarterial chemoembolization (TACE) may be chosen first, then elective surgery should be planned [34].

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Medical Treatment

Several decades ago, the major cause of death of patients was the untreated effects of the hormone excess state; therefore, it is important to control the hormone levels [4,7], which can be achieved with the combined use of medical, surgical, and radiologic therapies.

Both somatostatin analogues and interferon have been shown to be effective in the control of symptoms in rare PanNETs [35]. Somatostatin analogues provide effective symptom control in patients with VIPomas, GRHomas, and glucagonomas [35]. Long-acting somatostatin analogues are also reported to be effective in controlling the excess hormone secretion in some cases of somatostatinomas. If somatostatin analogues are ineffective or lose efficacy in controlling the hormone excess state, interferon may be effective at controlling the symptoms, either alone or in combination with somatostatin analogues.

Somatostatin analogues also have antigrowth effects on PanNETs. For the control of symptoms, somatostatin analogue therapy should be initiated with the short-acting substance for 1–2 days with titration according to clinical response. The patient can then be transferred to slow-release lanreotide-SR IM, lanreotide Autogel-SC, or octreotide long-acting release IM every four weeks [36]. Likewise, interferon treatment may help control symptoms of the hormone excess state in rare PanNETs, although it has been less well studied than the use of somatostatin analogues. It is reported to be effective in VIPomas not responding to somatostatin analogues and also in isolated cases when combined with somatostatin to control the symptoms of a rare PanNET, which with somatostatin treatment alone was inadequately controlled; however, this requires confirmation in future studies [37].

Prospective studies of mammalian target of rapamycin (mTOR) inhibitors with or without octreotide and tyrosine kinase inhibitors have shown significant prolongation of survival time in patients with gastrinoma. New cytotoxic chemotherapy with temozolomide and capecitabine has also been reported to be effective.

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Treatment of Neuroendocrine Neoplasia of the Pancreas and Biliary Tract

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Introduction

Neuroendocrine neoplasia (NEN) of the pancreas, duodenum, and biliary tract constitute a rare and heterogeneous group of neoplasms. Historically, the term "carcinoids" has been used to define these tumors. Modern pathology classification based on grading utilizing the Ki-67 index, or number of mitoses per 10 high-powered fields (HPF), has introduced the term "neuroendocrine neoplasia." Neuroendocrine neoplasms may be classified as neuroendocrine tumors (NET) or neuroendocrine carcinoma (NEC). Grade 1 (NET) have a Ki-67 of <3% or <2 mitoses per 10 HPF. Grade 2 (NET) have a Ki-67 of between 3% and 20%, or between 2 and 20 mitoses per 10 HPF. Grade 3 NEN have a Ki-67 of >20%, or >20 mitoses per 10 HPF, and can be subclassified into G3 NET and G3 NEC; this is on the basis of their differentiation: G3 NET are well differentiated and G3 NEC are poorly differentiated [1].

A hallmark of NEN is the secretion of amines and peptides capable of inducing distinct clinical syndromes. Beside tumor-specific hormones including insulin or gastrin, proteins such as neuron-specific enolase (NSE), chromogranin A (CgA), pancreastatin, and synaptophysin—commonly expressed in neuroendocrine cells—are produced. Such proteins serve for immunohistochemical NEN diagnosis, and have been recognized as clinically useful tumor markers. Some pancreatic NEN (PanNEN) secrete multiple hormones and may show secondary changes in the secreted hormone profiles during their clinical course. Additional characteristic features of NEN encompass specific amine uptake mechanisms and cell surface peptide receptors, i.e., for somatostatin, that have utility in diagnosis and treatment [2].

Recently, circulating multianalyte biomarkers have been introduced in the management of NEN which allow disease detection and prediction of treatment effectiveness and prognosis [3]. Other novel biomarkers such as circulating tumor cells, cell free DNA, circulating tumor DNA, mRNA, and microRNA still require validation in clinical practice.

Neuroendocrine neoplasia can occur sporadically or as a component of the genetically determined autosomal dominant syndromes including von Hippel–Lindau, multiple endocrine neoplasia type 1 (MEN 1), neurofibromatosis type 1, and tubular sclerosis. In cases of heredity, multicentric tumor manifestation should be expected.

Neuroendocrine Neoplasia of the Pancreas

Of the NEN originating from the pancreas, 65–80% are hormonally active. Whilst the majority secrete insulin or gastrin, less commonly, secretion of vasoactive intestinal polypeptide (VIP), glucagon, growth hormone-releasing factor (GRF), or somatostatin is observed. Particularly rare are serotonin-producing tumors. Tumor nomenclature depends upon the hormone predominantly secreted, namely insulinoma, gastrinoma, VIPoma, glucagonoma, GRFoma or somatostatinoma.

There has been significant progress in the understanding of genomic events that characterize PanNEN; such mutations and other molecular alterations have a role in pathogenesis of these tumors but also determine their prognosis [4]. Surgery plays a central role in management of PanNEN and is considered as a first-line treatment option for patients with resectable disease. Under consideration of favorable long-term survival of

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many surgical patients with G1 or G2 PanNEN, long-term pancreatic functional impairment in terms of diabetes mellitus and/or pancreatic exocrine insufficiency has to be taken into account, particularly when planning extensive pancreatic resections in those with preexisting morbidity [5]. Several areas are subject to ongoing debate, such as extent of resection in MEN 1-associated gastrinoma, primary tumor resection in the presence of nonresectable liver metastases, managment of patients with incidentally discovered small nonfunctional Pan NEN, clinical significance of lymph node metastases in PanNEN, and the role for neoadjuvant treatment for borderline resectable tumors [6].

Insulinomas

Insulinomas represent 60% of functional PanNEN. More than 90% of such tumors are benign lesions measuring 1–2 cm in size (Fig. 115.1). Approximately 10% of insulinomas are multicentric, and most of them are associated with MEN 1. Malignant insulinomas metastasize to the regional lymph nodes and liver. Localized or diffuse islet cell hyperplasia is a very rare cause of hyperinsulinemic hypoglycemia, and has been reported in adults and children (nesidioblastosis). The clinical hallmark of the disease is neuroglycopenia, followed rather regularly by catecholaminergic responses.

The diagnosis of insulinoma is based on following criteria:

- the signs and symptoms of hypoglycemia during periods of fasting or exertion
- documented blood glucose levels near or below 40 mg/dL (<2.2 mmol/L)
- concomitant insulin levels of ≥6 μU/mL (43 pmol/L)
- elevated C-peptide levels (≥0.2 nmol/L)
- absence of sulfonylurea in the plasma.

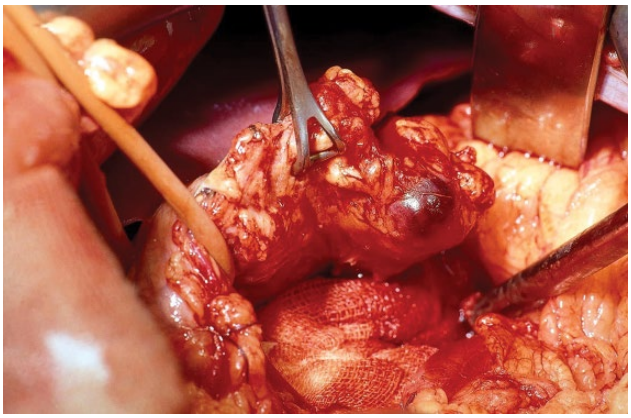


Figure 115.1 Intraoperative finding of a 1 cm insulinoma at the tail of the pancreas.

As the most reliable investigative test, 72-h fast has been traditionally considered. In the presence of insulinoma, 80% of patients will become symptomatic within 24 hours of fasting. With the introduction of upgraded assays for insulin, proinsulin, and C-peptide, the standard full 72-h fast might be replaced by the 48-h fast [7]. Although rarely required, provocative tests (tolbutamide test, glucagon test, calcium infusion test) can be of help in cases of anomalous or equivocal results. After establishing a biochemical diagnosis of insulinoma, a search for adenopathies typical for MEN 1 and meticulous evaluation of the family history must be carried out. The diagnosis of MEN 1-associated insulinoma can be confirmed by DNA analysis and by proof of menin gene mutations most commonly detected in exons 2, 7, 9, and 1.

Localization Studies

The striking advantage of preoperative localization of PanNEN has been recognized. In the presence of newer imaging techniques and refinement of standard radiologic procedures, the vast majority of lesions can be accurately identified prior to surgery.

A high-quality arterial and portal venous phase computed tomography (CT) according to a pancreatic protocol is the gold standard imaging modality for primary tumor staging and direction of therapy. Apart from tumor localization within the pancreas, it ascertains the vascular anatomy of the pancreas, identifies biliary and pancreatic duct abnormalities, and assesses for invasion of peripancreatic structures and nodal metastases. Features suggestive of a PanNEN on CT include the presence of a hypervascular or hyperdense lesion within the pancreas; however, they can also appear cystic or contain calcifications. Most insulinomas are <2 cm in size and solitary. On CT, they tend to be hypervascular with either uniform or target enhancement; however, given that they are often noncontour-conforming, detection of the vascular blush is essential to localize them (the chance of detection can be maximized by timing the images 25 seconds after contrast injection). Magnetic resonance imging (MRI) features include low signal intensity on T1-weighted images and the lesions are particularly well seen on fat-suppressed (T1- and T2-weighted) images [8].

The sensitivity of transabdominal ultrasound strongly depends on the experience of the examiner and has been reported to be around 60–70%. The use of contrast with microbubbles (CEUS) improves the sensitivity of US due to hypervascularity of most NEN. For endoscopic ultrasound (EUS) imaging of PanNEN, overall sensitivity and accuracy of up to 95% have been reported but this is operator dependent [9]. Either as a single technique or in combination with fine needle aspiration biopsy, which can confirm the diagnosis and inform tumor grade, it has

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emerged as one of the most valuable modalities in the imaging of PanNEN.

Previously widely used ^{111}In-pentetreotide scintigraphy (Octreoscan®) was not very effective in the radiologic interrogation of insulinomas since most of the lesions do not express somatostatin receptor subtype 2, necessary for binding of the radiolabeled octreotide. Glucagon-like peptide-1 receptor imaging (^{111}In-DTPA-exendin-4 SPECT/CT) has recently been reported as an effective second-line imaging modality for patients with negative results on standard imaging [10].

Intraoperative ultrasonography enables identification of the lesion, and provides additional information concerning the relation of the tumor to the pancreatic duct, common bile duct, portal vein, and superior mesenteric vessels. Particularly for tumors located within the uncinate process, exposure of the complete gland is crucial.

Assignment of insulinomas to regions of pancreas is possible by selective transhepatic portal venous sampling for insulin. The method regionalizes the lesion to a certain part of the pancreas but it does not determine the specific location. Since this highly invasive technique is extremely demanding, it is reserved mainly for reoperations and MEN 1-associated tumors [11]. Further improvement of tumor regionalization can be achieved by selective arterial calcium stimulation and blood sampling for insulin gradients in the hepatic veins, a technique originally reported by Imamura and Takahashi for regionalization of gastrinomas [12].

Perioperative Management of Serum Glucose

The main goal of the preoperative preparation is to avoid severe hypoglycemia. Intravenous administration of glucose is recommended the night before surgery. Severely hypoglycemic patients may be treated with diazoxide or octreotide. Intraoperatively, blood glucose monitoring should continue. Increases in blood sugar levels may confirm successful insulinoma removal. More reliable confirmation concerning completeness of surgery can be gained by insulin measurement with intraoperative rapid insulin assay. Shortly after insulinoma removal, transient hyperglycemia usually occurs. Since glucose levels rarely exceed 200 mg/dL, no specific treatment is necessary.

Surgical Management

In patients with tumors expressing malignant features, or in the presence of contradicting imaging results, a standard surgical approach to the pancreas and exploration of the liver for metastases includes meticulous exposure of the whole organ including the uncinate process, allowing visual assessment of anterior and posterior pancreatic surfaces. Even if the lesion is already visible, intraoperative US should be performed to assess the relationship of the tumor to the surrounding structures. Regardless of the specific site of the tumor, enucleation or limited parenchyma-sparing resection should be attempted as the "gold standard" for surgical treatment of benign insulinoma. When selecting patients for enucleation, the distance of the tumour of more than 2–3 mm from the main pancreatic duct should be considered as one of the inclusion criteria.

Blunt dissection close to the capsule of the tumor with the aim of avoiding injury to the main pancreatic duct is recommended in order to prevent fistula formation. The parenchymal defect can be closed or left open. Local application of sealants can lower the incidence of postoperative fistulae, traditionally reported with an incidence of 13–40%, irrespective of the management of the enucleation cavity [13]. Perioperative octreotide administration has not been shown to reduce the risk of postoperative pancreatic fistulae.

Laparoscopic resection of PanNEN is feasible and safe, particularly in left-sided lesions [14]. The value of robotic surgery in treatment of PanNEN is currently under investigation [15]. The majority of patients with sporadic insulinomas localized on imaging and selected patients with MEN 1-associated insulinomas nowadays undergo laparoscopic resections. The rate of fistulae, however, remains comparable to that in open surgery. If the tumor is not identifiable, blind resections cannot be recommended. Rather than performing a blind distal pancreatectomy, the procedure should be stopped and the patient referred to a center with the possibility of advanced localization techniques and adequate surgical experience [16].

Larger lesions within the body or tail are managed by distal pancreatectomy with preservation of the spleen, if technically feasible. Very rarely seen large tumors within the head of the pancreas, or tumors located deeply within the parenchyma and in close proximity to the pancreatic duct, require partial cephalectomy or even pancreaticoduodenectomy. For tumors located within the middle portion of the gland that cannot be enucleated due to proximity to the main pancreatic duct, central segmental pancreas resection may be the appropriate technique.

Insulinomas associated with the MEN 1 syndrome are invariably multifocal and scattered throughout the whole pancreas. Although the number of well-documented patients is rather small, distal subtotal pancreatectomy with splenic preservation and enucleation of any tumors in the head and/or uncinate process appears to be the best procedure. Peripancreatic lymphadenectomy is recommended in patients with concomitant gastrinoma or suspected malignancy [17].

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Gastrinoma

Zollinger–Ellison syndrome (ZES) is the clinical manifestation of gastrinomas. Whilst virtually all gastrinomas derive from the duodenum, some patients present with additional pancreatic lesions. In 60–90% of cases, gastrinomas can be found within the "gastrinoma triangle" defined by the junction of the cystic and common bile duct posteriorly, the junction of the second and third portion of the duodenum inferiorly, and the junction of the pancreatic neck and body medially. Although subject to controversial debate, the existence of primary lymph node gastrinomas has been postulated [18]. The majority of the duodenal gastrinomas are multicentric and only a few millimeters in size. Approximately 40% are linked to the MEN 1 syndrome [19]. In contrast to insulinomas, sporadic gastrinomas are frequently malignant and greater than 2 cm in diameter. Depending upon primary tumor size, liver metastases in combination with paraduodenal and peripancreatic lymph node metastases can be found at initial diagnosis in up to 70% of patients [20].

Localization Studies

Sensitivity of standard imaging techniques (US, CT, MRI) has been reported to be between 40% and 70% for pancreatic gastrinomas sized 1–3 cm [21]. Endoscopic ultrasonography provides 75–90% sensitivity for pancreatic gastrinomas and 50–70% sensitivity for duodenal wall lesions [22]. For the majority of localized gastrinomas and for metastatic disease, SR-based imaging utilizing PET/CT technology (e.g., gallium-68 [^{68}Ga]1,4,7,10-tetra-azacyclododedcan-4,7,10-tricarboxy-methyl-1-yl-acetyl-D-Phe^{1} Try^{3}–octreotide [^{68} Ga-DOTATOC], ^{68} Ga-DOTATOC PET/CT) is the single most accurate localization method [23]. In order to preoperatively localize gastrinomas which remained undetectable by standard imaging techniques, Imamura et al. developed the selective arterial secretagogue injection (SASI) test with secretin or calcium, which can guide surgical management [12].

Surgical Management

Surgical exploration with an attempt at tumor resection is recommended for all sporadic gastrinomas in the absence of multiple nonresectable liver metastases [24]. Compared with medical treatment, surgical tumor removal significantly reduces the risk of metachronous liver metastases [25]. If the test result indicates a tumor within the duodenum only, 80% of patients with sporadic gastrinomas might be successfully treated with resection of the single tumor and periduodenal lymphadenectomy [26]. The remaining 20% typically have multiple duodenal gastrinomas, or a combination of duodenal and pancreatic tumors. In patients presumed to have a sporadic gastrinoma in whom no preoperative SASI test was carried out, pancreatic and duodenal exploration is necessary. Intraoperative US, careful palpation, and endoscopic transillumination of the duodenal wall are extremely valuable aids. For larger gastrinomas in the head of the pancreas without duodenal tumor, pylorus-preserving pancreatoduodenectomy is recommended. Small tumors (<5 mm) can be enucleated from the submucosa while larger tumors require full-thickness excision. In the case of duodenal and pancreatic lesions, pancreatoduodenectomy presents the appropriate therapy. Distal pancreatectomy with regional lymphadenectomy is the treatment of choice for gastrinomas within the body or tail of the pancreas [27].

For MEN 1-associated gastrinomas, recommendations for surgery are much more controversial concerning timing and extent of the procedure [28]. While some authors are in favor of less aggressive surgery encompassing spleen-saving distal pancreatectomy, enucleation of NEN within the head and uncinate process, duodenotomy and excision of NEN, and regional lymph node dissection, others propose more aggressive duodenopancreatic resections in order to achieve durable eugastrinemia [29].

Liver metastases are the main prognostic determinant in patients with gastrinomas. No uniform guidelines for management of tumors in advanced metastatic stage exist. Treatment options are the same as those for other NET metastasized to the liver or primary NET of the liver (see below).

Nonfunctioning Tumors

Patients with nonfunctioning (NF) (nonsecreting) pancreatic NETs have no clinical symptoms related to hormonal hyperfunction, and negative biochemistry for peptides secreted by the pancreatic islets. Immunohistochemically, however, expression of hormones in tumor cells can be revealed. The reported incidence of NF pancreatic NEN varies between 15% and 53% [30] and the majority of such tumors are malignant. Lesions can occur sporadically or within the MEN 1 syndrome. At time of diagnosis, most symptomatic patients are between 40 and 60 years old, presenting with abdominal pain, jaundice, and weight loss. Tumors located within the body or tail of the pancreas may be clinically silent yet palpable as a bulky mass. In the past, the majority of tumors were diagnosed at an advanced stage. Nowadays, however, small NF NEN are increasingly diagnosed incidentally on imaging for reasons unrelated to the pancreas.

Upon diagnosis, differentiation from pancreatic adenocarcinoma must be considered. In general, patients with NF NEN are in a better clinical condition. Synchronous metastases in the liver and/or lymph nodes

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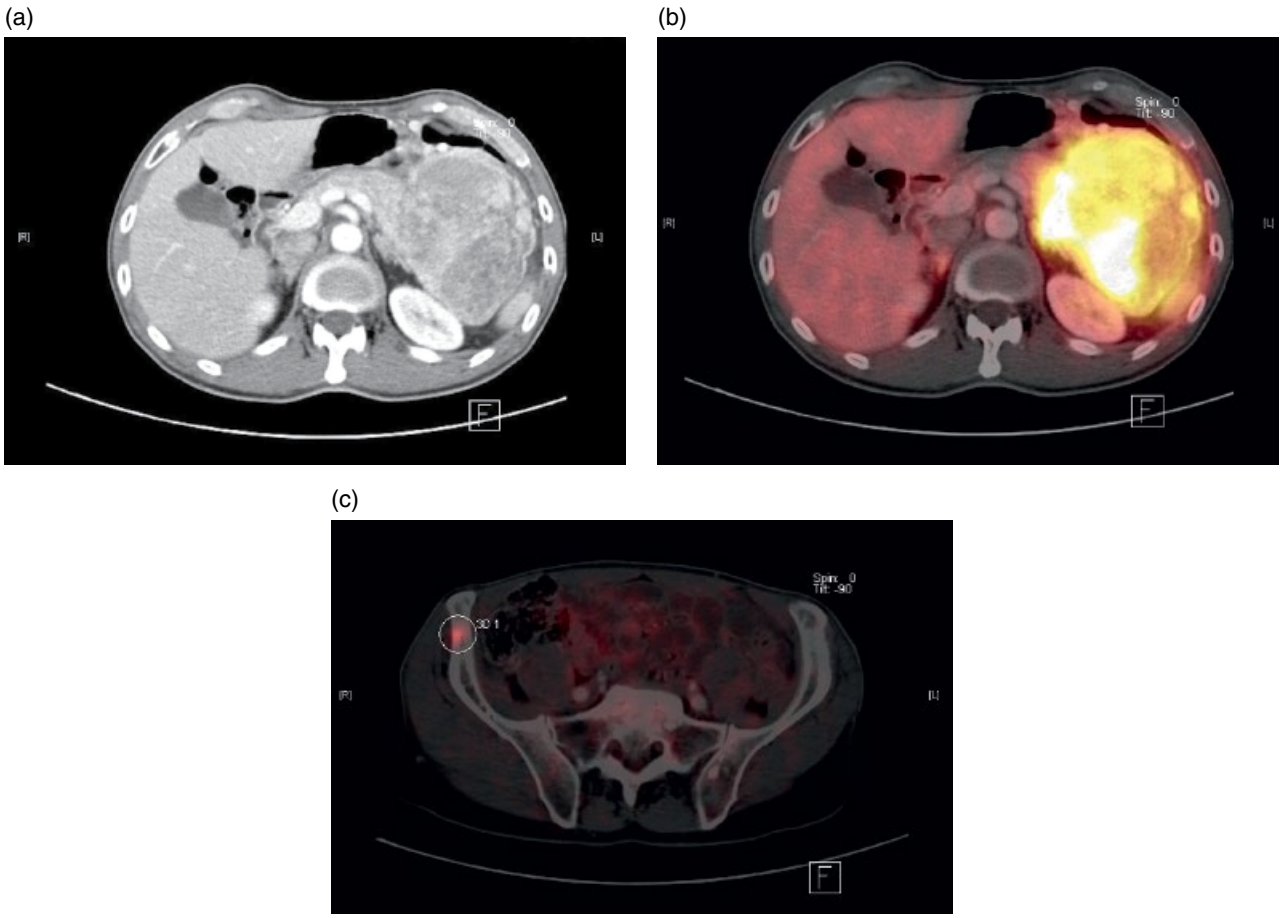


Figure 115.2 Preoperative imaging studies in a patient with a nonfunctioning NENof the pancreas. (a) On CT scan, a 20 cm diameter tumor in the left abdomen is shown. (b) ^{68}Ga-DOTATOC PET/CT demonstrates significant radionuclide uptake in the left upper abdomen. (c) Additionally, pathologic uptake, indicating a metastasis, is demonstrable within the right ilium (c). This finding was not seen on CT scan.

are frequently present. In our experience, ^{68} Ga-DOTATOC PET/CT is the most valuable imaging technique for staging well-differentiated and moderately differentiated NF NEN (Figure 115.2). For higher grade tumors or poorly differentiated neuroendocrine carcinomas, ^{18}F-fluorodeoxyglucose PET/CT (^{18}F-FDG PET/CT) is a more accurate imaging modality.

Resection is the treatment of choice for sporadic nonfunctioning G1/G2 and selected G3 PanNEN [30]. Resection rates of 26–79% with an overall five-year survival of 30–80% are reported [31]. In locally advanced tumors, multivisceral resections might be required to achieve an R0 situation. Because of the protracted natural history of these tumors, and given that many are symptomatic and difficult to palliate without resection (e.g., tumor bleeding), the criteria for what determines unresectable disease may not be the same as those for adenocarcinoma of the pancreas. The MD Anderson experience suggests that, in high-volume centers, major venous reconstruction can be performed safely, but only rarely should arterial reconstruction (isolated hepatic artery involvement) or upper abdominal exenteration be performed, due to the associated high long-term morbidity [32]. Continuous somatostatin analogue infusions are recommended perioperatively for carcinoid tumors and/or patients with liver metastases to prevent intraoperative carcinoid crisis.

For MEN 1-associated NF NET of the pancreas, no uniform suggestions exist. While some authors suggest resection of all tumors regardless of size as soon as visualized, others postulate that considering risk–benefit ratios, surgery may not be necessary in tumors less than 2 cm in diameter [33]. Controversy also exists regarding management of sporadic small (<2 cm) NF NEN; while in the opinion of some groups these tumors can be treated conservatively, others recommend surgical resection since both liver metastases and lymph node metastases have been reported in single patients with NF NEN less than 2 cm in size [34]. Currently, patients should be assessed regarding fitness for surgery and an

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informed decision made with the patient regarding strategy under consideration of operative morbidity and mortality risks. Central pancreatectomy may be feasible for selected smaller tumors and has the advantage of reducing the risks of postoperative diabetes and exocrine pancreatic insufficiency. A formal resection with lymphadenectomy should be performed for all potentially malignant tumors as lymph node metastases are common.

Another topic of ongoing debate is the resection of primary NF pancreatic NEN in the setting of unresectable liver metastases. Although evidence quality of the existing reports in favor of primary tumor resection is rather poor, the resectional aproach can be justified in selected patients with tumors amendable for distal pancreatectomy and synchronous liver metastases suitable for interventional or medical treatment [35]. Recently, peptide receptor radionuclide therapy has been introduced in the multimodal management of advanced pancreatic NET as a potential tool for downstaging in patients with primarly nonresectable tumors [36].

Neuroendocrine Tumors of the Duodenum

Duodenal NEN accounts for 2.5–3% of all tumors originating from the gastrointestinal tract [37]. Their management is not standardized, with smaller tumors considered for endoscopic mucosal resection and larger for surgical resection. The location within the duodenum is of prognostic relevance and plays a role in the decision regarding extent of surgery [38]. Histopathologically, five types of duodenal NEN can be discriminated, namely duodenal gastrinomas, somatostatinomas, nonfunctioning serotonin-, gastrin, or calcitonin-producing tumors, poorly differentiated and predominantly ampullary NE carcinomas, and duodenal gangliocytic paragangliomas. Approximately 30% of duodenal NEN are related to von Recklinghausen disease (neurofibromatosis type 1 [NF1]), MEN 1, and/or pheochromocytomas. The majority of duodenal NEN express CgA and NSE.

Gastrinomas located in the first and second portion of the duodenum account for approximately two-thirds of all duodenal NEN. These tumors occur either sporadically or as a component of the MEN 1 syndrome. Sporadic as well as hereditary tumors are generally small (<1 cm), but are multifocal in cases of familial determination. Although of small size and growth limited to the mucosa and submucosa, duodenal gastrinomas frequently present with lymph node metastases [39]. In contrast to pancreatic gastrinomas, distant metastases rarely occur in sporadic and hereditary duodenal tumors [28].

Duodenal somatostatinoma, located either within the ampulla of Vater or periampullary, account for 15% of all duodenal NEN. Insular growth pattern and psammoma body formation are the histologic hallmarks of these tumors. With muscularis propria infiltration, malignancy must be assumed. Tumor size and mitotic activity have no correlation with metastatic potential [40]. Somatostatinoma syndrome, typical for pancreatic NEN expressing somatostatin, does not occur in these duodenal tumors. Due to the unpredictable behavior of ampullary or periampullary NEN, a radical surgical approach, most frequently in form of a Whipple procedure, is recommended [40].

Nonfunctioning duodenal NEN has complex prognoses. While well-differentiated tumors confined to submucosa behave benignly, advanced metastases are frequently associated with poorly differentiated neoplasms. Gangliocytic paragangliomas represent a unique subgroup of duodenal NEN located within the periampullary region, and despite a tumor size >2 cm and infiltration of the muscularis propria, they generally have benign clinical course.

With the exception of ampullary/periampullary NEN, duodenal NEN smaller than 1 cm, and in the absence of signs of invasion of the muscularis propria and of metastases, may be excised locally by endoscopic resection with or without submucosal saline injection [41]. In this regard, endoscopic ultrasonography proved to be of extremely high value. It should be stressed, however, that lymph node metastases can be found in tumors less than 1 cm size [42]. For tumors between 1 and 2 cm or larger, local full-thickness excision through an open transduodenal approach or segmental duodenal resection with a side-to-side duodenostomy and regional lympadenectomy are recommended in order to achieve complete and curative resection (28). For larger tumors, formal pancreatoduodenectomy including lymphadenectomy might be required.

Neuroendocrine Neoplasia of the Liver

Despite the liver being the predominant site of neuroendocrine tumor metastases, primary NEN arising within the liver are rare. In a study of 13 715 carcinoid tumors accumulated by the National Cancer Institute in Bethesda over a 50-year period, only 45 primary hepatic tumors were documented [43]. Prior to the assumption that a hepatic NEN presents a primary lesion, a meticulous search for extrahepatic tumor manifestation is pivotal for effective management of such patients.

Patients with these tumors present with nonspecific hepatic clinical syndromes such as biliary obstruction or upper abdominal discomfort. In contrast to

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neuroendocrine liver metastases, flushing, diarrhea, bronchial constriction, and carcinoid heart syndrome, which are pathognomonic for the classic carcinoid syndrome, will be found in only about 5% of cases [43]. On transabdominal ultrasound, the tumor appears as a hyperechoic lesion, although the appearance on radiologic imaging is not characteristic.

The treatment strategy comprises several curative and palliative options including surgery, locally destructive techniques such as radiofrequency or laser-induced thermoablation, transarterial embolization alone or with chemotherapy, selective internal radiotherapy, somatostatin analogues, targeted medical therapy, and peptide receptor radionuclide therapy. In contrast to the poor overall five-year survival of 18.4% reported in early studies [43], a more radical surgical approach including advanced hepatic resections or liver transplantation in selected cases and multimodal treatment concepts achieve three-year disease-free survival rates of more than 75% [44].

Neuroendocrine Neoplasia of the Extrahepatic Biliary Tract

These very unusual neoplasia account for 0.2–2% of all gastrointestinal neuroendocrine tumors [45]. In approximately 60% of patients, the tumor develops within the common bile duct [46]. Further locations are the perihilar region (28%), cystic duct (11%), and common hepatic duct (3%). Unlike adenocarcinomas of the extrahepatic biliary system, biliary NEN predominantly affects female patients younger than 50 years. The symptom most frequently seen is painless jaundice with or without pruritus. The diagnostic work-up spectrum includes US, CT, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography. For tumor staging purposes, somatostatin receptor-based imaging provides valuable information.

As in other tumors originating from the biliary system, accurate preoperative diagnosis remains difficult, particularly regarding delineation from cholangiocarcinoma. Upon microscopic examination, the tumors present with a trabecular or nesting pattern with occasional tubule formation, and cells expressing CgA, synaptophysin, serotonin, pancreatic polypeptide, and/or somatostatin. Whereas local invasion is not common, metastatic lymph node involvement and liver metastases can be found in 30% of patients [47].

An aggressive surgical approach provides an overall favorable long-term prognosis. In early tumor stages and in the absence of metastases, five-year survival of 60–100% has been documented [48]. The extent of resection depends mainly upon the size, stage, and location of the tumor. Common bile duct resection and Roux-en-Y hepaticojejunostomy is the standard treatment of choice for lesions within the central portion of the common bile duct. For tumors affecting the hepatic duct bifurcation, resection of the bifurcation, in some cases in combination with partial hepatectomy, is necessary. Tumors of the distal part of the common bile duct require either segmental bile duct resection or partial pancreaticoduodenectomy (Whipple procedure). Extensive hilar lymphadenectomy is a mandatory part of the procedure.

Neuroendocrine Neoplasia of the Gallbladder

Approximately 0.2% of all NEN of the gastrointestinal tract originate from the gallbladder [49]. They usually affect females, causing right upper abdominal discomfort and jaundice. As in NEN of the extrahepatic biliary tree, the diagnosis is frequently made first after surgery for presumed cholecystitis or adenocarcinoma of the gallbladder although specific features on imaging helping to delineate them from adenocarcinoma have been reported [50]. Histologically, the tumor cells are positive for Grimelius staining and CgA, and less commonly for NSE or pancreatic polypeptide.

Although laparoscopic resection might be feasible in a small NEN confined to the wall of the gallbladder, the majority of the patients, particularly those with NEC, require a more radical surgical approach in terms of hepatic resection, removal of the extrahepatic bile duct, and extended hilar lymphadenectomy. An overall five-year survival of approximately 60% has been reported [43].

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Survival after Treatment of Endocrine Tumors

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Introduction

Pancreatic neuroendocrine neoplasm (PanNENs), representing 1–2% of pancreatic neoplasms, comprise an array of heterogeneous, mostly slow-growing tumors. Over recent decades, PanNEN incidence has persistently increased due to early detection of localized and asymptomatic tumors made possible by highly sensitive and specific imaging modalities. This wide spectrum ranges from indolent, hormone-secreting, localized, and easily accessible tumors to nonfunctioning, widely metastatic, and surgically less amenable tumors, at various time points on the tumor growth trajectory. These tumors may differ in tumor entity, clinical presentation (symptomatic versus asymptomatic), hormone secretion (functioning versus nonfunctioning), genetic background (sporadic versus hereditary), anatomic location (pancreatic head versus body and tail; anterior versus posterior pancreas), staging (primary tumor size, lymph node metastasis, and distant metastases), and grading (well-differentiated versus poorly differentiated PanNENs). Given the longevity of many patients with PanNENs, many observation periods were different in duration and the intensity of clinical monitoring.

Because treatment must be commensurate with the extent of disease, surgical and nonsurgical patients from selected groups defy standardization of therapy. Many series lumped together disparate endocrine tumors and no high-quality outcome studies have been forthcoming for any of these scenarios, leaving univariate risk factors unvalidated. Although some general principles have emerged from institutional series and tumor registries, the role and extent of surgery remain to be delineated for a number of clinical settings.

Risk Stratification of Pancreatic Neuroendocrine Neoplasm

Tumor Staging

In 2006, the European Neuroendocrine Tumor Society (ENETS) developed the first staging system for neuroendocrine tumors from the combined published experience of single centers at the level of the neuroendocrine tumor patient. A competing staging system, derived from a cancer registry database by the International Union Against Cancer, now the Union for International Cancer Control (UICC), in 2010 and now endorsed by both the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO), followed suit (henceforth referred to as the UICC/AJCC/WHO TNM). Disease stage and tumor grade are the two major independent prognostic parameters.

It is noteworthy that the UICC/AJCC/WHO TNM, unlike the ENETS TNM, is the same as for exocrine pancreatic tumors and not meant for high-grade PanNETs. As a consequence, tumor definition and stages differ greatly between the ENETS TNM and UICC/AJCC/WHO TNM staging systems. Of note, the UICC/AJCC/WHO TNM requires information on peripancreatic soft tissue invasion regardless of tumor size, a feature difficult to assess, to distinguish between UICC/AJCC/WHO categories pT2 and pT3.

The newly revised AJCC 8th edition staging system introduces the classification criteria asserted by ENETS and shows several significant changes. First, the PanNEN staging system is a separate system and applies only to G1 (ENETS/WHO 2019 grade 1), G2 (ENETS/WHO 2019 grade 2), and well-differentiated G3 tumors

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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(ENETS/WHO 2019 grade 3) The remaining poorly differentiated G3 (ENETS grade 3) neuroendocrine carcinoma follows staging of exocrine pancreatic cancer. Second, the size of the tumor has become an important criterion to distinguish the T category and invasion of soft tissue around the pancreas was excluded from staging criteria. Third, adjacent organ invasion has been categorized as T4, together with unresectable cases such as major vascular invasion. Fourth, the M1 category has been included according to metastatic sites. A recent study proved that the AJCC 8th edition staging system for PanNETs provides better discrimination compared to the 7th edition and ENETS TNM system [1].

Disease-free Survival

A recent study compared the AJCC system to the ENETS system by analyzing 472 patients who had undergone surgery for PanNETs [1]. The disease-free survival (DFS) curves of the 8th AJCC classification were well separated between all stages. Compared with stage I, the hazard ratio of II, III, and IV was 3.808, 13.928, and 30.618, respectively (P = 0.007, P <0.001, and P <0.001). In the ENETS staging system, there was no significant difference in DFS between stage IIB versus IIIA (P = 0.909) and IIIA versus IIIB (P = 0.291).

Overall Survival

One hundred and sixty five eligible patients with surgically resected PanNEN were evaluated to investigate the prognostic value of the two systems—ENETS and AJCC. Using the ENETS classification, the overall survival (OS) rate differences of patients with functional PanNETs were statistically significant when comparing stage I with stages III and IV (I vs III, P <0.001; I vs IV, P <0.001), as well as stage II and stages III and IV (II vs III, P = 0.009; II vs IV, P <0.001); differences in OS of stage I with II or stage III with IV were not significantly different (I vs II, P = 0.409; III vs IV, P = 0.499). Using the AJCC criteria, only patients with stage I functional tumors showed a significantly better OS rate than those with stage III and IV tumors (I vs III, P <0.001; I vs IV, P <0.001), while there were no significant differences when comparing patients in stages I and II, stages II and III, stages II and IV and stages III and IV (all P >0.05). Similarly, using the ENETS system to compare patients with nonfunctional tumours, stages I, II, and III had a significantly better survival than those with stage IV tumors (I vs IV, P = 0.005; II vs IV, P <0.001; III vs IV, P = 0.026). However, there were no OS differences when comparing patients in stage I with those in stages II and III, or between those in stages II and III (all P >0.05) [2]. The ENETS system might have potential advantages when applied to all PanNETs and to the functional subgroup, while the AJCC system might be clinically more practical for nonfunctional PanNETs.

Tumor Grading

Since the WHO 2010 classification, PanNENs have been graded according to Ki-67 index and mitotic count. The 5th edition of the WHO classification of digestive system tumors published in 2019 discussed advancements that have been made in the understanding of etiology and pathogenesis of several digestive system tumors. The 2019 WHO classification relies mainly on histopathologic criteria, including Ki-67 proliferative index and mitotic index, to predict the tumor's grade and biological behavior. There is no upper limit to the proliferation index of NET G3, and the degree of cell differentiation is one of the key points of differentiation.

Using this stratification system, PanNENs are classified as well-differentiated NET and poorly differentiate NEC. In addition, well-differentiated NET is further subdivided into "well-differentiated low-grade NET (G1)," "well-differentiated intermediate-grade NET (G2)," and "well-differentiated high-grade NET (G3)." The current WHO classification includes three grades (G1, G2 and G3) for NETs. NECs are no longer graded, as they are recognized to be uniformly high grade by definition, but continue to be separated into small and large cell types [3]. NETs are graded into G1, G2, and G3 based on the proliferation activity assessed by mitotic rate and/or Ki-67 proliferation index.

An important change in the 8th edition of the AJCC system is that G3 was not included in the PanNET staging system, unlike the previous ENETS system. This reflects the results of previous studies showing that exocrine tumors and neuroendocrine tumors have different tumor biology and prognosis [1].

The current WHO classification for endocrine organs (WHO 2019) was devised for PanNETs alone. This classification endorses the WHO 2010 principles, but introduces the definition of NET G3 for neoplasms that are well differentiated in morphology but display a proliferation index in the G3 range. WHO 2017 and 2019 classifications split the heterogeneous G3 gastroenteropancreatic (GEP)-NENs into well-differentiated NET G3 and poorly differentiated NEC. Clinical history, histomorphology, and genetics (*DAXX/ATRX/MEN1* mutation in Pan-NET G3, *p53* mutation or *RB* loss in NEC G3) help in separating the groups.

Another important change concerns the recognition that well-differentiated NETs may be high grade (G3 in the WHO grading system, defined as having a mitotic rate >20 per 2 mm^2 or Ki-67 >20%), but these neoplasms

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remain well differentiated genetically and distinct from poorly differentiated NECs. G3 NETs were first recognized and are most common in the pancreas, but they can occur throughout the gastrointestinal tract. The WHO 2019 classification strongly emphasizes the association of well-differentiated morphology with the NET definition, and poorly differentiated morphology with the NEC definition. The 2019 WHO grading, based on the mitotic count (<2, 2–20, and >20 mitoses per 10 high-power fields) and the Ki-67 index (<3%, 3–20%, and >20%), holds important prognostic information, especially in the absence of staging information.

Surgical Considerations for Pancreatic Endocrine Tumors

While multiple treatment options exist for PanNETs, a recent study showed that surgical resection is indicated for localized PanNETs that are >1–2 cm, grade 2, symptomatic, functional, or with evidence of regional lymph node metastases in patients who are acceptable candidates for pancreatectomy [4]. Preoperative evaluation of localized PanNETs should consider tumor size, the presence of unspecific symptoms, functional activity, localization of the lesion, and signs of local invasiveness.

Unlike functional PanNETs presenting with signs and symptoms of hormone excess, nonfunctioning PanNETs do not produce identifiable symptoms. Some clinically "nonfunctioning" tumors synthesize hormones in quantities too low to elicit complaints (e.g., glucagonoma) or hormones unable to produce symptoms in humans (e.g., pancreatic polypeptide). Because curative surgery determines survival more than tumor stage, the patient's clinical outcome hinges on the feasibility of complete tumor resection.

Several studies have demonstrated the safety of a "watch and wait" strategy instead of surgery for asymptomatic NF PanNETs ≤2 cm [5,6]. Surgery is recommended for young patients and in cases where signs of local invasiveness (e.g., dilation of the main pancreatic duct and/or presence of jaundice and/or suspicion of nodal involvement) are present. In the latter condition, a standard pancreatectomy with lymphadenectomy is recommended, whereas a parenchyma-sparing resection (e.g., enucleation or central pancreatectomy) should be routinely considered when the indication for surgery is related to long life expectancy. Moreover, surgery is mandatory in the presence of functioning PanNETs irrespective of tumor size. Curative resection of localized PanNETs seems generally associated with improved long-term survival and a low risk of recurrence [7].

A standard pancreatectomy (pancreaticoduodenectomy or distal pancreatectomy) with regional lymphadenectomy is recommended for PanNENs >2 cm [8]. Enucleation may represent an alternative approach to standard pancreatectomy in selected cases [9]. Functioning PanNENs such as insulinomas <2 cm represent ideal lesions to be enucleated, given that they are safely distant from the main pancreatic duct. Other functioning PanNENs are recommended for standard surgical methods. The role of enucleation for NF-PanNENs is currently limited to selected patients with small lesions in whom a "watch and wait" approach is contraindicated.

Nonfunctioning Tumors

Localized Tumors

A tumor size of 2 cm is the cut-off value proposed by current international guidelines as the main criterion of choice between conservative management and a surgical approach in asymptomatic patients with sporadic NF-PanNETs [6]. Zhang et al. retrospectively evaluated a large single-institution experience of patients with NF-PanNETs and found that surgery was significantly associated with improved survival, although this effect disappeared when tumors were <1.5 cm [10]. In a systematic review, Partelli et al. found observation to be a safe strategy for small NF-PanNETs with no disease-related mortality among patients initially undergoing active surveillance. In this study, 14% of patients who chose initial observation ultimately underwent surgical resection: 41% for tumor growth, 39% because of patient preference, and 15% for physician preference [5].

Unifocal Tumors

Localized tumors are easier to cure surgically when they are small, stay clear of large vessels and the bile duct, and involve only the anterior aspects of the pancreas, preferably the body or tail. To develop an effective surgical treatment plan, a thorough clinical work-up is essential to settle these important points before the operation and ensure that no additional tumors are missed.

There are basically three surgical techniques, each of which may be adequate depending on the circumstances of the case: tumor enucleation (leaving peritumoral tissue behind); excision (clearing peritumoral tissue together with the tumor); and pancreatic resection, which is bound to vary greatly in extent and scope depending on tumor location and type. Pancreatic surgery that leaves gross tumor behind is unlikely to benefit the patient. In patients without distant disease, every effort should be made to clear the mesenteric vessels of malignancy.

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Multifocal Tumors

When additional endocrine tumors are present or the family history is suggestive of hereditary disease, specifically multiple endocrine neoplasia type 1 (MEN 1) or von Hippel–Lindau syndrome (VHL), the surgical plan needs to be adjusted accordingly. Intraoperatively, the pancreas should be mobilized to allow for careful examination of the posterior aspect of the organ. Owing to the variety of constellations conceivable, multiple tumors are notoriously difficult to standardize, hampering predictions about clinical outcome.

Metastatic Tumors

Lymph Node Metastases

Studies have previously demonstrated that the risk of lymph node or distant metastasis in resected well-differentiated PanNETs progressively increased based on tumor size, including rates of 18% and 11%, respectively, for tumors measuring 1–2 cm [11].

A multiinstitutional study found that the rate of lymph node metastasis and tumor recurrence was higher for tumors measuring 1.5–2.0 cm compared with tumors measuring 1.0–1.5 cm [12]. These data hint at an interrelation between primary tumor size, lymph node metastasis, and liver metastasis, which signifies increasing cancer-specific mortality for these three risk factors.

Distant Liver Metastases as the Sole Systemic Manifestation

The debate over observation versus resection for well-differentiated NF-PanNETs is based on the uncertain potential for regional or metastatic spread compared with the potential morbidity of pancreatic surgery. Surgical resection may even be indicated in the setting of locally advanced disease requiring vascular resection or liver metastases amenable to liver resection/ablation [13,14].

Several retrospective studies have focused on liver metastases, the predominant manifestation of systemic disease, as the sole clinical appearance of PanNET. In 291 patients with poorly differentiated PanNETs, distant metastasis (hazard ratio [HR] 2.41; P <0.001), lymph node metastasis (HR 2.10; P = 0.004), and poor differentiation (HR 6.96; P = 0.032) were independent predictors of worse survival, with distant metastasis having a significant impact (0% versus 43%; P = 0.036) on five-year overall survival [15]. Enucleation of hepatic metastases, leaving surrounding parenchyma behind, is associated with greater short-term morbidity than hepatic resection, which entails the excision of metastases together with the surrounding liver parenchyma.

In light of these data, it is challenging to conduct head-to-head comparisons between enucleation of and hepatic resection for liver metastases from PanNETs. To facilitate surgical decisions, information about the biological behavior of the PanNET at hand (low versus high risk) is needed. According to current thinking, debulking needs to reduce the liver tumor burden by as much as 90% to improve outcome [16]. In some patients, total hepatectomy with subsequent liver transplantation has been used. Liver resection has been shown to improve symptom relief and survival compared with nonsurgical therapy [17].

Widespread Systemic Disease

Surgery with curative intent is indicated for PanNETs with liver metastases, provided there is absence of extrahepatic metastases, diffuse bilobar liver involvement, or compromised hepatic function. However, the majority of PanNETs present with unresectable stage IV disease, and the benefit of surgery to the primary lesion, particularly in asymptomatic nonsecretory tumors, remains controversial. Palliative resection of NF PanNETs requires potentially morbid surgery and is not widely recommended, despite emerging data demonstrating a similar survival benefit in this cohort [18].

Functioning Tumors

In general, all sporadic, localized F-PanNETs should be resected in patients healthy enough for surgery. Whereas NF tumors often become clinically apparent through complaints caused by tumor expansion, invasion, or metastatic disease, functional tumors, such as insulinoma, gastrinoma, and vasoactive intestinal peptide-releasing tumor (VIPoma), tend to be diagnosed at earlier stages when they present with signs and symptoms of hormone excess. Hormone excess typically produces clinical complaints that are more debilitating and diminish health-related quality of life more than those produced by tumor expansion, invasion, or metastatic disease. Hormonal symptoms cannot resolve if secondary hormone-secreting tumors are missed on enucleation or pancreatic resection, usually in hereditary conditions, or may occur again, if the resection is inadequate, failing to remove the tumor in its entirety.

Insulinoma

Surgery is generally recommended for insulinomas; when indicated, a minimally invasive approach is preferable. Pancreatectomy with lymphadenectomy is recommended for malignant insulinomas [19]. Because it almost always is benign, insulinoma forms an ideal surgical target for enucleation. Surgical cure rates for insulinoma are excellent, approaching 99% in experienced hands. In patients

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with insulinoma, the clinical–histopathologic risk profile is heavily stacked in favor of surgical cure: small tumors, benign in nature; young patients with few, if any, comorbidities; enucleation or very limited pancreatic resection required only. Insulinomas have low malignant potential and thus pancreas-preserving approaches without routine lymphadenectomy are generally sufficient and are associated with high rates of biochemical cure and low rates of recurrence. A recent study showed that the 10- and 15-year disease-free rates of insulinoma after surgery were 95.6% and 85.4%, respectively [20].

Gastrinoma

For gastrinomas, the high malignant potential is assumed, and resection with lymphadenectomy is recommended. Gastrinomas with MEN 1 exhibit metachronous recurrences, so care must be taken to avoid excessive surgery [21].

Formal pancreatectomy with regional lymph node resection is recommended. For example, regional lymph node dissection for gastrinoma is associated with improved biochemical cure and potentially survival.

Glucagonoma, Somatostatinoma, and VIPoma

As rare functional pancreatic NENs other than insulinomas and gastrinomas (e.g., glucagonomas, VIPomas, somatostatinomas, GRFomas, PPomas, ACTHomas, and PTHomas) are highly malignant, pancreatectomy with lymphadenectomy is recommended [22]. Most glucagonomas and somatostatinomas are considered "nonfunctional" even when they present with characteristic signs and symptoms, as with necrolytic migratory erythema, which is pathognomonic of glucagonoma. Somatostatinomas, lacking characteristic stigmata, are often so large at the time of diagnosis that they can no longer be enucleated. VIPoma typically causes Verner–Morrison syndrome, which is characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA). These tumors, being the subject matter of single reports or small case series, are extremely rare, precluding the generation of comprehensive evidence-based data.

Conclusion

Although great strides have been made in terms of staging and grading of PanNEN, it has proved challenging to assemble large enough series of patients with PanNEN and sufficiently long follow-up periods to permit the adjustment of postoperative outcomes for a large number of confounding variables: tumor entity, clinical presentation, hormone secretion, genetic background, location within the pancreas, tumor stage and grade, type and extent of surgery, surgical margins, and neoadjuvant and adjuvant therapies. There is a dire need for predictive molecular markers that afford better risk stratification of PanNETs than currently provided for by Ki-67 grading and current imaging modalities.

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Section 8

Neoplastic Tumors of Exocrine Tissue: Pancreatic Cancer

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Epidemiology of Pancreatic Cancer

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Incidence, Mortality Trends, Survival Prognosis

In 2020, worldwide, there were approximately 495 773 individuals diagnosed with pancreatic cancer and approximately 466 003 individuals died from their disease, making pancreatic cancer the seventh most common cause of cancer death [1]. Pancreatic cancer is strongly associated with increased age, with the majority of cases occurring after age 60. In the United States, from 2014–2018 the incidence of pancreatic cancer in whites increased from 3 per 100 000 or less before age 45, to 33.4 per 100 000 in individuals aged 60–64, and 97.3 per 100 000 in individuals aged 80–84 [2]. Incidence is approximately equal in men and women. The disease burden is strongest in developed countries compared to developing countries [1]. This difference is likely driven, in large part, by differences in age structure as well as access to medical care necessary for the diagnosis of pancreatic cancer [3].

In developed countries, the overall incidence of pancreatic cancer is expected to continue to increase with the general aging of the population, particularly in high-income countries [4,5]. Pancreatic cancer is projected to become the second leading cause of cancer death in the United States by 2030 [6]. However, other countries have seen a recent decrease in the incidence of pancreatic cancer that seems to reflect patterns in cigarette consumption. As discussed later, cigarette smoking is a major risk factor for pancreatic cancer and never smoking or smoking cessation is strongly associated with a decrease in risk. In contrast, increased body mass index (BMI) and diabetes mellitus are both associated with a greater risk of pancreatic cancer and the increasing prevalence of these risk factors is projected to lead to a rise in incidence of pancreatic cancer.

Pancreatic cancer is associated with an extremely poor prognosis with an estimated average and a five-year rate of ~10% in the US [4]. Survival rates have increased only slightly since the mid-1970s, from 4–5% to around 10% in the United States [2]. The low survival rates are mainly due to advanced stage at diagnosis, with only ~33% of patients presenting with local disease [2]. Among patients who undergo surgical resection, the five-year survival rate is ~15–25% [7]. Outcomes after surgical resection of the pancreas are highly dependent on the experience of the surgeon and the hospital; mortality rates are 70% lower among high-volume surgeons compared with low-volume surgeons, and hospitals with a high patient volume compared with low-volume hospitals [8].

Cigarette Smoking

Of modifiable risk factors, the relationship between active cigarette smoking and pancreatic cancer risk is well established. Approximately 20% of all pancreatic cancers are attributable to cigarette smoking [9–11]. Numerous studies have explored the relationship between smoking and pancreatic cancer. A metaanalysis of 82 epidemiologic studies published between 1950 and 2007 [9] reported a 1.74-fold (95% confidence interval [CI] 1.61–1.87) increased risk of pancreatic cancer among current smokers and a 1.2-fold (95% CI 1.11–1.29) increased risk of pancreatic cancer among former smokers when compared with never smokers. Pooled analysis of individual-level data from the nested

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case–control studies within the Cohort Consortium (PanScan) [11] as well as analysis of data from 12 case–control studies in the Pancreatic Cancer Case-Control Consortium (PanC4) [10] showed that smokers have a 75–120% increased risk of pancreatic cancer compared with never smokers, and the risk persists for 10–20 years after smoking cessation [10,11]. Risk also increased according to the number of cigarettes consumed per day; smokers of more than 35 cigarettes per day have a threefold (95% CI 2.2–4.1) increased risk of pancreatic cancer compared with never smokers [10].

Quitting smoking is associated with a reduced pancreatic cancer risk with a decreased odds ratio in former smokers when compared with active smokers. Studies suggest that the risk in former smokers returns to that of never smokers 15–20 years after smoking cessation [10,11].

Diabetes

The relationship between diabetes and pancreatic cancer is quite complex; many newly diagnosed pancreatic cancer patients report a recent onset of diabetes, and those with long-standing diabetes report a recent worsening of diabetes. Thus, it is generally considered that while long-standing diabetes is a risk factor for pancreatic cancer, diabetes can also result as a consequence of pancreatic cancer.

There is considerable variability when estimating the prevalence of diabetes and/or glucose intolerance among newly diagnosed pancreatic cancer patients [12]. It has been estimated that up to 80% of newly diagnosed pancreatic cancer patients have glucose intolerance or diagnosed diabetes [13]. Studies that rely on patient or medical records of reported diabetes show lower prevalence estimates, including a large Mayo Clinic case–control study in which 40% of patients reported diabetes [14]. Over 75% of pancreatic cancer patients who develop diabetes, do so within the two years preceding their pancreatic cancer diagnosis [15]. Thus, there is considerable interest in examining populations of newly diagnosed diabetics to determine whether this might enable earlier detection of pancreatic cancer. While initial studies have indicated that up to to 1% of newly diagnosed diabetics develop pancreatic cancer within three years of their diabetes diagnosis [16], subsequent studies have shown a lower incidence of <0.3% [17].

While many pancreatic cancer patients develop diabetes as a consequence of their disease, there is considerable support from numerous population-based studies that long-standing diabetes (>3 years) is associated with a modest increase in the risk of pancreatic cancer. Overall, the risk of pancreatic cancer in long-standing diabetes ranges from 1.5- to 2.4-fold [18–21]. However, as the duration of diabetes increases, the association between diabetes and pancreatic cancer weakens, with some studies showing only modest or no increase in pancreatic cancer risk 15–20 years after diagnosis with diabetes [21,22]; however, some studies still support an association with diabetes of 20 years or more [20].

In patients with new-onset diabetes who undergo surgical resection, diabetes often resolves after removal of the pancreatic cancer. In contrast, diabetes does not resolve in patients with long-standing diabetes after surgical removal of their cancer [23].

Body Mass Index

In addition to diabetes, increased weight or BMI has consistently been associated with increased risk of pancreatic cancer. The World Health Organization (WHO) defines overweight individuals as those with a BMI of 25.0–29.9 kg/m^2 and obese individuals as those with a BMI >30.0 kg/m^2.

Over the past 15 years, many studies have demonstrated an increased risk of pancreatic cancer among obese individuals. In 2001, Michaud et al. reported a relative risk of pancreatic cancer of 1.72 (95% CI 1.19–2.4) for individuals with a BMI >30 kg/m^2 compared with individuals with a BMI <23 kg/m^2 after controlling for the effect of age, smoking, and diabetes among participants of the Health Professionals Follow-Up Study and the Nurses' Health Study [24]. Many subsequent studies have confirmed this finding; a pooled analysis of data from 13 prospective cohort studies reported an odds ration (OR) for pancreatic cancer of 1.33 (95% CI 1.12–1.58) when comparing individuals in the lowest quartile of BMI with those in the highest quartile after controlling for the effects of age and smoking. Adjusting for the effect of diabetes attenuates this association slightly (OR 1.21; 95% CI 1.01–1.44) [25].

Alcohol

Numerous studies have examined the association between alcohol consumption and risk of pancreatic cancer. The results of these studies have been inconsistent, with some studies showing an association and others showing no relationship. One challenge to these studies is the strong relationship between smoking and heavy alcohol use, making it difficult to assess the independent association between alcohol use and pancreatic cancer risk. However, several recent large-scale studies that have pooled data across several studies, using data from either prospective

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cohort studies or retrospective case–control studies, have demonstrated that high levels of alcohol intake are associated with an increased risk of pancreatic cancer. These studies consistently report a ~20–45% increased risk of pancreatic cancer among heavy drinkers (defined as three drinks/day or ≥30 grams/day of alcohol), compared with non- or occasional drinkers [26–28]. In addition, in a pooled analysis of data from the Pancreatic Cancer Case-Control Consortium [29], the risk increases up to 60% among extremely heavy alcohol drinkers (≥9 drinks/day).

Heavy alcohol consumption is associated with pancreatitis, an established risk factor for pancreatic cancer. Furthermore, acetaldehyde is an established carcinogen. Thus, the association between alcohol and pancreatic cancer risk could be either via alcohol-induced pancreatitis or as a direct effect of acetaldehyde.

Pancreatitis

The relationship between pancreatitis and pancreatic cancer has been well established. Individuals with hereditary pancreatitis, a rare inherited condition, have a remarkably high lifetime risk of pancreatic cancer of 40% [30]. The risk is further increased by cigarette smoking [31]. Quantifying the association between pancreatitis and pancreatic cancer is challenging given the difficulties in diagnosis and differentiation between chronic and acute pancreatitis [32]. In addition, like diabetes, pancreatitis is both a risk factor and a manifestation of pancreatic cancer.

The inflammation and damage of long-standing pancreatitis can lead to the development of pancreatic cancer. However, individuals with pancreatic cancer also experience pancreatitis as a consequence of their cancer. A recent large-scale study of 5048 cases of ductal pancreatic adenocarcinoma and 10 947 controls from 10 case–control studies within the Pancreatic Cancer Case-Control Consortium examined the association between pancreatic cancer and pancreatitis. Overall, 6% of pancreatic cancer patients reported a history of pancreatitis compared to 1% of control individuals. The association between a recent diagnosis of pancreatitis (<1 year) and pancreatic cancer was remarkably high (OR 21.35; 95% CI 12.03–37.86) [33]. In contrast, the association between pancreatitis and pancreatic cancer was nearly threefold at intervals of >2 years between diagnoses (OR 2.71; 95% CI 1.96–3.74 [33]. The association between pancreatitis and pancreatic cancer persisted after controlling for other risk factors including smoking, alcohol consumption, BMI, and diabetes. Interestingly, there was evidence of effect modification by age, with a stronger association between pancreatitis and pancreatic cancer in patients diagnosed before the age of 65 [33].

Dietary Factors

Given the generally late age of onset of pancreatic cancer and the complexity of lifetime dietary factors, identification of dietary factors that are consistently associated with pancreatic cancer risk has been remarkably challenging. Several studies have suggested a diet rich in fruit and vegetables may protect against pancreatic cancer with risk reduction in the order of 30–40%, when comparing the highest intake to the lowest intake of fruits and vegetables [34–36]. While a diet rich in fruit and vegetables may protect against pancreatic cancer, several studies have demonstrated an increased risk of pancreatic cancer among individuals who are frequent consumers of smoked or processed meats [37]. A metaanalysis including 6643 pancreatic cancer cases from 11 prospective studies reported that eating at least one serving of processed meat a day was associated with a 19% increased risk of pancreatic cancer [37].

Gastrointestinal Microbiome

In recent years, the importance of the microbiome in human health and disease has gained recognition. Several studies have shown that periodontal disease and tooth loss are associated with pancreatic cancer risk [38]. In 2007, a study among males participating in the Health Professionals Follow-up Study reported that individuals with a history of periodontal disease had a hazard ratio (HR) of pancreatic cancer of 1.54 (95% CI 1.16–2.04) compared with those without such a history [39]. A recent study examined the association between specific oral pathogens and pancreatic cancer risk using prospective samples collected within the PLCO trial. This study found that individuals with circulating antibodies to *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* had higher odds of pancreatic cancer (OR 1.60; 95% CI 1.15–2.20, and OR 2.20; 95% CI 1.16–4.18, respectively), compared with noncarriers [40].

While some studies have shown an association between pancreatic cancer risk and *Helicobacter pylori* infection, not all studies have shown a positive association. One possible explanation for these inconsistent results is that the relationship may vary between CagA-positive and CagA-negative infections; CagA-negative infection is positively associated with disease and CagA-positive infection potentially has a protective effect. A recent metaanalysis found an overall association of OR 1.13; 95% CI 0.86–1.50 for *H. pylori* infection an pancreatic cancer risk. The association was OR 0.78; 95% CI 0.67–0.91, and OR 1.30; 95% CI 1.02–1.65 for CagA-positive and CagA-negative strains, respectively [41].

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Allergy

Individuals with a history of allergies, including hay fever, allergic rhinitis, atopic dermatitis, and atopic asthma, may have a lower risk of developing pancreatic cancer. A metaanalysis published in 2005 reported an overall association between allergies and pancreatic cancer risk of relative risk (RR) 0.82; 95% CI 0.68–0.99. A stronger protective effect was reported in atopic allergies (RR 0.71; 95% CI 0.64–0.80) and no association was reported for asthma or food allergies [42]. A recent pooled analysis of data from the Pancreatic Cancer Case-Control Consortium reported a protective effect of hay fever and animal allergies (OR 0.74; 95% CI 0.56, 0.96, and OR 0.62; 95% CI 0.41, 0.94, respectively), and no association with asthma [43]. In contrast, a recent case–control study from Spain reported a protective effect of both allergy and asthma (OR 0.66; 95% CI 0.52–0.83, and OR 0.64; 95% CI 0.47–0.88, respectively) [44].

Family History

One of the strongest risk factors for pancreatic cancer is having a family member with pancreatic cancer. The clustering of pancreatic cancer in families was first reported in the 1970s. Large-scale observational studies have consistently estimated an increased risk of pancreatic cancer among those with a family history of pancreatic cancer [45–53]. A recent pooled analysis of data from one case–control and six cohort studies estimated the odds of pancreatic cancer to be 1.76 higher (95% CI 1.19–2.61) among individuals who had at least one first-degree relative with pancreatic cancer compared with those with no family history of pancreatic cancer [51]. Risk is even higher in familial pancreatic cancer kindreds (defined as a having at least one pair of first-degree relatives with pancreatic cancer) with a 6.79-fold increased risk of pancreatic cancer among first-degree relatives. Mutations in the following genes have been associated with a markedly increased risk of pancreatic cancer: *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *CDKN2A*, *STK11*, *PRSS1*, *MSH2*, *MLH1*, *MHS6*, and *PMS2* [54–60].

Conclusion

Pancreatic cancer is a leading cause of cancer mortality in developed countries. Unlike other cancers, the incidence of pancreatic cancer has increased in recent years. Major modifiable risk factors include cigarette smoking, diabetes, obesity, and alcohol intake. Nonmodifiable risk factors include age and family history of pancreatic cancer.

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Smoking, a Risk for Pancreatic Cancer: Experimental and Clinical Data

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Introduction

Smoking is a well-established, avoidable risk factor accounting for approximately 16% of pancreatic cancer cases in Europe [1]. The increase in cancer risk is dose dependent but a long duration at lower intensity seems to be worse than a higher intensity over a shorter period of time and the use of a small daily number of cigarettes is sufficient to sharply increase the pancreatic cancer risk [2]. Interestingly, smoking is not associated with the transformation of intraductal papillary mucinous neoplasms (IPMNs) to invasive IPMN, indicating different pathways between IPMN transformation and developing pancreatic ductal adenocarcinoma [3]. While clear epidemiologic associations exist between inhaled cigarette smoke and pancreatic disease, our ability to delineate this association remains limited. Of note, no similar association has been demonstrated between smokeless tobacco and pipe or cigar smoking and pancreatic cancer.

Experimental Data Regarding Smoking: A Risk Factor for Pancreatic Cancer

Due to the large number of chemicals in cigarette smoke, the effect of cigarette smoke on the pancreas is likely multifactorial and complex. Several of these chemicals display toxic, carcinogenic, or pharmacologically active properties, of which many have not yet been identified, contributing to our incomplete understanding on the effects of cigarette smoking on the pancreas.

This problem was addressed by several experiments utilizing *in vivo* treatment with tobacco smoke or *in vitro* treatment with cigarette smoke condensate. Several effects of cigarette smoking observed in humans could be reproduced experimentally. *In vivo* experiments demonstrated that smoking induced pancreatic inflammation and sustained endothelin upregulation as well as mitochondrial dysfunction [4,5]. *In vitro*, cigarette smoke extracts induced oncogenic AKT signaling by the induction of maturation of miR-25-3p, a complex mechanism linking cigarette smoking to pancreatic cancer development [6]. Furthermore, cigarette smoke extracts induced stem cell features in cancer cells via 7α nAChR-mediated PAF1 expression [7]. In contrast to cancer-inducing pathomechanisms, cigarette smoke extracts increased the protective properties of pancreatic cells by increasing intracellular glutathione by NFκB activation, thus increasing the protection against radical oxygen species [8].

Two mechanisms of action have been described for the compounds identified in cigarette smoke. First, chemicals such as polycyclic aromatic hydrocarbons have obvious carcinogenic properties that damage genomic DNA. Second, chemicals such as nicotine exert pharmacologic effects on cells, contributing to neoplasia.

Genetic analysis has revealed that the risk of a smoker developing pancreatic cancer is associated with the gene locus on 2q.21.3 in intron 5 of the transmembrane protein 163 (TMEM163) and upstream of the cyclin T2 (CCNT2) [9]. Once pancreatic cancer is developing, genetic alterations in 12 signaling pathways are found in over 67% of patients independent from cigarette smoking [10]. Some of these pathways include integrin signaling, apoptosis, DNA damage control, and regulation of the G1/S phase, to name a few. Carcinogens derived from cigarette smoke are likely contributing to genetic

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alterations such as these. Following inhalation, carcinogens travel through the bloodstream to the pancreas where they are taken up by acinar or ductal cells. Once carcinogens reach their target tissue, they then begin to exert their toxic properties. For example, 80 days of oral 2-aminoanthracene, a member of the anthracene family, was found to induce pancreatic acinar cell necrosis with formation of duct-like structures [11]. Other carcinogens have to be metabolized to more active compounds before they exert their toxic properties, especially nitrosamines, nitroaromatic hydrocarbons, and aromatic and heterocyclic compounds which are metabolized to reactive electrophiles. These reactive electrophiles are then able to interact with DNA to exert their genotoxic carcinogenic effects [12,13].

Several enzymatic systems are available for pancreatic carcinogen metabolism, of which the cytochrome P450 system, glutathione S-transferases, and the UDP-glucuronosyltransferases are the most important. NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), the most abundant and best studied carcinogen in cigarette smoke, undergoes CYP 450-dependent oxidation to form NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) whose S-enantiomer shows high adduct formation with pancreatic DNA [14]. This results in the creation of DNA adducts to either thymidine or guanine [15]. It can be postulated that these DNA adducts induce mutations and act as key steps in pancreatic cancer development if these mutations are randomly formed in critical gene loci such as *KRAS* or *P53*.

In addition to DNA mutations in critical loci, a disturbance of epigenetic regulation of gene expression can be induced by cigarette smoke through aberrant DNA methylation by benzo[a]pyrene, shown to be present in significantly high concentrations in cigarette smoke. This effect of aberrant DNA methylation has been previously demonstrated in the pancreas of mice treated with benzo[a]pyrene [16]. The carcinogen-induced DNA methylation can interfere with the expression of a variety of crucial genes in the pancreas.

Apart from their carcinogenic properties, compounds such as nicotine or NNK, NNN (N-nitrosonornicotine), and NDMA (N-nitrosdiethylamine) exert pharmacologic effects by functioning as ligands for cell surface receptors. These substances contained in cigarette smoke at high concentrations interact and activate nicotinergic acetylcholine receptors (nAChRs). These receptors are expressed not only on normal acinar and ductal cells but also on pancreatic cancer cells [17]. Each substance can be found in different concentrations in cigarette smoke, with nicotine demonstrating the highest concentration, followed by NNK and NNN.

In addition to the varying quantities of these chemicals, substantial discrepancies in binding affinities also exist. NNK preferentially binds to α7 nAChRs while NNN has a higher affinity for α2-α6 nAChRs [18]. This activation of nAChRs contributes to cigarette smoke-induced pancreatic carcinogenesis [17]. NNK not only activates nAChRs; by activating β2-AR signaling, it also induces HIF1 upregulation which then leads to increased proliferation of pancreatic cancer cells and increased pancreatic cancer cell invasion [19]. Benzapyrene and dioxine may also activate aryl hydrocarbon receptors, inducing IL-22 mediated pancreatic fibrosis [20].

Independent of pancreatic carcinogenesis, nicotine is associated with the development of pancreatic inflammation. The inflammatory effects of nicotine on acinar cells are thought to occur in a calcium-dependent mechanism. In isolated acinar cells, nicotine activates nAChRs, promoting the influx of calcium into the acinar cell and enhancing the secretion of digestive enzymes [21]. This appears to be a key event in the development of cigarette smoke-associated acute and chronic pancreatitis since pancreatic acinar cell damage can be observed experimentally following prolonged nicotine treatment [22]. While the mechanism is not well described, the influence of nicotine on calcium signaling also promotes tumor cell viability, even after the development of pancreatic cancer [23].

Apart from calcium signaling, nicotine also exerts its effects through other pathways and cell types. Nicotine activates stellate cells via α7 nAChR-mediated JAK2/STAT3 signaling inducing pancreatic fibrosis and promoting the differentiation of myeloid-derived suppressor cells to tumor-associated macrophages and dendritic cells, thus supporting carcinogenesis [24,25]. Of note, treatment of pancreatic ductal epithelial cells and pancreatic cancer cells with nicotine previously resulted in a dose-dependent secretion of adrenaline and noradrenaline, contributing to cellular proliferation. This nicotine-induced autocrine catecholamine loop was mediated by 3α, 5α, and 7α nAChRs [26].

In addition, pancreatic ductal cells and pancreatic cancers cells secrete the neurotransmitter GABA following combined stimulation with nicotine and catecholamines. GABA can also act as a potent tumor suppressor, mitigating the damaging effects of chronic nicotine exposure in cells coincubated with GABA [27]. Interestingly, nicotine is able to reduce GABA secretion in a time-dependent manner. This is thought to be mediated by downregulation of the GABA-synthesizing enzymes GAD65 and GAD67 in a 4α nAChR-dependent manner, abrogating the GABA-induced growth inhibition [27].

In addition to its effects on cellular proliferation, nicotine also influences the ability of tumor cells to migrate, invade surrounding tissues, and metastasize.

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In pancreatic cancer cell lines, cigarette smoke extracts and nicotine induce the expression of MUC4 in a α7 nAChR-dependent manner [28]. MUC4 is a mucin which promotes tumorigenesis and tumor progression. Additionally, MUC4 is aberrantly expressed in pancreatic cancer and its expression is upregulated in progressively worsening pancreatice intraepithelial neoplasia (PanIN) lesions [29].

Nicotine has also been found to stimulate pancreatic cancer growth, invasion, and metastasis by inducing the expression of osteopontin, a secreted molecule expressed in many cancers. Following nicotine-dependent activation of nAChRs, osteopontin confers tumorigenicity to cells, resulting in increased cell survival, cell motility, tumor growth, and metastasis. This effect is mitigated in the presence of nAChR antagonists, preventing nicotine-induced osteopontin expression [30]. Nicotine further has the ability to hypermethylate tumor suppressor genes by 7α nAChR and MAP kinase pathways, inducing epigenetic alterations supporting carcinogesis [31], and can induce epithelial–mesenchymal transition (EMT) in pancreatic cancer cells [32].

These pathways represent only a fraction of the pathways involved in cigarette smoke-associated pancreatic damage. The carcinogenic effects that are conveyed to many different types of cancer are not specific to the pancreas. Therefore, pancreas-specific effects of cigarette smoke must be involved, rendering the pancreas susceptible to damage from cigarette smoke. These effects are also mediated by the activation of nAChRs that regulate the secretory function of the pancreas. This is evident when cholecystokinin (CCK)-stimulated acinar cells are treated with nicotine, resulting in a reduction of CCK-stimulated amylase secretion [33].

Additionally, it has been shown that chronic nicotine treatment not only reduces the secretion of amylase but also increases the intracellular amylase content in pancreatic acinar cells [34]. Somewhat similar observations were made with cigarette smoke inhalation over a period of 12 weeks. Cigarette smoke inhalation induced a dose-dependent increase in trypsinogen expression but did not influence the expression of genes associated with pancreatic ductal cells [35]. These secretory alterations were associated with focal inflammatory lesions detected throughout the pancreas [36]. When nicotine treatment was performed over a prolonged period in mice carrying a constitutively active *k-ras* gene, comparable effects were observed in the pancreas. Nicotine treatment in conjunction with active *k-ras* induced pancreatic acinar cell damage leading to higher grade PanIN lesions and increased acinar-to-ductal metaplasia [37]. This was associated with a loss of GATA6 expression that could be reversed by metformin. After full transition to pancreatic cancer cells, nicotine induced a cancer stem cell phenotype by interacting with α7 nAChR and further induced EMT, promoting cell migration. Similarly, these effects were also reversible with GATA6 overexpression [37]. These pathways appear to be crucial steps in cigarette smoke-induced pancreatic damage. Another mechanism by which nicotine leads to pancreatic cancer progression and metastasis is by inducing MUC4 expression in a dose-dependent manner [28].

Even though pancreatic inflammation and acinar-to-ductal metaplasia are very likely to be associated with pancreatic carcinogenesis, nicotine alone is not the sole factor in tobacco-associated pancreatic carcinogenesis but enhances its occurrence. Acinar cell stimulation plays an important role in these mechanisms since the stimulation of acinar cells by CCK also significantly increased the rate of pancreatic cancer formation, indicating that nicotine may enhance the fatal action of carcinogens by altering the secretory function of acinar cells.

Other carcinogens are also able to induce acinar-to-ductal metaplasia. This has been demonstrated in rodent models of ductal adenocarcinoma in which 7,12-dimethylbenz(a)anthracene (DMBA) crystals are surgically implanted in the pancreatic tissue. In this model, histologic alteration of the exocrine pancreas was observed, described as tubular complexes, representative of acinar-to-ductal metaplasia [38].

In summary, experimental evidence of cigarette smoke-induced pancreatic carcinogenesis can be placed into two categories. The first is that carcinogens can induce genetic or epigenetic changes resulting in DNA damage. Second, carcinogens mediated their pharmacologic effects through nACh receptors. The latter can be further subcategorized. The first subset of nAChR-dependent mechanisms centers on the enhancement of procarcinogenic events mediated by a variety of substances. The second subset of mechanisms involves alterations in acinar cell secretory function, contributing to the development of pancreatic inflammation.

Clinical Data Supporting the Experimental Findings

Clinical data on cigarette smoke-induced pancreatic damage largely consists of epidemiologic correlations between smoking, pancreatic inflammation, and cancer. Some of the key elements, such as carcinogen accumulation and interference with the regulation of pancreatic enzyme secretion, have been confirmed in clinical studies. Prior research has demonstrated that carcinogens do accumulate in pancreatic juice of smokers. In these

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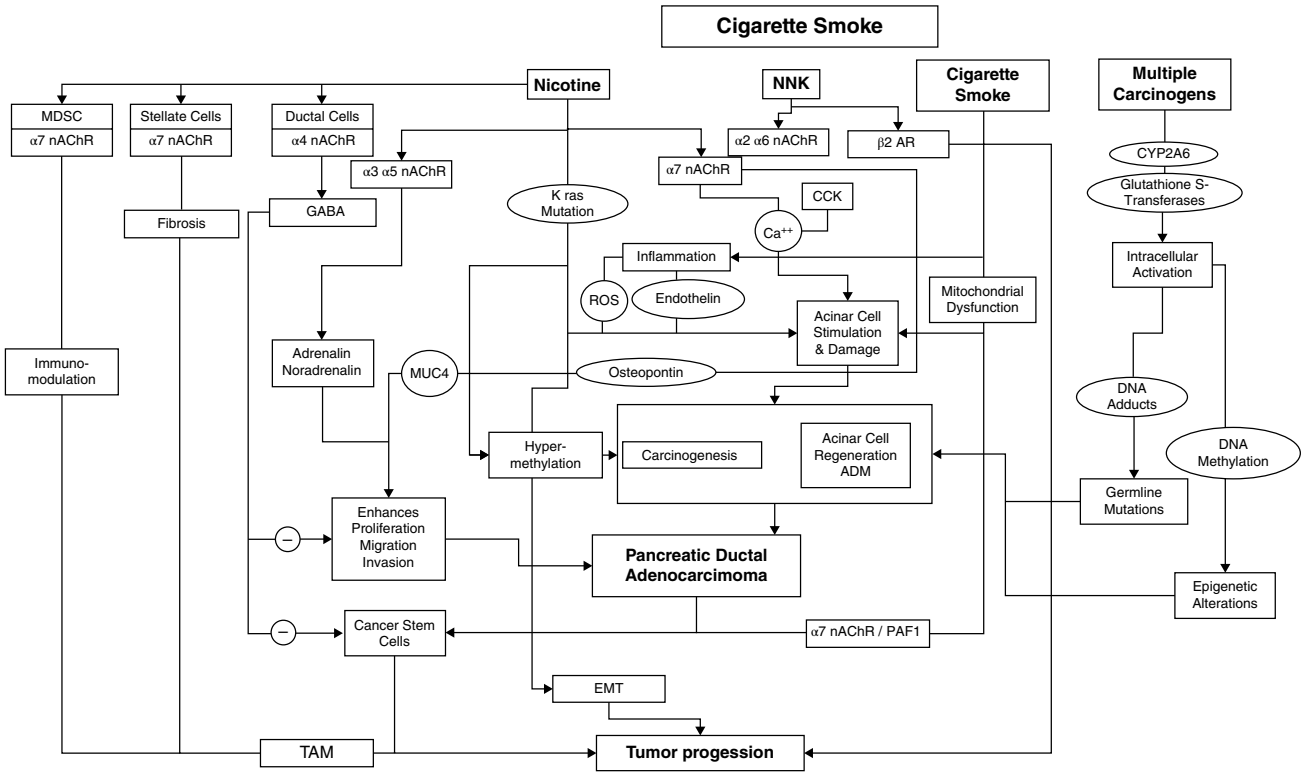


Figure 118.1 Summary of experimental and clinical data on the effects of cigarette smoking on pancreatic carcinogenesis. The pharmacologic activity of cigarette smoke on the pancreas is mediated by nicotinergic acetylcholine receptors (nAChR) and induces pancreatic acinar cell damage and mediates a variety of adverse events. In addition to that, the carcinogenic action is induced after the intracellular activation of carcinogens by cytochrome P450 enzymes. Glutathione transferases seem to be involved in the intracellular detoxification.

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studies, NNK was detectable in 83% of smokers [39]. Previous studies have also demonstrated that inhaled carcinogens are delivered to the pancreas and that enzymes metabolize these compounds into active electrophiles, at which point they can exert their genotoxic properties within the pancreas [40]. As an example of their clinical relevance, the phenotypic variation of carcinogen-metabolizing enzymes, such as CYP450 2A6, influenced the pathogenesis of pancreatic cancer. In an adjusted categorical analysis, subjects in the uppermost quartile of CYP2A6 activity carried an 80% greater risk of acquiring pancreatic cancer [41].

Similar observations have been made for glutathione S-transferases (GSTs), a family of phase II isoenzymes believed to protect cells from reactive chemical intermediates [42]. In this study, the adjusted odds ratios of pancreatic cancer for heavy smokers with the GSTT1-null genotype were 5.0 (95% confidence interval [CI] 1.8–14.5) for women and 3.2 (95% CI 1.3–8.1) for men, indicating that the combination of heavy smoking and a deletion polymorphism in GSTT1 is associated with an increased risk of pancreatic cancer.

Tobacco-derived carcinogens are undoubtedly involved in the carcinogenesis of pancreatic cancer. While 32P-postlabeling analysis indicates a specific adduct pattern in smokers, increased adducts in pancreatic DNA were observed in smokers but an association with BMI was also observed [43]. No clear association of DNA adducts in the pancreas with the individual smoking history utilizing chromatography has yet been established. This could be due to the relatively limited amount of DNA adducts present or this quantity being below the limit of detection [39,40]. Independent of detection method, nonsmokers must also be exposed to many environmental carcinogens, inducing the formation of DNA adducts similar to those observed in smokers.

Similar to experimental observations, cigarette smoke exerts widespread pharmacologic effects on the human pancreas which are mediated by nicotine and other tobacco-derived carcinogens displaying pharmacologic activities. In the 1970s, the relationship of cigarette smoking with the pancreatic secretion was discovered [44]. In a clinical experiment, smoking induced immediate and reproducible effects on the pancreatic secretion in volunteers. After smoking cigarettes, the fluid and bicarbonate secretion was immediately altered and returned to normal within 30–60 minutes. This effect directly correlated with the serum nicotine concentration. In accordance with this observation, cotinine, a derivate of nicotine with a longer half-life, was detected in the pancreatic juice of active smokers with an average concentration of 129<ts>ng/mL [39]. The concentration of these compounds has not been measured in pancreatic tissue, but the differential expression of nACh receptors has been demonstrated on human pancreatic acinar and ductal cells [17,26].

The effects of cigarette smoke on pancreatic exocrine function are thought to be responsible for the induction of pancreatic acinar cell damage and have been shown to have a clear association with both acute and chronic pancreatitis [45]. While a small subset of patients experience inflammation of the entire gland, in most patients the cigarette smoke-induced pancreatic damage is only present in small focal areas of the pancreas where remodeling is occurring at the same time as sample acquisition. Similar to experimental data, an increase in small inflammatory foci with ongoing pancreatic regeneration was observed in humans as well. In this context, focal acinar cell dysplasia has been described at the time of autopsy and in surgical specimens. These acinar cell lesions were found to be acquired and correlated to history of smoking. Additionally, they were detectable in 83% of heavy smokers [46]. Acinar cell lesions are also associated with simple and atypical ductal hyperplasia, indicating that either the cigarette smoke-induced damage leads to ductal lesions as well, or it can be speculated that these ductal lesions are the result of acinar-to-ductal metaplasia [47].

Conclusion

Today evidence for cigarette smoke-induced pancreatic disease remains incomplete, but available experimental and clinical data propose potential pathomechanisms of cigarette smoke-induced pancreatic carcinogens that remain to be further investigated in both experimental and clinical studies. The pancreas is susceptible to the effects of carcinogens found in cigarette smoke partly as a result of acetylcholine receptor-mediated events, or by mutations, e.g., of tumor suppressor genes. These contribute to the induction of proliferative signaling pathways and pancreatic inflammation. These events provide a fertile environment for pancreatic ductal adenocarcinoma to develop, at which point the smoking history appears to have no impact on the clinical course [48]. However, patients who continue to smoke following surgical resection of a ductal adenocarcinoma have an increased perioperative risk and decreased survival compared to individuals who refrain from smoking [49]. The fact that the risk sharply decreases after smoking cessation and a risk similar to never smokers is reached after approximately 15 years may encourage smokers to stop smoking [2,50].

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Molecular Understanding of the Development of Ductal Pancreatic Cancer

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Introduction

Pancreatic cancer is the third leading cause of cancer in the United States and is predicted to be the second leading cause of cancer death by the year 2030 [1,2]. A fundamental understanding of the molecular underpinnings of pancreatic cancer will not only provide insight into the pathophysiology driving this neoplasm, but will also provide new tools that can be used to detect early curable pancreatic neoplasms and to treat advanced cancers.

The groundwork for our understanding of the genetic drivers of ductal adenocarcinoma was laid decades ago, but this knowledge has exploded in recent years. The first gene identified as targeted in ductal adenocarcinoma was the *KRAS* oncogene in the mid-1980s [3–5]. It took almost another decade before the *TP53* tumor suppressor gene was shown to be inactivated in most of these cancers [6,7]. In the 1990s, a team led by Scott Kern extensively characterized the allelic losses in a series of ductal adenocarcinomas and identified a number of recurrent genetic alterations, including homozygous deletions on chromosomes 9p, 13q, and 18q that correspond to three additional tumor suppressor genes [8–10]. The homozygous deletion identified on chromosome 9p proved to target the *p16*/*CDKN2A* tumor suppressor gene, the deletion on 13q led to the discovery of the *BRCA2* gene, and the homozygous deletion on 18q led to the discovery of *SMAD4* [11,12]. Thus, by the mid-1990s the four genes most frequently targeted in ductal adenocarcinomas had been discovered (*KRAS*, *TP53*, *SMAD4*, *p16*/*CDKN2A*), as had one of the major familial pancreatic cancer genes (*BRCA2*). Over the ensuing decade, a number of additional genes were found to be targeted in ductal adenocarcinomas, often using candidate gene approaches [13–15]. Most of these proved to be low-prevalence genes (altered only in a small fractions of the cancers), such as *BRAF* and *FBXW7* [15].

The draft map of the human genome was completed in 2001, providing a foundation for dramatically changing the pace of gene discovery in ductal adenocarcinomas [16]. Jones and colleagues used the draft map to Sanger sequence the complete exomes of a series of 24 well-characterized ductal adenocarcinomas, providing a first complete catalogue of protein-coding mutations in this cancer type [17]. This work had several important results: the oncogene *KRAS* and the tumor suppressor genes *TP53*, *SMAD4*, and *p16*/*CDKN2A* were confirmed to be the most commonly targeted "mountains" in ductal adenocarcinoma (Table 119.1), and a number of "hills" with less prevalent mutations were also identified (Table 119.2). In addition, the Jones study led to the discovery of a familial pancreatic cancer gene (*PALB2*) [18–20]. For the first time, a comprehensive understanding of the genetic drivers of pancreatic tumorigenesis was possible. A number of large-scale studies followed, and in recent years several groups, including the Pan-Cancer Analysis of Whole Genomes (PCAWG), the International Cancer Genome Consortium (ICGC), and the Cancer Genome Atlas (TCGA), have extended Jones' whole-exome sequencing study by sequencing the exomes and even whole genomes of ductal adenocarcinomas [21–25]. The time is now ripe to translate this understanding to patient care.

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Table 119.1 "Mountains" of pancreatic tumorigenesis.

Gene	Chromosome	Gene type	Function	Mechanism of alteration
KRAS	12	Oncogene	MAPK signaling	Point mutation (hotspots)
P16/CDKN2A	9	Tumor suppressor	Cell cycle regulation	Point mutation/LOH, homozygous deletion, methylation
TP53	17	Tumor suppressor	DNA damage response	Point mutation/LOH
SMAD4	18	Tumor suppressor	TGF-β signaling	Point mutation/LOH, homozygous deletion

LOH, loss of heterozygosity; MAPK, mitogen activated protein kinase; TGF-β, transforming growth factor β.

Table 119.2 Examples of genetic "hills" of pancreatic tumorigenesis.

Gene	Mechanism of alteration	Prevalence/tumor type
AKT2	Amplification	10–20%
ARID1A	LOH + IM	5–10%
ARID2	LOH + IM	<5%
ATM	Often germline	<5%
AXIN1	LOH + IM	<5%
CTNNB1	LOH + IM	<5%
EP300	LOH + IM	<5%
FBXW7	LOH + IM	<5%
GATA6	Amplification	10%
GNAS	Point mutation	Colloid variants
MAP2K4	LOH + IM	<5%
MLL3	LOH + IM	5–10%
MYB	Amplification	10%
MYC	Amplification	5%
PBRM1	LOH + IM	<5%
ROBO2	A number	5–10%
SMARCA2	LOH + IM	Undifferentiated with rhabdoid
SMARCA4	LOH + IM	Undifferentiated with rhabdoid
TGF βR1	HD	<5%
TGF βR2	HD, LOH + IM	Microsattelite unstable cancers

HD, homozygous deletion; IM, intragenic mutation; LOH, loss of heterozygosity.

Genetic Alterations: The Four Mountains

KRAS

The *KRAS* oncogene is activated in >90% of ductal adenocarcinomas, usually by a point mutation at codon 12, 13 or 61 [26]. *KRAS* gene mutations activate a complex cascade of downstream signaling pathways, including the mitogen activated protein kinase and phosphoinositide 3′-kinase pathways [27–30]. *KRAS* gene mutations also contribute to the "Warburg effect" and increase autophagy in the neoplastic cells [27–29]. The resultant changes caused by *KRAS* gene mutations combine to promote tumorigenesis.

KRAS wild-type ductal adenocarcinomas can have other distinctive genetic alterations [15,31]. Some *KRAS* wild-type tumors harbor *BRAF* mutations, and others, as will be discussed in greater detail below, are microsatellite unstable [15,22,31] or harbor kinase fusion genes [32].

p16/CDKN2A

The *p16/CDKN2A* tumor suppressor gene on chromosome 9p is inactivated in 90% of ductal adenocarcinomas [8,33]. In ~40% of the cancers, the gene is inactivated by an intragenic mutation in one allele coupled with loss of the second allele (loss of heterozygosity, LOH). In another 40%, the *p16/CDKN2A* gene is inactivated by homozygous deletion, and in 10–15% of the cancers it is inactivated by hypermethylation of the *p16/CDKN2A* gene promoter [33,34]. Loss of p16 protein function leads to loss of a major regulator of the cell cycle. The *MTAP* gene on chromosome 9p is often included in the homozygous deletions that target *p16/CDKN2A* [35]. As will be discussed later, the deletion of *MTAP* has potential therapeutic implications.

TP53

The *TP53* tumor suppressor gene on chromosome 17p is inactivated, usually by an intragenic mutation in one allele coupled with LOH in the remaining allele, in ~75% of ductal adenocarcinomas [18,36]. Loss of p53 function disrupts a number of critical tumor suppressive pathways, including response to DNA damage, apoptosis, cell cycle arrest, and senescence [37]. Aberrant protein expression patterns, as seen on immunohistochemical

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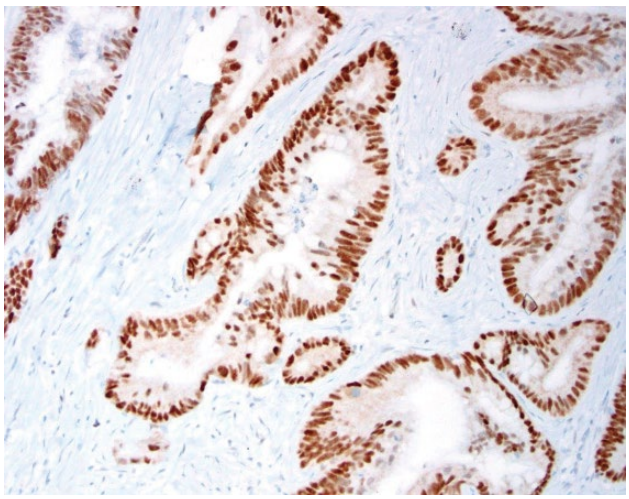


Figure 119.1 Aberrant p53 protein expression in *TP53* mutant ductal adenocarcinoma. Immunohistochemistry for p53 shows strong diffuse nuclear labeling, which is strikingly different from the occasional weak nuclear labeling seen in the nonneoplastic stromal cells.

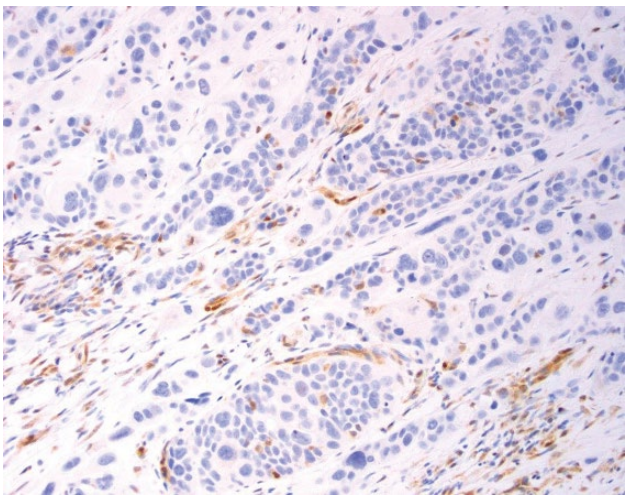


Figure 119.2 Loss of SMAD4 protein expression in *SMAD4* mutant ductal adenocarcinoma. Immunohistochemistry for SMAD4 shows loss of protein expression in malignant cells, while retained expression in nonneoplastic stromal cells serves as an internal control.

assays, are correlated with gene mutation—these include strong diffuse nuclear expression (Fig. 119.1) as well as complete absence of expression.

SMAD4

The *SMAD4* tumor suppressor gene on chromosome 18q is inactivated in ~55% of ductal adenocarcinomas [12]. As noted earlier, *SMAD4* was discovered by Scott Kern and colleagues as a recurrent homozygous deletion identified using a panel of microsatellite markers [12]. Subsequently, *SMAD4* has been shown to encode a protein that functions in the transforming growth factor (TGF)-β pathway. Immunolabeling for the SMAD4 protein is a good surrogate marker for *SMAD4* gene inactivation, as inactivating mutations in *SMAD4* are associated with loss of SMAD4 protein expression (Fig. 119.2) [38].

Genetic Alterations: The Hills

In addition to the four "mountains" (the four genes targeted in >50% of pancreatic cancers), a growing number of genes have been found that are altered in only a small fraction (usually <10%) of ductal adenocarcinomas (see Table 119.2) [18,22–24]. For example, Biankin and colleagues sequenced the exomes of close to 100 ductal adenocarcinomas and reported that genes coding for embryonic regulators of axon guidance, including *ROBO* and *SLIT*, are targeted in a minority of these cancers [23]. Sausen and colleagues reported uncommon mutations in chromatin regulating genes (such as *MLL3* and *ARID1A*) that are associated with improved survival [39]. Others have reported focal gene amplifications in ductal adenocarcinomas, including amplification of *MYC*, *GATA6*, *BRAF*, *CDK6*, and *MET* [24,40-42]. Genetic alterations in *p15/CDKN2B*, *CCNE1*, and *MAP2K4* have also been reported [21].

Chromosome Instability

In addition to the specific genes noted above that are targeted by focal chromosomal alterations, ductal adenocarcinomas of the pancreas are also characterized by larger chromosome abnormalities [24,43,44]. These larger chromosome abnormalities were first noted in karyotyping studies of pancreatic cancer [43]. Subsequently, the exact loci involved were defined better in whole-genome sequencing studies [24]. These latter studies also showed that chromosome instability is associated with the inactivation of DNA maintenance genes (*BRCA1*, *BRCA2* or *PALB2*) and a DNA damage repair deficiency mutational signature [24].

Microsatellite Instability

A small fraction (2–3%) of pancreatic cancers have microsatellite instability, with defective DNA repair pathways leading to a large number of point mutations [31,45,46]. Some pancreatic cancers with microsatellite instability (also known as MSI high cancers) arise

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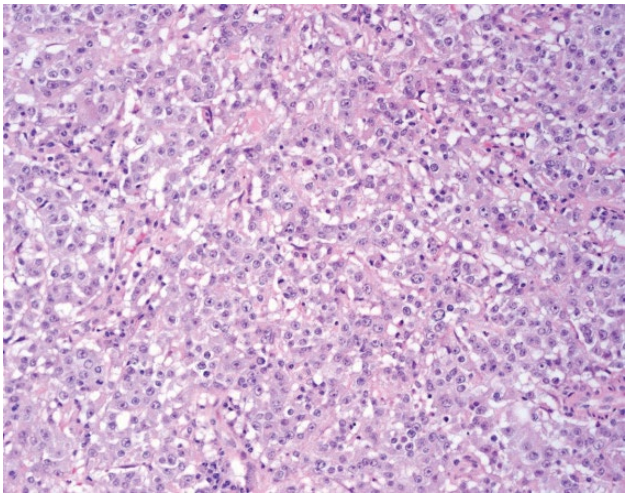


Figure 119.3 Medullary carcinoma. The characteristic morphology of medullary carcinoma (poor differentiation, syncytial growth, pushing borders) is frequently seen in tumors with microsatellite instability.

in association with intraductal papillary mucinous neoplasms (IPMNs) and others have a characteristic medullary histology that includes poor differentiation, a syncytial growth pattern, and pushing tumor borders (Fig. 119.3) [45]. These carcinomas are important to recognize because, despite their poor differentiation, they are associated with a good prognosis [45,46]. In addition, as will be discussed later, MSI high pancreatic cancers may be particularly sensitive to immunotherapies [47].

Kinase Gene Fusions

KRAS wild-type ductal adenocarcinomas frequently harbor kinase gene fusions. Various gene fusions involving *BRAF*, *FGFR2*, *RAF1*, *ALK*, *RET*, *NTRK1*, *ERBB4*, *FGFR2*, *EGFR*, and *MET* have been identified in 12% of *KRAS* wild-type ductal adenocarcinomas [48]. In many of these gene fusions, a serine/threonine kinase or tyrosine kinase catalytic domain is fused to an oligomerization domain [48]. In addition to gene fusions mentioned above, *NRG1* gene fusions have also been reported in *KRAS* wild-type ductal adenocarcinomas [49–51]. *NRG1* gene fusions promote tumor proliferation and survival by activating pathologic signaling via MAPK, PI3K-AKT, and NF-κB [32]. Though data are still limited, pancreatic cancer patients with cancers that harbor gene fusions may benefit from targeted kinase inhibitors. For example, pancreatic cancer patients with cancers with *NRG1* gene fusions have shown significant response to afatinib [50] and erlotinib/pertuzumab [51], and patients with cancers with *ALK* gene fusions have demonstrated stable disease after treatment with ceritinib [52].

Taken together, these studies highlight the importance of identifying a subset of patients whose pancreatic cancers harbor gene fusions, as they may benefit from specific targeted pharmacologic agents.

Mitochondrial Gene Mutations

Although we tend to focus on the nuclear genome, eukaryotic cells also have a mitochondrial genome. Jones and colleagues sequenced the mitochondrial genome (mtDNA) of a series of pancreatic cancers, and homoplasmic mtDNA somatic mutations were identified in nearly all of the cancers [53]. While it could not be determined if any of these mtDNA mutations were driving the neoplastic process, Jones and colleagues were able to show that mtDNA is greatly (6–8-fold) increased in ductal adenocarcinoma cells relative to normal cells. This finding suggests that mtDNA mutations may be easier to detect than nuclear mutations and that mtDNA mutations may be useful in screening and disease monitoring tests [53,54].

Expression Changes

A number of genes are overexpressed in ductal adenocarcinomas relative to normal nonneoplastic pancreatic ductal cells [55–61]. Many of these overexpressed genes were identified at the mRNA level using techniques such as serial analysis of gene expression (SAGE) and expression microarrays, and protein overexpression has been confirmed using Western blotting or immunohistochemical labeling [55–61]. Other overexpressed proteins were discovered using mass spectrometry and other proteomic approaches [62]. Transcriptomics studies based on gene arrays and RNA sequencing have also demonstrated that pancreatic ductal adenocarcinomas have distinct subtypes, including basal-like and classic subtypes [63]. While basal-like subtype (median survival time of 11 months and one-year survival rate of 44%) is associated with worse outcome compared to classic subtype (median survival time of 19 months and one-year survival rate of 70%), patients with basal-like tumors have shown better response to adjuvant chemotherapy [63]. Additional molecular subtypes have also been described in recent studies based on RNA and DNA sequencing [64].

The list of genes and proteins overexpressed in ductal adenocarcinomas is long and includes mesothelin, claudins, annexins, S-100 related proteins, and others [57,65–70]. Pandey and colleagues have reviewed the literature and established a centralized resource for the collection and sharing of these overexpressed genes [71,72]. More recently, a "proteogenomic" study that integrated

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Table 119.3 Precursors to ductal adenocarcinoma.

Precursor	Abbreviation	Location	Size	Key genetic alterations
Pancreatic intraepithelial neoplasia	PanIN	Head = Tail	<0.5 cm	Early: *KRAS*, *CDKN2A* Late: *TP53*, *SMAD4*
Intraductal papillary mucinous neoplasm	IPMN	Head > Tail	≥1 cm	Early: *KRAS*, *GNAS*, *KLF4*, *RNF43*, *CDKN2A* Late: *TP53*, *SMAD4*
Mucinous cystic neoplasm	MCN	Tail > Head	Broad range	Early: *KRAS*, *RNF43*, *CDKN2A* Late: *TP53*, *SMAD4*

proteomic, phosphoproteomic, and glycoproteomic analyses with whole-genome, whole-exome, methylation, and RNA sequencing was completed [73]. This comprehensive study not only provides a number of candidate biomarkers but also sheds light on the impact of genetic alterations on protein expression and posttranslational modifications [73]. As discussed below, differentially expressed genes may be useful targets for developing early detection tests and novel therapies. The technologies to quantitatively distinguish peptides are now so refined that normal proteins can be distinguished from mutant proteins created by some of the DNA mutations discussed above [74].

In addition to overexpressed genes, a number of genes are downregulated in ductal adenocarcinomas. Promoter hypermethylation often accounts for this downregulation [75]. Genome-wide analyses of DNA methylation in ductal adenocarcinomas have identified over 1000 genes that are differentially methylated in pancreatic cancer relative to normal pancreatic ductal cells, and many of these differentially methylated genes are differentially expressed at the protein level [75,76].

MicroRNAs are small noncoding RNAs that have emerged as important regulators of a number of cell functions, and the expression of a number of microRNAs is dysregulated in ductal adenocarcinomas of the pancreas [77]. These microRNAs include miR-21, miR-101, miR-155, miR-192, miR-193, miR-194, miR-196, miR-210, and miR-335 [77,78]. Some of these microRNAs have been proposed as prognostic markers and may also be potential therapeutic targets in ductal adenocarcinomas [79].

Precursor Lesions

Most invasive ductal adenocarcinomas of the pancreas are widely metastatic and incurable at the time of diagnosis [80]. We believe that early detection is one of the best hopes to impact the dismal prognosis associated with these cancers. An understanding of the biology of the precursor lesions that give rise to invasive carcinoma is therefore essential.

Three precursor lesions are currently recognized: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs) (Table 119.3). A number of studies have examined the genetic alterations and gene expression changes in these precursors, and increasing degrees of dysplasia are associated with the accumulation of genetic alterations and changes in gene expression [78,81–83]. Lesions with high-grade dysplasia have many of the same changes that are found in invasive ductal adenocarcinomas [78,81–83]. For example, most of the microRNAs overexpressed in invasive ductal adenocarcinoma are also overexpressed in precursor lesions with high-grade dysplasia. In addition, studies of IPMNs have shown that when multiple precursor lesions are present, they often arise from independent clones [84], and low- and high-grade lesions have distinct mutations [85]. Specifically, low-grade IPMNs harbor hotspot mutations in *KLF4*, which encodes a member of the Kruppel family of transcription factors [85]. Together, these findings suggest that gene mutations and changes in expression may be useful markers for the early detection of pancreatic neoplasms [78].

Neoplasms with ACINAR DIFFERENTIATION

Although the vast majority of "pancreatic cancers" are ductal adenocarcinomas, malignancies with acinar differentiation do occur, and these cancers are clinically and molecularly unique [86]. Acinar cell carcinomas form solid masses in older adults and have a poor prognosis. Recent whole-exome sequencing studies have revealed

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that acinar cell carcinomas exhibit striking genomic instability, commonly having either microsatellite instability or chromosomal instability [86]. There is striking heterogeneity in the genes altered among different acinar carcinomas with no single gene mutated in >30% of cancers [86]. Uncommon mutations have been observed in well-characterized drivers of ductal adenocarcinoma (*SMAD4*) and pancreatic cystic neoplasms (*GNAS*), as well as genes commonly altered in other tumor types (*APC*, *BRAF*). Recurrent rearrangements involving *BRAF* and *RAF1* have also been identified in 23% of acinar cell pleuralcarcinomas [87]. Targetable genetic alterations, including *BRCA2*, *PALB2*, *ATM*, and *JAK1*, have also been reported in acinar cell carcinomas [86].

Pancreatoblastoma, the most common pancreatic tumor in childhood, can contain a variety of cell types but at minimum contains an acinar component and squamoid nests. These neoplasms contain far fewer somatic mutations than acinar cell carcinomas, and alterations in the Wnt pathway (*APC*, *CTNNB1*) as well as loss of a highly imprinted region on chromosome 11p are the most common genetic alterations in this tumor type [86,88].

Clinical Applications

These are exciting times. We are on the cusp of translating our growing understanding of the underlying biology of pancreatic cancer to patient care. We anticipate that in the near future, new molecular approaches will be developed to enhance the early detection, diagnosis, treatment, and monitoring of pancreatic cancer. Let us give examples of each of these.

Early detection is one of the most promising areas for the translation of molecular genetics to patient care. For example, mutant *GNAS* shed from noninvasive IPMNs can be detected in secretin-stimulated pancreatic secretions (pancreatic juice) collected at the time of endoscopic ultrasound (EUS) [89]. Similarly, mutant *KRAS* shed from early-stage (operable) ductal adenocarcinomas of the pancreas is detectable in the blood [90]. Panels of new biomarkers, such as tumor-specific genetic mutations, applied to the right biosamples, will provide exciting new opportunities for the early detection of curable pancreatic neoplasms.

Molecular genetics can also be used to supplement tissue diagnoses. For example, in patients with a known pancreatic cancer, it can be difficult to determine if an adenocarcinoma in a distant site, such as the lung, represents a metastasis or a new primary. In these instances, the loss of SMAD4 expression, as determined by immunohistochemical labeling, supports the diagnosis of a metastasis from a pancreatic primary over a second lung primary (see Fig. 119.2) [38].

Remarkable advances have also been made in the application of molecular genetics to personalized therapy of ductal adenocarcinomas. Five examples are listed below.

- Approximately 2–3% of pancreatic cancers are microsatellite unstable (MSI high), and these cancers appear to be remarkably sensitive to immunotherapy, particularly with PD-1 blocking agents [47].
- Most pancreatic cancers overexpress mesothelin, and a number of antimesothelin-specific vaccines [91,92] and chimeric antigen receptor T cells targeting mesothelin [93–95] have been developed.
- Pancreatic cancers with a mutation signature indicative of DNA damage repair deficiency (including those with *BRCA2* mutations) are likely to respond to specific chemotherapeutic regimens, including platinum agents and poly ADP ribose polymerase (PARP) inhibitors [96,97].
- *KRAS* wild-type ductal adenocarcinomas often harbor *BRAF* mutations, and these *BRAF* mutant cancers are highly sensitive to targeted BRAF inhibition [22].
- As mentioned earlier, the *MTAP* gene on chromosome 9p is homozygously deleted with *P16/CDKN2A* in 30–40% of pancreatic cancers. This gene codes for the enzyme methylthioadenosine phosphorylase (MTAP), and MTAP-deficient cells may be differentially sensitive to methylthioadenosine (MTA, the substrate for the MTAP enzyme) and to small molecular inhibition of protein arginine methyltransferase 5 (PRMT5, an enzyme upstream from MTAP) [98,99].

Finally, a molecular genetics approach can be used to monitor patients for response to therapy. Neoplasms release mutant DNA into the circulation (circulating tumor DNA, ctDNA) and this ctDNA can be quantified [39,90]. Velculescu and colleagues have shown that monitoring ctDNA can be used to quantify the response of a neoplasm to therapy [39].

Conclusion

These are the best of times. Hundreds of ductal adenocarcinomas of the pancreas have been sequenced, and the fundamental drivers of tumorigenesis in the pancreas are now defined. These drivers give us new tools for the early detection of pancreatic neoplasms, and it is hoped that these early detection efforts will save lives, especially when applied to high-risk populations, such as individuals with a deleterious germline variant in a familial pancreatic cancer gene. Despite our best efforts at early detection, we recognize that most patients will still be diagnosed with an invasive carcinoma, and new

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approaches to personalized therapies are needed. These may include immunotherapy for MSI high cancers and poly ADP ribose polymerase inhibitors for *BRCA2* mutant cancers. In the near future, we will also be able to follow the effectiveness of new therapies using novel approaches, such as monitoring circulating tumor DNA (ctDNA). The future is bright!

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From Tissue Turnover to the Cell of Origin of Pancreatic Cancer: An Updated View

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is highly aggressive [1]. Despite enormous advances in understanding molecular tumor biology, the overall survival rate of PDAC patients has remained unchanged for the past 20 years. This may be partially attributed to the fact that PDAC is a histopathologically defined tumor entity with extreme heterogeneity on clinical, histologic, transcriptional, and genetic levels. Various molecular subtypes with distinctive tumor biologies exist, but current therapies are applied without taking these putative differences into account [2].

Pancreatic ductal adenocarcinoma originates from the exocrine cells of the pancreas containing mainly acinar and duct cells. The exocrine cells constitute the predominant cell mass of the human pancreas, in which approximately 70% of all pancreatic cells are acinar cells and 18.5% are ductal cells [3]. As described before, acinar cells produce a variety of digestive enzymes (i.e., amylase and lipase) and duct cells generate bicarbonate and transport the digestive enzymes to the duodenum [4]. Thus, dissecting exocrine cells' self-renewal and regenerative capacities is essential to our understanding of pancreatic physiology and carcinogenesis.

Both ductal and acinar cells display considerable heterogeneity in the human and murine pancreas. Based on the subtle difference in transcriptional profiles, acinar and duct cells can be further categorized into subpopulations with different self-renewal and regenerative capacities. Taking advantage of single-cell analysis with advanced bioinformatic tools, we are now beginning to understand the biological significance of such cellular heterogeneity within the same cell type. In addition, several rare stem/progenitor cells with uni- or multipotent differentiation potential, which are usually not abundant enough to be visible in single-cell analysis, were recently identified in both the acinar and duct compartments. They also contribute significantly to physiologic tissue turnover, organ regeneration upon severe tissue damage, and pancreatic carcinogenesis [5,6].

Previously, we hypothesized that a subset of cells that renew the adult organ physiologically or regenerate it after acute pancreatitis would be more susceptible to oncogenic transformation than others [7]. Here, we provide an updated view on this issue, focusing on literature published after 2015. In addition, as the cell of origin is implicated as a significant source of PDAC heterogeneity for the molecular tumor subtypes, we also summarize and discuss the recent literature on this topic.

Molecular and Phenotypic Characterization of Acinar- and Duct-Derived PDAC

Despite its heterogeneity, most human PDACs contain so-called founder/driver mutations, including oncogenic KRAS mutations (e.g., $KRAS^{G12D}$) and mutations in tumor suppressors (e.g., p53 and p16) [8]. These founder mutations can be induced in the adult pancreas in a cell type-specific manner (e.g., acinar and duct cells); they have been widely used to generate acinar- and duct-derived PDAC models.

Apart from founder mutations, recent *in vivo* studies revealed that the general risk factors for PDAC, such as pancreatitis, promote pancreatic carcinogenesis. Mature pancreatic acinar cells are primarily refractory to transformation following activation of oncogenic Kras [9]. It has also been shown that Kras mutations appear in the pancreas of healthy individuals [10]. This supports the notion that oncogenic Kras alone is insufficient for

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induction of carcinogenesis, and a transformation-permissive environment needs to be established first. Indeed, in the presence of acute or chronic inflammation (e.g., as induced by caerulein injection), pancreatic acinar cells in the adult pancreas become susceptible to oncogenic Kras-mediated transformation [9].

Here, pancreatic acinar cells undergo a metaplastic process called acinar-to-ductal metaplasia (ADM) induced by oncogenic Kras and an (external) inflammatory stimulus. Under physiologic circumstances, ADM is the default and reversible metaplastic process in which acinar cells transiently adopt a ductal phenotype with the acquisition of progenitor-like features, and they are capable of redifferentiating into acinar cells. However, in response to oncogenic Kras signaling and caerulein-induced pancreatitis, this metaplastic phenotype of acinar cells is irreversible. The ADM lesions progress into pancreatic intraepithelial neoplasia (PanIN) lesions and eventually into PDAC, forming a distinctive acinar–ADM/PanIN–PDAC transformation pathway [11–13].

However, pancreatic duct cells cannot initiate PDAC development in such a model derived by oncogenic Kras and caerulein-induced pancreatitis [14]. Thus, pancreatic duct cells may assume a specific transformation route in the context of inflammation-driven carcinogenesis, and caerulein-induced pancreatitis is not an appropriate stimulus. To test this, we used another widely used model of pancreatitis—ductal obstruction—as it is a common etiology being both cause and consequence of human chronic pancreatitis [15]. Indeed, ductal obstruction-induced pancreatitis promotes the formation of preneoplastic lesions from the pancreatic ductal compartment. These duct-derived preneoplastic lesions show a highly proliferative potential with persistent activation of the intrinsic inflammatory pathway; however, no PanIN lesions were observed in these animals. Instead, these preneoplastic lesions presented in tubular complex structures surrounded by desmoplastic stroma. Likely, pancreatic duct-derived PDAC follows a transformation pathway bypassing the PanIN stage (see below). Later on, these observations were confirmed by another independent study published by Shi and co-authors [16]. Taken together, the type and extent of inflammation determine whether PDAC can be initiated from pancreatic acinar or duct cells.

Having illustrated that pancreatic duct and acinar cells can initiate PDAC in mice, four independent studies have systematically compared acinar- and duct-derived tumors (Table 120.1) [17–20]. In 2016, Bailey and co-workers used the Hnf1b^{CreERT2} (HNF1 homeobox B) and Mist1^{CreERT2} (also known as Bhlha15 [basic helix-loop-helix family, member a15]) Cre line to drive Kras^{G12D} and p53^{R172H} mutations in the adult duct and acinar cells, respectively [17]. All mice were injected at 7–9 weeks of age with 5 mg tamoxifen for three consecutive days to induce Cre-mediated genetic recombination. Here, *Mist1^{CreERT2}; LSL_Kras$^{G12D/+}$; LSL_p53$^{R172H/+}$* mice developed acinar-derived ADMs/PanINs and PDACs as early as two months after tamoxifen treatment; however, no duct-derived tumor was observed in *Hnf1b^{CreERT2}; LSL_Kras$^{G12D/+}$; LSL_p53$^{R172H/+}$* mice after six months follow-up. Further experiments uncovered that the expression of two alleles of mutant p53^{R172H} was required to initiate duct-derived tumors: *Hnf1b^{CreERT2}; LSL_Kras$^{G12D/+}$; LSL_p53$^{R172H/R172H}$* mice succumbed to lethal PDAC within 2–3 months and no PanIN lesions were observed in these animals. Histologic evaluation of the respective tumors revealed that acinar-derived tumors are less proliferative but contain better organized collagen deposition adjacent to tumor cells than duct-derived tumors. Moreover, the acinar-derived tumors follow an acinar–ADM/PanIN–PDAC transformation pathway while the duct-derived tumors bypass the PanIN stage. This notion was further verified in Ferreira's study in which they used the Elastase1^{CreERT2} and Krt19^{CreER} Cre lines to mediate genetic recombination in adult acinar and duct cells, respectively (see Table 120.1). As mentioned above, caerulein-induced pancreatitis was used to accelerate acinar-derived PDAC formation in this study. However, these two studies are complicated by either using different genetic drivers (*p53$^{R172H/R172H}$* vs *p53$^{R172H/+}$*) or additional manipulations (with or without pancreatitis) to drive pancreatic carcinogenesis, making a direct side-by-side phenotypic comparison of acinar- and duct-derived tumors impossible.

Later on, this issue was resolved in two studies by Lee and Flowers [19,20]. At 3–4 weeks of age, the same driver mutations (Kras^{G12D} and loss of p53) were introduced to "juvenile" acinar and duct cells using the Ptf1a^{CreERTM} and Sox9-creER^{T2} Cre line, respectively. No additional intervention was performed and all mice were monitored for PDAC development [19]. Here, duct-derived tumors displayed a more aggressive progression pattern than acinar-derived ones, showing earlier tumor initiation and metastasis. In histology, acinar-derived tumors contained a full spectrum of PanIN lesions (PanIN1–3), while duct-derived tumors had only PanIN3 lesions (carcinoma *in situ*). These data suggest that pancreatic duct cells are primed to form carcinoma *in situ*, bypassing the earlier PanIN stages. Interestingly, this phenotypic difference between acinar- and duct-derived tumors disappeared when the above-mentioned driver mutations were introduced to adult acinar and duct cells at 8–10 weeks of age [20].

Taken together, acinar- and duct-derived PDAC are two different tumor entities with potentially different biological phenotypes and progression patterns. Despite certain

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Table 120.1 Phenotypic comparison of acinar- and duct-derived PDAC.

Reference	Cre line	Genotype	Age of Cre induction	Survival	PanIN	Proliferation	Fibrosis
[17]	Acinar *Mist1*^{CreERT2}	*LSL_Kras*$^{G12D/+}$; *LSL_p53*$^{R172H/+}$	7–9 weeks 5 mg ×3	12 ± 2 weeks	Yes	PDAC^{acinar} < PDAC^{duct}	PDAC^{acinar} > PDAC^{duct}
	Duct *Hnf1b*^{CreERT2}	*LSL_Kras*$^{G12D/+}$; *LSL_p53*$^{R172H/R172H}$	7–9 weeks 5 mg ×3	12 ± 2 weeks	No		
[18]	Acinar Elastase1^{CreERT2}	*LSL_Kras*$^{G12D/+}$; *Fbw7*$^{fl/fl}$	8 weeks 100 mg/kg of body ×5	Unknown	Yes	Unknown	Unknown
	Duct Krt19^{CreER}	*LSL_Kras*$^{G12D/+}$; *Fbw7*$^{fl/fl}$	8 weeks 100 mg/kg of body ×2	Unknown	No	Unknown	Unknown
[19]	Acinar Ptf1a^{CreERTM}	*LSL_Kras*$^{G12D/+}$; *p53*$^{fl/fl}$ *LSL_Kras*$^{G12D/+}$; *p53*$^{fl/f}$	3–4 weeks 125 mg/kg of body ×3	18.3 weeks	Yes (PanIN1–3)	Unknown	Unknown
	Duct Sox9-creER^{T2}		3–4 weeks 125 mg/kg of body ×3	11.7 weeks	Yes (PanIN3)	Unknown	Unknown
[20]	Acinar Ptf1a^{CreERTM}	*LSL_Kras*$^{G12D/+}$; *p53*$^{fl/fl}$ *LSL_Kras*$^{G12D/+}$; *p53*$^{fl/fl}$	8–10 weeks 5 mg ×3 8–10 weeks 5 mg ×3	19.6 weeks 36.1 weeks	Yes	Unknown	Unknown
	Duct Sox9-creER^{T2}				No	Unknown	Unknown

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discrepancies among different studies, it is rather conclusive that acinar-derived tumors tend to follow a classic transformation route of acinar–ADM/PanIN–PDAC, while duct-derived tumors assume an oncogenic route of duct–carcinoma *in situ*–PDAC, bypassing the PanIN stage.

Tissue Turnover Dynamics and Carcinogenesis in the Exocrine Pancreas

Although adult acinar and duct cells can give rise to PDAC, the exact identity of such mature cells susceptible to transformation still remains unclear. Hypothetically, a subset of cells that renew the adult organ under physiologic circumstances or regenerate it upon severe tissue damage would be more likely to be the cell of origin for PDAC [7]. The recent discovery of telomerase reverse transcriptase (Tert)- and doublecortin-like kinase-1 (Dclk1) cells provides strong evidence for a potential causal link between tissue turnover dynamics and carcinogenesis in pancreatic acinar cells [5,6]. Using lineage tracing from the Tert locus, a rare subpopulation (1.9%) of acinar cells is marked by Tert expression. Of note, Tert-positive acinar cells are responsible for renewing the pancreas under physiologic conditions and quickly regenerating the acinar compartment after acute pancreatitis. Compellingly, expression of oncogenic Kras in Tert-positive acinar cells causes the ADM/PanIN formation with increased Kras downstream signaling [5]. In contrast, expression of oncogenic Kras in random acinar cells had no such effect. Dclk1-positive acinar cells are also rare, accounting for about 0.08–0.4% of all pancreatic epithelial cells [6]. Using genetic lineage tracing, Dclk1-positive subpopulations are long-lived, quiescent acinar cells that do not contribute to the physiologic acinar cell renewal. However, they can be activated by caerulein-induced pancreatitis and contribute to subsequent acinar cell regeneration. Indeed, Dclk1-positive acinar cells are primarily resistant to oncogenic Kras-mediated transformation, but they become potent cancer-initiating cells after acute pancreatitis.

These data collectively demonstrate that the physiologic maintenance of the acinar cell pool is mainly carried out by the Tert-positive subpopulation, and regeneration of the acinar cell compartment upon severe tissue damage requires both Tert- and Dclk1-positive acinar cells. Although both acinar cell subpopulations are rare, they are readily transformable by oncogenic Kras in the context of tissue turnover.

As for the duct compartment, the exact identity of a ductal subpopulation mediating the tissue turnover and contributing to duct-derived tumors remains largely unexplored. Recently, single-cell analysis of human major pancreatic duct uncovered a subpopulation of ductal cells labeled by activin-like kinase3 (ALK3), but not carbonic anhydrase II (CAII) [21]. These human ALK3-positive duct cells can differentiate into all pancreatic lineages upon transplantation into immunodeficient mice. However, further studies are required to elucidate their functions *in vivo*. Notably, Martens and co-authors recently reported a rare and atypical duct cell that expresses the basal cell transcription factor ΔNp63, an isoform of tumor protein P63 (TP63), in the human pancreas [22]. ΔNp63-positive duct cells account for 0.006% of all pancreatic cells, corresponding to 1.6% of duct cells. Given the fact that the basal-like molecular subtype of PDAC also is enriched for ΔNp63 expression and resembles duct-derived tumors at multiple levels (see below), it is likely that the rare ΔNp63-positive duct cells serve as the cells of origin for duct-derived tumors.

Molecular Subtypes of Human PDAC

Three major molecular subtypes consisting of classic, quasi-mesenchymal (QM-PDA), and exocrine-like pancreatic cancers have been initially identified using transcriptional profiles from physically microdissected tumor epithelium (Table 120.2) [23]. The classic subtype shows a high expression of epithelium-associated genes, whereas the quasi-mesenchymal subtype presents a high expression of mesenchyme-associated genes. The exocrine-like subtype expresses relatively high levels of digestive enzymes. Importantly, these three molecular subtypes of PDAC produce different clinical outcomes and therapeutic responses. Patients with the classic subtype tend to have a better prognosis and are more likely to benefit from targeted therapy (e.g., erlotinib), whereas patients with the QM-PDA subtype have a worse prognosis but are likely to respond to conventional chemotherapy (e.g., gemcitabine). Using patient-derived xenograft (PDX) models, HNF1A (HNF1 homeobox A) and KRT81 (cytokeratin 81) were identified as surrogate subtyping markers for exocrine-like and QM-PDA, respectively [24]. Notably, the exocrine-like subtype was largely resistant to tyrosine kinase inhibitors and paclitaxel due to the high expression of CYP3A5 (cytochrome P450 3A5), which is responsible for metabolizing these compounds.

Recently, this transcriptomic classification system has been further developed using a large RNA-sequencing dataset [24]. The original QM-PDA has been reclassified as a squamous subtype as it is associated with adenosquamous carcinomas (only in a small subset of PDACs) on histology. The squamous subtype continues to be a poor prognostic factor, with a median survival of 13.3 months. The exocrine-like subtype is categorized as an aberrantly differentiated endocrine exocrine subtype (ADEX) because

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Table 120.2 Summary of molecular subtypes in human PDAC.

Molecular subtype	Applied classifier	Therapeutic hints	Overlap with other defined subtypes
Classic QM-PDA exocrine-like	Transcriptome Physically micro-dissected tumor epithelium	Classic: Erlotinib QM-PDA: Gemcitabine Exocrine-like: resistant to tyrosine kinase inhibitors and paclitaxel	
Squamous pancreatic progenitor Immunogenic ADEX	Transcriptome RNA-sequencing data using bulk tissues	Immunogenic: immune modulators	Squamous = QM-PDA ADEX = exocrine-like Pancreatic progenitor = classic
Basal-like vs classic	Transcriptome Virtually micro-dissected tumor epithelium	None	50% overlap with QM-PDA (squamous)

the transcriptional networks responsible for both exocrine and endocrine lineages at a later stage are enriched in this subtype. Importantly, the classic subtype was defined as a pancreatic progenitor characterized by preferential gene expression in early pancreatic development. Characterized by enriched immune networks related to an acquired immune suppression, a novel immunogenic subtype has been identified. It may potentially be therapeutically accessible to novel immune modulators.

One hallmark of PDAC is the extensive stromal reaction. A recent study performed nonnegative matrix factorization (NMF) analysis to digitally separate gene expression for tumor, stroma, and normal components in PDAC samples [25]. This virtual microdissection identified two molecular subtypes: the classic and basal-like subtypes. The basal-like subtype expresses high levels of basal-like genes (e.g., specific laminins and keratins) similar to basal subtypes in breast cancers [26]. The basal-like subtype labels a PDAC cohort with a median survival of 11 months that most likely benefits from adjuvant chemotherapy (hazard ratio [HR] 0.38; 95% confidence interval [CI] 0.14–1.09). Interestingly, approximately 50% of previously described QM-PDA (squamous) subtypes were basal-like subtypes.

In summary, the basal-like/squamous/QM-PDA molecular subtype labels a cohort of PDAC patients with aggressive tumor biology and poor prognosis; the classic/progenitor molecular subtype shows favorable survival.

Cell of Origin Constitutes a Significant Source of Heterogeneity for Molecular Subtype

Although these studies have consistently proven the existence of molecular subtypes of PDAC, the underlying source of such molecular heterogeneity remains unclear. So far, three major sources have been described: (i) allelic imbalance of KRAS; (ii) differential activation of AP-1 (activator protein-1)-dependent enhancer network; (iii) cell of origin (acinar- vs duct-derived tumors). Initially, an increased dosage of mutant KRAS was reported to be associated with aggressive undifferentiated phenotypes of PDAC [27]. Later on, the integrated whole-genome analysis found that the basal-like/squamous subtype is enriched for KRAS allelic imbalance favoring the mutant allele [28]. Recently, this observation was confirmed in xenograft PDACs generated by intraductal transplantation of human PDAC organoids [29]. Here, human PDAC organoids belonging to the basal/squamous subtype are more likely to contain KRAS imbalance. Secondly, a landmark study by Cobo et al. identified a subclinical inflammatory state of acinar cells, mediated by AP-1 activity and responsible for triggering PDAC initiation [30]. As for the molecular subtype, Tu and co-authors demonstrated that cJUN/AP1 activation and its associated enhancer network were related to basal-like/squamous subtype specification; the JUNB/AP1-dependent enhancer network is enriched in the classic subtype [31].

Importantly, it has recently been demonstrated that different cell origin contributes to the phenotypic and molecular specification of PDAC [19,20,32]. As earlier illustrated, duct-derived PDAC had shorter latency in cancer development, and was associated with a dedifferentiated phenotype, whereas acinar-derived PDAC tended to have a "mild" progression [19]. Furthermore, acinar-derived tumors are positive for KRT20 (keratin 20), which is a putative marker for the classic molecular subtype. This was the first evidence that acinar-derived tumors in mice might be comparable to the classic molecular subtype in humans. Later on, transcriptional analysis revealed that the signatures of duct- and acinar-derived murine PDAC were enriched in the basal-like/squamous and classic molecular

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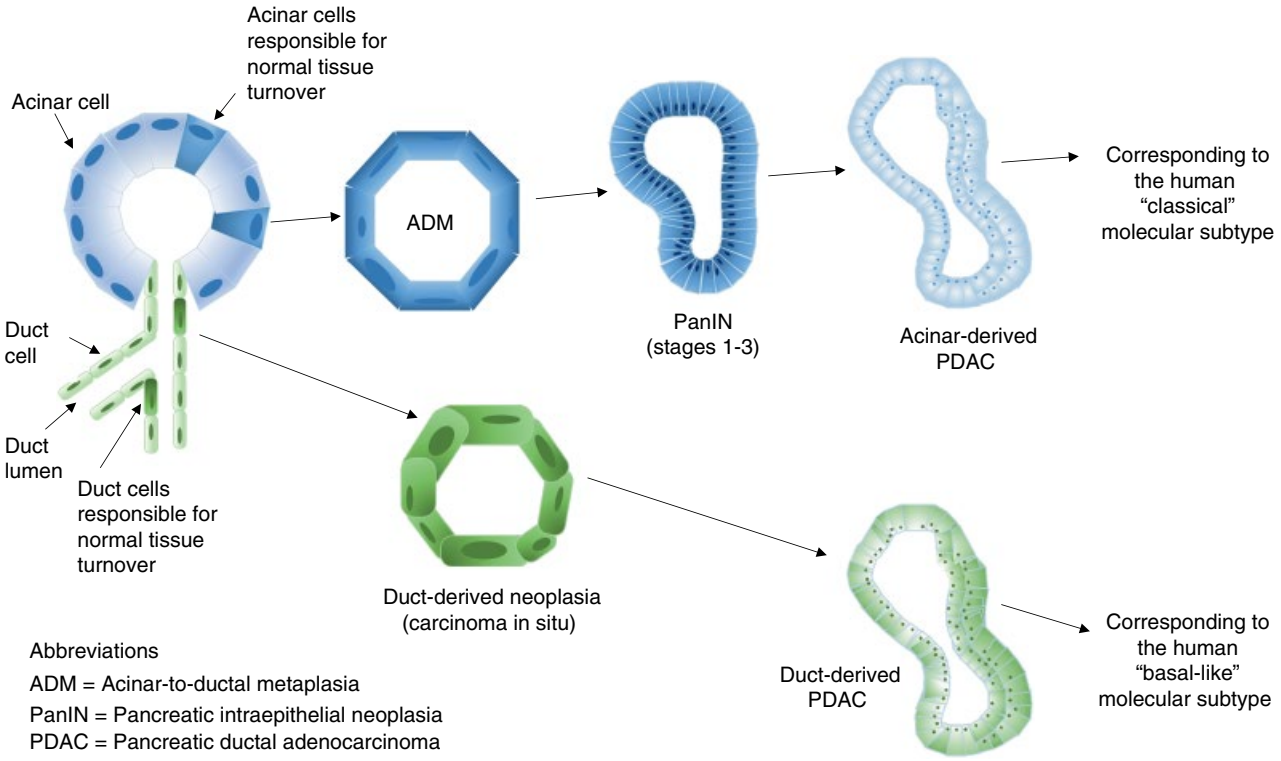


Figure 120.1 Different transformation routes of acinar- and duct-derived tumors and their counterpart molecular subtypes in humans.

subtype, respectively [20]. A recent study demonstrates that the basal-like/squamous and classic subtypes have distinctive DNA methylation patterns and preserve the remnant footprints of normal ductal or acinar cells [32].

Thus, acinar- and duct-derived tumors are similar to classic and basal-like/squamous molecular subtypes at transcriptional and epigenetic levels. This descriptive evidence points to two different origins, etiologies, and evolutional trajectories of classic and basal-like/squamous molecular subtypes.

Taken together, KRAS allelic imbalance, AP-1-dependent enhancer network, and different cell origins are three major contributors that collectively determine the molecular subtype of human PDAC. Thus, disentangling complex interactions among them is crucial to developing molecular subtype-specific therapies.

Conclusion

As described, acinar- and duct-derived PDAC are likely two different tumor entities with different etiologies and transformational trajectories corresponding to classic and basal-like molecular subtypes in humans. Acinar-derived tumors follow a classic oncogenic route of acinar–ADM/PanIN–PDAC, whereas duct-derived tumors assume a route of duct–carcinoma *in situ*–PDAC, bypassing the PanIN stage (Fig. 120.1). The pancreatic acinar cell compartment is a suitable "sub-organ" system for studying tissue turnover dynamics and carcinogenesis; rare subpopulations (e.g., Tert- and Dclk1-positive) of acinar cells involved in organ renewal/regeneration are readily transformable by oncogenic Kras in the context of tissue turnover. In this respect, more studies on the pancreatic duct compartment are still required.

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Microbiome of Pancreatic Cancer: Involvement in Cancer Development and Chemo-/Immunotherapy

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Introduction

The human microbiome drives the tolerogenic innate and adaptive immunity, and resistance to many diseases like diabetes, hypertension, and autoimmune diseases because of its function in maintaining the fine balance in key cellular processes such as inflammation, detoxification, hormones, nutrition, metabolism, and immune. Over the past century, with the revolutionary development of reliable murine models and advanced sequencing technologies, our understanding of the microbiome and its role in cancer initiation and progression has evolved significantly.

However, the microbiota is just beginning to be recognized as an important player in pancreatic carcinogenesis and the interplay among microbes is greater than expected [1]. The microbiome is constantly evolving throughout life in each individual due to several extrinsic (environment, food, drugs, lifestyle, exercise) as well as intrinsic factors (sex, age, hormones, genetics/genotype, stress, and bile secretion) and thus forms the basis for microbial diversity, which has a huge impact on the host immune response and natural history of disease [2]. Hence, microbiotic homeostasis is important for maintenance of a healthy pancreatic microenvironment [3,4]. Risk factors for pancreatic ductal adenocarcinoma (PDAC) can easily impact the microbiome and influence the pancreatic microenvironment and its function. The exact mechanism for microbiota migration to the pancreas has been revealed, such as translocation via the pancreatic duct, portal circulation or mesenteric lymph nodes [5]. Unexpectedly, a 1000-fold increase in tumoral milieu bacteria was found in human PDAC compared with normal pancreatic tissue [6–8].

Collectively, specific well-studied oral, gastrointestinal, and intrapancreatic microbes and some kinds of hepatotropic viruses and bactibilia may have potential etiologic roles in pancreatic carcinogenesis or the modulation of individual responses to oncotherapy [9–11]. In addition, higher abundance and distinct compositions of fungi were also detected in PDAC.

The microbiome is an emerging frontier that provides new avenues for identifying microbial-based biomarkers for diagnosis, prognosis, predicted drug or therapy responses in patients with PDAC [7,12–14]. For instance, recently, McAllister and colleagues analyzed the microbiomes from tumors of long-term survivors (LTS) and short-term survivors (STS) of PDAC using 16S rRNA gene sequencing [8]. They found higher α-diversity in the tumor microbiome of LTS patients and identified an intratumoral microbiome signature highly predictive of long-term survivorship, which demonstrates the potential role of microbial communities with prognostic impact in PDAC individuals. Colonization of *Fusobacterium* was associated with a worse prognosis; Gammaproteobacteria were correlated with resistance to gemcitabine; *Acidovorax ebreus* has a positive impact on metastasis and high tumor grade in PDAC [15]. Modulating the microbiome, via tumor-promoting or inhibitory effects, might help in designing effective therapeutics, which opens a new strategy for this highly fatal disease.

In this chapter, we elaborate on the mechanisms of involvement of microbiota in cancer development, and interactions between the microbiota and chemo-/immunotherapy therapeutic resistance in PDAC.

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Mechanisms of Involvement of Microbiota in Cancer Development

Although sufficient evidence has indicated that pancreatic disorders are often accompanied by microbial dysbiosis, the time sequence and causality of these two phenomena are difficult to define [11]. The emerging link between the microbiota and PDAC exhibits the following properties: bidirectional, heterogeneous, and dynamic [11]. Concrete mechanisms mainly involve supporting pancreatic oncogenic signaling, perpetuating inflammation, regulating the immune system microbe–tumor axis, altering metabolism, and remodeling the tumor microenvironment [10,16]. The role of the microbiome in the development of pancreatic cancer is well supported by recent research in genetically engineered murine models [7,17,18].

First, inflammatory pathologies like pancreatitis and obesity are associated with increased gut permeability and dysbiosis, thereby leading to possible bacterial translocation. Furthermore, persistent inflammation state and excessive oxidative stress exposure result in gene instability and facilitate tumor angiogenesis [19]. Peripancreatic inflammation promoted by the microbiome potentiates oncogenic signaling and suppresses innate and adaptive immunity. Tumor-associated microbiome was shown to promote an epithelial-mesenchymal transition process, thereby leading to epithelial barrier alterations and tumor-promoting inflammation. Viruses, including HBV/HCV, may promote the development of PDAC via activation of the inflammation process and modulation of the PI3K/AKT signaling pathway [20].

Together, these results suggest that the microbiota not only contributes directly to oncogenesis within the tumor microenvironment, but also induces a systemic inflammatory response that facilitates PDAC development [21].

Second, preclinical and epidemiologic studies suggested that the microbiota shapes systemic as well as tumor-specific immunity in pancreatic cancer [22]. On one hand, specific microbes are essential for the education and maturation of the host immune system [23,24], especially the alteration of Treg and Th17 cells which can maintain intestinal homeostasis and immune responses [25]. Possible mechanisms include stimulating goblet cells to secrete mucin to ensure the integrity of the mucosa as well as bacterial recognition of dendritic cells and their metabolites to induce intestinal mucosa-associated lymphoid tissue development [25]. Intratumor microbes may act as a potent antigen that further activates the immune system, associated with immune infiltrates of LTS with pancreatic cancer by encouraging the proliferation of host immune cells and their vascularization [8]. Also, microbiome diversity and composition of PDAC shape immune responses, promoting T-cell activation which ultimately influences survival.

On the other hand, the microbiota promotes immune suppression and modulates carcinogenesis. Immune cells respond to microbiota/pathogen/damage-associated molecular patterns (MAMPs/PAMPs/DAMPs) through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). Mechanistically, the microbiome in primary PDAC exerts potent suppressive influences on the inflammatory tumor microenvironment, establishing the tumor-promoting inflammatory program by activating TLRs on myelomonocytic cells, which leads to the expansion of myeloid-derived suppressor cells (MDSCs) and antiinflammatory M2-like tumor-associated macrophages (TAMs). These tolerogenic innate immune cells promote the differentiation of suppressive populations of $CD4^+$ T cells and prevent the expansion of cytotoxic $CD8^+$ T cells [26]. Specifically, bacterial ligands stimulate TLRs and cause downstream immune suppression, leading to development of PDAC in the setting of genetic risk [27]. The activation of TLR2 and TLR5 facilitates downstream immune suppression and promotes PDAC development [7]. The intratumoral fungi could promote PDAC by activating the complement cascade (C3) and tumor progression by ligation of mannose-binding lectin (MBL) [28]. How MBL and the complement system integrate with the rest of the immune system during PDAC progression is still an unresolved question.

Third, abnormal microbial components and metabolism lead to the production of certain carcinogenic metabolites, such as cancer-promoting secondary bile acid, which could penetrate the systemic circulation of the host and be transported to the site where they exert hormone-like effects [29]. These bioactive metabolites can modulate signal transduction in the host to affect various pathways involved in the regulation of gene expression and transcription, enhance tumorigenic properties such as tumor proliferation, migration, invasion, and evasion of apoptosis, leading to immune suppression, or cause DNA damage [21]. In addition, microbiome communities from LTS and STS are associated with different metabolic pathways. The LTS cases exhibited enrichment in the pathways related to metabolism of amino acids, xenobiotics, lipids, terpenoids and polyketides, besides other cellular functions. Significantly better outcomes were predicted for PDAC patients demonstrating enrichment in xenobiotics biodegradation and lipid metabolism pathways [30]. This study revealed that microbial dysbiosis leads to the development of PDAC and drug resistance increased butyrate and decreased propionate in diabetes.

Finally, the mutual interplay between microbiome and PDAC is complicated; the microbiota and immune system have coevolved and affect each other directly

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via intricate crosstalk. For example, KRAS mutant signaling alone is not sufficient to initiate invasive pancreatic cancer, but additional microbe-induced inflammation can potentiate oncogenesis, and intratumoral bacteria negatively impact antitumor immunity by promoting a tolerogenic immune microenvironment [7]. Meanwhile, microbiota-induced activation of PRRs recruits MyD88 or TRIF adaptor proteins to enhance MAPK and NF-kB signaling in pancreatic cancer cells, which synergizes with KRAS signaling [21]. Bacterial ligands sensed by TLRs create a Th1/Th2/Th17 imbalance in the tumor microenvironment and, in combination with oncogenic KRAS mutation, promote pancreatic tumorigenesis [27].

In brief, the complex role of the microbiota in pancreatic carcinogenesis is yet to be elucidated in detail. Parallel in-depth tumor, immune, metabolism and microbiome phenotyping may generate insight into the mechanisms.

Microbiota Involvement in Chemo-/Immunotherapy

Late-stage pancreatic cancer harbors a fibrotic and immune-excluded tumor microenvironment that impedes the efficacy of chemotherapy and immunotherapy. Accumulating studies suggest that cancer treatments reshape the microbiota profile in the microenvironment; for example, chemotherapeutic agents are known to imbalance the functional composition of microbes [31]. For instance, paclitaxel decreased the abundance of the butyrate-producing bacteria, while increasing the relative abundance in *Mucispirillum* in the colon, which may lead to chemotherapy-induced neuroinflammation. Moreover, irinotecan induced an increase in the relative abundance of Proteobacteria and Fusobacteria in fecal microbiota in male Sprague–Dawley rats, which may result in gastrointestinal dysbiosis [32]. Conversely, the microbiome modulated the therapeutic efficacy and side-effects of chemo-/immunotherapy. Rapid development of treatment resistance by modulation of various enzymes and drug transporters limits overall survival in PDAC patients.

Research has demonstrated that the gut microbiota and intratumoral microbiome may impact therapeutic drug sensitivity and disease survival [8]. Ablation of the microbiome with antibiotics reshapes the tumor microenvironment, inducing T-cell activation, improving immune surveillance, and increasing sensitivity to immunotherapy in tumors [33]. Accordingly, future studies should focus on detection of the dynamic evolution and detailed mechanisms of these processes; adjusting and reshaping the microbiota to enhance the efficacy of therapy is a fascinating direction.

The relationship between microbiota and therapeutic resistance of PDAC is multidimensional and complicated, not only because of the existing crosstalk between microbiota and therapeutic effect and host response. In addition, this effect is systemic, influencing more than the intratumor or adjacent areas. The microbiota influences PDAC chemotherapy resistance through the following aspects.

First, the gut microbiota directly affects drug absorption, metabolism, and bioactivity in both enteral and parenteral administration. Hence, the gut microbiota plays an pivotal role in altering the efficacy of pharmacotherapeutics involved in cancer treatment. Second, microorganisms have specific effects on certain drugs by regulating gene expression and metabolic pathways. For example, the presence of PDAC intratumoral Gammaproteobacteria has the potential to inactivate gemcitabine sensitivity and confer chemoresistance via the bacterial enzyme cytidine deaminase [6]. *Fusobacterium nucleatum*, which promotes oxaliplatin and 5-FU resistance to PDAC by modulating autophagy, was associated with poor prognosis [34].

Furthermore, the gut microbiota may mediate drug toxicity through a series of transformation processes. A typical demonstration is irinotecan, which can be converted to the active metabolite SN-38 with the help of tissue carboxyl esterase; it then exerts its anticancer effect via single-stranded DNA breaks (SSBs). SN-38 could be transformed into the inactive SN-38-G form by UDP-glucuronosyltransferases (UDPGTs) in the liver before being excreted in the gut. However, SN-38-G can be reconverted into the active form SN38 by the bacterial βglucuronidases, which are mainly found in the Firmicutes phylum [35]. SN-38 can induce serious intestinal toxicity similar to diarrhea. Ablation of βglucuronidase-positive bacterial species using specific antibiotics, certain inhibitors for βglucuronidase, and probiotics will help to overcome this defect [36,37].

Nevertheless, the existence of certain commensal microbiota is essential for the efficacy of chemotherapy drugs. Germ-free or antibiotic-treated mice exhibit a reduced anticancer response to oxaliplatin by reducing the production of reactive oxygen species (ROS) in myeloid cells [38], because reactive ROS can lead to DNA damage and apoptosis.

Thus, an intact commensal microbiota is vital to optimal responses to cancer therapy because of its role in modulating cell functions in the tumor microenvironment. Understanding this process provides the basis for the manipulation of microbiota for therapeutic purposes in cancer patients.

Microbial heterogeneity determines the impact on the efficacy of immunotherapy. Recent studies have shown that immune cell effector functions and responses to checkpoint

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inhibitors are regulated by gut microbiome composition [39–41]. *Pseudoxanthomonas*, *Saccharopolyspora*, *Bacillus clausii*, *Streptomyces*, *Bacteroides*, and *Clostridia* species have a long-term and short-term effect on survival in PDAC. Treatment of a PDAC murine model with antibiotics in combination with anti-PD-1 displayed synergistic antitumor efficacy by restoring T-cell activation [8]. Specifically, bacterial eradication promotes immunogenic reprogramming towards an activation phenotype and enhances the efficacy of checkpoint-targeted immunotherapy in PDAC, including a decrease in myeloid-derived suppressor cells and an increase in tumor-protective M1 macrophage polarization, upregulating PD-1 expression by promoting intratumoral $CD4^+$ and $CD8^+$ T-cell activation [7,18].

Thus, antibiotic therapy combined with immunotherapy potentially represents a new strategy for treating patients with PDAC. Conversely, *Bifidobacterium* is believed to promote beneficial effects on the host immune system to enhance an anticancer response and improve immune checkpoint blockade treatment outcomes [23,42]. Based on these findings, clinical trials have been recruited to evaluate the synergistic effects of immunotherapy and antibiotics for PDAC.

Scientists had found evidence of crosstalk between human gut and tumor bacteria, and based on this they performed human fecal microbial transplants into mouse models of the disease, differentially altering tumor growth and immune profile, indicating a possible mechanism for bacteria to regulate tumors. Fecal microbiota transplantation (FMT) from LTS is more protective against tumor in murine models of PDAC compared to those who received FMT from either STS or those without PDAC [43]. Moreover, FMT has shown potential in dealing with the adverse effects of chemotherapy that cause diarrhea in other malignancies [44]. This indicated that restoring the gut with a favorable bacterial population is a feasible approach that can be used with other treatment regimens and might be very effective in treating cancer. That is, successful modulation of the microbiota can enhance the therapeutic response.

Clinical trials focusing on microbiota-modulating agents such as antibiotics and probiotics, diet and prebiotics may allow a tumor-specific and more personalized approach to sensitize tumors to facilitate the enhanced delivery of therapy and establish microbial-based combined treatment strategies.

Conclusion

The involvement of microorganisms in the initiation, progression, maintenance, drug resistance, and modulation of the immune environment in patients with PDAC has been increasing recognized. Identifying and picturing a distinct landscape of microbiota in a large cohort of the PDAC specimens is an imperative, which could be used to stratify patients into different subtypes and enable personalized interventions [8,45]. A better understanding of the microbiota in PDAC might generate insight into the establishment of screening or early-stage diagnosis methods, implementation of cancer bacteriotherapy, adjustment of therapeutic efficacy, including possibly alleviating the adverse effects, creating new opportunities and fostering hope for desperate PDAC patients [10].

Although there is a wide gap that needs to be filled by in-depth research exploring the diversity and composition of the microbiota and their differential occurrence and dysbiosis which is only partially understood, the future of cancer treatment looks promising for PDAC patients. Clinical trials are now underway and microbiome-modulating agents are poised to become *bona fide* anticancer strategies, complementing current treatments such as surgery, chemotherapy, targeted therapy, radiotherapy, and immunotherapies. These results could enhance our understanding of whether altering the composition of the microbiota is safe and effective or likely to impose other health issues and complications. Regulating the microbiota in the pancreatic tumor microenvironment may generate not only direct anticancer but also synergistic effects with other treatments, providing new directions in cancer therapy [11]. Combining microbiome profiling with liquid and tissue biopsy may enable more precise prognoses and personalized identification of tumor vulnerabilities, and validate the treatment approach of microbiome modulation.

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Molecular Subtypes and Clinical Applications

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Pancreatic Ductal Adenocarcinoma (PDAC) Genomics and Clinical Applications

Large-scale sequencing studies have mapped the genomic events that drive PDAC [1–6]. These studies have identified highly recurrent genetic alterations (deleterious single nucleotide variants and copy number losses) in a core set of oncogenes and tumor suppressors, including *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, that are key members of hallmark oncogenic signaling pathways. Greater than 50% of PDAC tumors harbor a deleterious genetic alteration in at least one of these core driver genes [6]. Mutational heterogeneity exists within most tumors and additional low-frequency driver events in genes including *KDM6A*, *MLL3*, *ARID1A*, *TGFBR2*, *RBM10*, and *BCORL1* are found in 5–10% of samples [3,4,6] (Fig. 122.1a). Importantly, recurrently altered driver genes can be grouped into 10 core pathways that control key aspects of tumor growth and survival [1,3,4] (Fig. 122.1b). A single tumor may harbor multiple genetic alterations affecting one or more of these pathways contributing to complex tumor genotypes that are only now being characterized in preclinical models (Fig. 122.1a).

Activating *KRAS* mutations are the most common initiating genetic alteration and occur in ~90% of PDAC [6]. *KRAS*-activating mutations constitutively activate MAPK-ERK signaling in PDAC cells driving proliferation, survival, and migration [7]. Virtually all *KRAS* mutations in PDAC are single nucleotide variants occurring in codon 12 (~91%), 13 (~2%), and 61 (~7%) [1–5,8]. *KRAS* allelic imbalances caused by copy number gains are commonly associated with metastatic disease and may result in increased RAS signaling [9]. The 10% of PDAC with wild-type (wt) *KRAS* typically harbor genetic alterations in alternative drivers such as mutations or amplifications in *BRAF*, *FGFR1* or *ERBB2* or fusions involving *NRG1-NTRK1* [10–12].

Single gene aberrations or so-called actionable mutations that can be matched to a selective therapy, such as *NRG1-NTRK1* fusions [12], *ERRB* amplifications [13] or *BRAF* mutations [14], are rare in PDAC. In fact, actionable mutations in PDAC occur at a prevalence of less than 5% with a median of less than 1% [3,15]. As an example, mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2* occur at a frequency of ~1–3% in PDAC [3,16]. MMR genes normally recognize and repair erroneous nucleotide insertions, deletions or misincorporation of bases that can arise during DNA replication and recombination. Mutations in MMR genes can cause microsatellite instability (MSI) and exceptionally high mutational burdens that may result in greater sensitivity to immune checkpoint inhibitors [17,18]. Importantly, most actionable mutations have not been clinically validated in PDAC and the clinical utility of matched therapies remains limited to a relatively small number of drugs and indications (Fig. 122.1c).

A growing catalogue of potentially actionable mutations in DNA damage response genes that cause homologous recombination deficiency (HRD), such as *BRCA1* and *BRCA2*, have been identified in PDAC [3,16,19]. Mutations in these genes cause chromosomal instability due to faulty homologous recombination and increase the rate at which somatic mutations occur. Evidence from nonrandomized clinical trials suggests that HRD is a biomarker of response to platinum-based chemotherapy in patients with advanced PDAC [20–23]. Furthermore, *BRCA1* and *BRCA2* germline variants have been associated with

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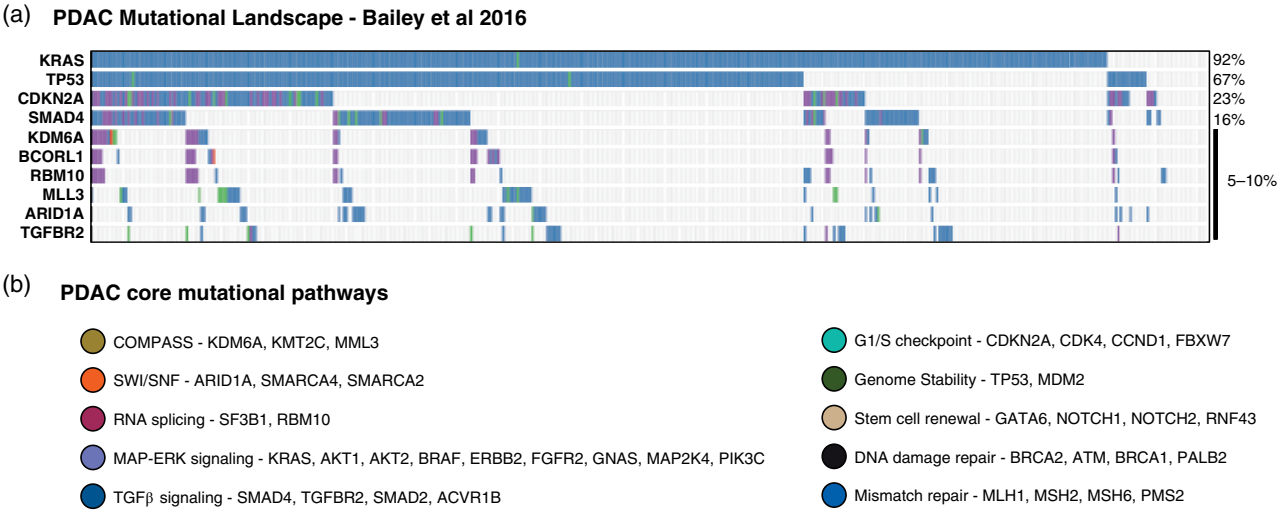


Figure 122.1 The mutational landscape of PDAC. (a) Oncoprint plot showing the most mutated genes in PDAC, using data generated in Bailey et. al. (2016). The prevalence of the mutations is shown on the right as a percentage. (b) Core pathways mutated in PDAC. (c) Gene mutations which have clinical utility in PDAC. The prevalence of genes indicative of response to therapy is shown in parentheses as a percentage.

improved progression-free survival in patients with platinum-sensitive metastatic PDAC treated with the poly ADP-ribose polymerase (PARP) inhibitor olaparib as maintenance therapy [23].

A meta-analysis of over 21 842 PDAC genomes has estimated that the pooled prevalence of germline and somatic mutations in genes causing HRD may be between 14.% and 16.5% [19]. Combined germline and somatic mutation prevalence was estimated at *BRCA1* (0.9%), *BRCA2* (3.5%), *PALB2* (0.2%), *ATM* (2.2%), *CHEK2* (0.3%), *FANC* (0.5%), *RAD51* (0%), and *ATR* (0.1%). Importantly, germline mutations make up the majority of HRD events in patient tumors. Germline testing in unselected populations with sporadic PDAC has shown that ~5% of patients harbor a germline mutation [24,25]. This percentage increases to 20% in patients with Ashkenazi Jewish ancestry [26]. Given that most newly diagnosed patients with a germline mutation do not have a family history of PDAC, current National Comprehensive Cancer Network guidelines recommend routine screening for germline variants including *BRCA1/2*, *ATM*, and *PALB2* [27]. An important caveat to these findings, however, is that the clinical relevance of HRD candidates, beyond *BRCA1*, *BRCA2*, and *PALB2*, has not been established [28].

Beyond single gene alterations in DNA repair genes, recent findings have demonstrated that patterns of genomic alterations such as structural variation and mutational signatures may predict whether a tumor is sensitive to therapy [3,29]. Waddell et al. identified four genomic subtypes based on genomic structural variations (SVs): Stable (20%, <50 SVs per genome); Scattered (36%, 50–200 SVs per genome); Locally rearranged (30%, >200 structural variants clustered on 1–2 chromosomes); and Unstable (14%, >200 SVs distributed across the genome) [3]. Of these, the Locally rearranged and Unstable genomic subtypes have potential clinical utility in PDAC. Locally rearranged genomes typically comprise focal gene amplification such as *ERBB2* or *FGFR* that are therapeutic targets, while the Unstable subtype is associated with HRD and mutations in *BRCA1/2* or *PALB2*, which are sensitive to both platinum and PARP inhibitors. Mutational signatures represent recognizable patterns of mutations (single nucleotide variants, insertions, and deletions) that have been linked to defined mutational processes such as HRD [30]. HRD mutational

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signatures have been demonstrated to predict responses to platinum-based chemotherapy [3,29]. Moreover, Waddell et al. demonstrated that by integrating different genomic readouts of HRD (i.e., mutation in *BRCA1/2*, Unstable genome and HRD mutational signature), patient outcomes following platinum or PARP inhibitor therapy may be improved [3].

The translation of genomic discoveries into the clinic has been a focus of intensive study. The "Know Your Tumor" clinical trial has performed a retrospective analysis on 1856 biopsy-confirmed PDAC of any stage using targeted sequencing [31]. This analysis found that 26% of 1082 samples comprised a known actionable mutation. Out of a total of 677 patients for whom outcome was available, 46 patients received a matched second-line therapy (most receiving standardized chemotherapy in first line). Those patients who received a matched therapy had significantly longer overall survival than 488 patients who did not receive a matched therapy. Most patients who benefited from therapy had *BRCA2* HRD mutations or MSI.

While this study confirms that genomic profiling can benefit small subgroups of well-defined patients, its wider clinical utility remains to be determined.

PDAC Transcriptomic Subtypes

Transcriptomic profiling of patient samples, using either array-based hybridization (microarray) methods or bulk RNA sequencing, has been demonstrated to improve prognostication and allow optimization of treatment strategies by defining subgroups of patients that share phenotypic characteristics [32–35]. Subgroup identification efforts at the mRNA level have the potential to augment established histopathologic and imaging approaches.

Microarrays or bulk RNA sequencing measure the relative expression of mRNA between patient samples and report a complex admixture of gene expression values representing not only neoplastic cells but also stromal cell populations such as cancer-associated fibroblasts (CAFs), endothelium, and immune cells. PDAC classification schemes have ostensibly defined intrinsic transcriptomic subtypes by modeling tumor complexity as a whole (i.e., including both stromal and neoplastic gene expression) [4,36–38] or by filtering out stromal signals using bioinformatic approaches or by laser capture microdissection (LCM) to enrich the cancer epithelium [9,39]. Several PDAC subtyping schemes have been described, most notably the Moffitt [39], Collisson/Sadanandam [37], Bailey [4], Puleo [38], Dijk [36], and Chan-Seng-Yue [9], which are prognostic for patient survival in resected patient samples and have potential clinical utility, as described in Table 122.1.

Collisson and Sadanandam, Bailey, Puleo, and Dijk performed transcriptomic profiling on predominantly chemo-naive primary resected patient samples and defined PDAC subtypes by combining stromal and neoplastic signatures. These studies identified common neoplastic subtypes comprising an overlapping mesenchymal-like subtype (referred to as quasi-mesenchymal/basal/pure-basal/squamous), a more canonical epithelial subtype (classical/pancreatic-progenitor/pure-classical), and a cryptogenic subtype which shares many features of the healthy pancreas (referred to as exocrine-like). Bailey and Puleo et al. also defined stromal subtypes which are enriched for specific stromal cell subsets [4,38]. The "Immunogenic" subtype as defined by Bailey et al. was enriched for immune cell populations, including T cells and B cells. Puleo et al. defined two additional stromal subtypes, namely Stroma Activated (moderately differentiated and enriched for activated stroma markers a-SMA, SPARC, and FAP) and Immune Classical (predominantly classical neoplastic with immune cell enrichment) which was reminiscent of the Bailey Immunogenic subtype.

Moffitt et al. performed transcriptomic profiling using data derived from normal pancreata, chemo-naive primary resectable and metastatic PDAC [39]. These authors informatically dissected stromal and tumor-intrinsic gene expression signatures and identified two subtypes in both the stroma (Normal and Activated) and the neoplastic cell compartment (Basal versus Classical). Chan-Seng-Yue et al. performed a *de novo* reclassification of PDAC subtypes using primary resectable and metastatic PDAC that had undergone LCM to identify five neoplastic subtypes referred to as Basal-like A, Basal-like B, Hybrid, Classical A, and Classical B [9]. This subtyping scheme split the previously defined Basal and Classical subtypes and identified a new Hybrid subtype that comprised gene signatures common to both the Classical and Basal subtypes. The Basal-like A subtype was preferentially enriched in metastatic disease.

Despite differences in subtyping nomenclature, there is strong alignment between the Classical/Pancreatic Progenitor and Quasi-mesenchymal/Basal-like/Squamous subtype signatures. Accordingly, the field has now largely adopted a two-tier system that aligns with the Moffitt subtyping scheme identifying:

- **Classical/Epithelial/Pancreatic Progenitor** subtype cancers that are associated with better outcomes. These tumors are well differentiated and express key endoderm transcription factors such as GATA6, HNF1A, and PDX1 that specify and maintain pancreatic identity; and
- **Basal-like/Squamous (mesenchymal)** subtype cancers that are associated with the poorest patient outcomes. These tumors are also less differentiated than

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Table 122.1 An overview of gene expression-based subtyping systems in PDAC. Indicated are first authors, treatment setting and source from which samples were obtained, and identified subtypes. Only studies that report independent classification systems are included. Subtypes are color coded to indicate similarity.

	Setting	Sample source	Subtype – overlap							
			Neoplastic subtypes					Stromal Subtypes		
Collisson et al., 2011	Primary resected	Bulk tumor (macro dissected), cell lines	Classical		–	Quasi-mesenchymal		Exocrine-like	–	
Moffitt et al., 2015	Primary resected and metastatic	Bulk tumor, cell lines, xenografts >10% cellularity	Classical		–	Basal-like		–	Stroma normal	Stroma activated
Bailey et a., 2016	Primary resected	Bulk tumor >40% cellularity	Pancreatic progenitor		–	Squamous		ADEX	Immunogenic	
Puleo et al., 2018	Primary resected	Bulk tumor	Pure Classical	Immune Classical	–	Pure Basal-like		–	Desmoplastic	Stroma activated
Dijk et al., 2020	Primary resected	Bulk tumor >30% cellularity	Epithelial		Compound	Mesenchymal		Secretory	–	
Chan-Seng-Yue et al., 2020	Primary and advanced	Laser Capture Micro dissected (LCM) >40% cellularity	Classical A	Classical B	Hybrid	Basal A	Basal B	–	–	

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Classical tumors and are associated with fibroblast-like cell morphology.

The Moffitt subtypes are prognostic for survival in multivariate analyses of patients with resected PDAC but not in patients with metastatic disease [9,39]. These subtypes may also guide therapy choice: Basal-like subtype patients had a relative (but nonsignificant) benefit from adjuvant treatment [37,39]. In contrast, in locally advanced and metastatic PDAC, Basal-like subtype tumors exhibited lower response rates for FOLFIRINOX than Classical tumors [40].

Although the Moffitt subtyping system provides a robust and easy to understand method for patient stratification using bulk transcriptomic data, an ever-growing number of single cell sequencing (scRNAseq) studies point to complex subtype diversity within tumors. scRNAseq has revealed that Basal-like and Classical subtype cells can be found in the same tumor [9,41]. These studies also suggest that the Basal-like and Classical subtypes may exist as a gradient within the same sample with Hybrid cells representing an intermediate state [9,41]. scRNAseq coupled with spatial transcriptomics and multiplexed immunofluorescence has revealed that Classical and Basal-like cells are associated with distinct immune cell types [42]. Notably, Classical subtype cells are associated with cytotoxic T cells and Basal-like cells are associated with increased macrophage infiltrates.

Understanding intratumoral complexity will be important for the design of effective therapies for PDAC and may also influence strategies for patient stratification in the future. Collectively, these findings underscore the utility of a simplified two-tier classification system but do not rule out the clinical importance of other PDAC subtypes, including stromal subtypes such as the Bailey Immunogenic subtype which may predict responses to selective immunotherapies.

Clinical trials in different disease settings are required to assess the utility of these transcriptional subtypes for both prognostication and clinical decision making. Several groups have established informatic methods for clinical use that can stratify patient samples based on transcriptional subtypes. These include PurIST (Purity Independent Subtyping of Tumors) based on the Moffitt subtypes which can be applied to low cellularity biopsied material or formalin-fixed samples using readouts obtained from low input targeted gene expression panels (e.g., Nanostring) [40]. Surrogate markers of the Classical and Basal-like subtypes may also be detected via *in situ* hybridization (ISH) or immunohistochemistry (IHC). Basal-like subtype cytokeratin markers (KRT17, KRT5, and KRT81) [43–45] and Classical-associated endoderm transcription factors (GATA6) [46] may assign subtype labels to a tumor and in addition identify subtype heterogeneity within the same sample. Ultimately, methods for patient stratification based on consensus subtyping will require validation in a CLIA-certified setting.

Translating Molecular Subtypes into the Clinic

Genomic profiling of advanced PDAC using targeted gene sequencing has defined small subgroups of patients that benefit from matched therapies [31,47,48]. The great majority of these patients harbor actionable mutations in DNA repair genes [19]. Clinical trials that have tested the utility of targeted sequencing for clinical decision making have been largely disappointing, with only 3–5% of patients showing any clinical benefit [31]. Systemic chemotherapy arguably remains the most effective therapy for the great majority of unselected PDAC patients. Importantly, several studies now suggest that transcriptomic subtypes may predict patient responses to standard chemotherapy, indicating that patient survival may be improved by selecting patients based on transcriptomic subtype [9,40]. Multiple clinical trials have now been established with the aim of developing optimal treatment strategies and medication regimens based on genomic profiling and subtyping.

The PANCREAS (NCT04683315) trial will perform PDAC subtyping on pretreatment EUS/FNA samples using PurIST. Neoadjuvant chemotherapy will then be selected according to subtype. Patients with Classical subtype tumors will receive mFOLFIRINOX whereas patients with Basal-like tumors will receive gemcitabine/nab-paclitaxel.

The EPPIC (Enhanced Pancreatic Cancer Profiling For Individualized Care Study) trial, which incorporates the COMPASS and PanGen studies, will perform integrated genomic and transcriptomic profiling of advanced PDAC in real time [49,50]. Patient molecular profiles will be related to chemotherapy responses.

The ESPAC-6 adjuvant trial (NCT05314998) in resectable patients and the ESPAC-7 neoadjuvant trial in locally advanced patients will evaluate responses to oxaliplatin- or gemcitabine-based chemotherapy randomized according to standard clinical criteria (control arms) or by transcriptomic stratification signatures (experimental arm). The transcriptomic stratification signature to be used in these trials is prognostic for therapy response and was developed *de novo* using matched transcriptomic and oxaliplatin- or gemcitabine-based chemotherapy response data.

The PASS-01 trial is a multicenter phase II trial that will evaluate responses to modified FOLFIRINOX and gemcitabine/nab-paclitaxel in patients with untreated metastatic PDAC. Approximately 150 patients diagnosed

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with untreated metastatic PDAC will be randomized to either arm. Patient samples will undergo high content molecular profiling with the trial to assess whether chemotherapy sensitivity signatures and/or GATA6/KRT5/KRT17 subtype biomarker status can predict response to chemotherapy. As an additional experimental component, patient-derived organoids will be generated from patient samples and transcriptomic profiles from both organoid and matched metastatic samples analyzed for concordance. This will test whether patient-specific organoids can be used as tumor avatars for therapeutic testing.

The PREDICT-PACA co-clinical trial is an integrated biopsy-based approach to predict response to chemotherapy for patients with stage IV PDAC. This study has established a predictive transcriptomic signature associated with chemotherapy response. It will also generate organoids from patient samples and identify potential alternative third-line treatments by genomic profiling and high-throughput drug screening.

Conclusion

Improvements in surgical technique and optimization of chemotherapy regimens have increased the five-year survival rate for PDAC from 2.5% to 10%, reviewed in [51]. These gains are extremely poor compared to other common cancer types. Molecular profiling of PDAC has identified several molecular taxonomies that hold promise to improve patient outcomes by matching a selective therapy to a molecularly identifiable subtype. These could be existing therapies for which the molecular subtypes are predictive, or novel or repurposed compounds that target a subtype's vulnerabilities. Targeted therapies for advanced PDAC based on actionable mutations show benefit in only 3–5% of patients who receive a genome-matched therapy [31]. Most of these patients have germline mutations in *BRCA1/BRCA2* or are MSI [31]. A growing catalogue of potentially actionable mutations in DNA repair genes have been identified in PDAC although the actionability of these mutations has not been assessed in clinical trials [19]. Transcriptomic profiling of PDAC has defined intrinsic molecular subtypes that provide a robust and reproducible framework for patient stratification [39,40]. Existing evidence suggests that the Basal-like subtype may be more chemoresistant than the Classical subtype [9]. Clinical trials, including COMPASS, Precision Promise, ESPAC-6/7, PREDICT-PACA, PANCREAS, and PASS-01, will now evaluate transcriptomic response signatures and/or molecular subtypes in different disease settings.

Indications from early translational studies and more recently clinical trials such as "Know Your Tumor" have estimated that up to 26% of PDAC harbor an actionable mutation [31,48]. While these estimates seem promising, the clinical reality suggests that only a very small number of patients with a therapy-matched mutation see any clinical benefit [31]. A significant difficulty in delivering molecularly targeted therapies to patients is the length of time required to obtain a patient sample, perform genomic sequencing, and guide a patient to a matched therapy. Precision oncology trials in PDAC have largely focused on advanced disease with genome-matched therapies offered in the second line. Often, timelines for intervention are significantly reduced in these patients. These timelines may be extended in the neoadjuvant setting with precision therapies offering greater benefit in the second line. Furthermore, most clinical trials in PDAC up until now have focused on single-agent matched therapies which result in recurrence due to the emergence of resistant subclones. Genomically directed targeted agent combinations may overcome drug resistance to single-agent therapy. Combination therapies based on defined molecular biomarkers are emerging in PDAC although these are complex and require robust preclinical *in vivo* evidence to commence clinical trials.

Transcriptomic subtypes and/or treatment response signatures have the potential to select even larger subgroups of patients for targeted therapies. Initial indications suggest that transcriptomic subtypes may improve outcomes for patients treated with systemic chemotherapy with resectable and metastatic disease [40,9]. It is currently unclear, however, whether transcriptomic subtypes have any prognostic value in the neoadjuvant chemotherapy setting. The ability to deploy treatment response and/or subtyping signatures in the clinic is challenging, especially when variation in sample cellularity is high. The use of gene expression panels such as Nanostring and the mechanical enrichment of the cancer tumor-epithelium via laser capture microdissection may improve the reproducibility of transcriptome-guided patient stratification. Alternatively, immunohistochemistry or *in situ* hybridization of surrogate subtype biomarkers such as GATA6 may have greater clinical utility, especially as these techniques are in routine clinical use.

Spatial transcriptomics and multiplexed imaging modalities, such as mass spectrometry imaging (MSI), are uncovering the complex cellular communities that make up patient tumors [42,44]. These exciting new platforms are revealing novel therapeutic opportunities by mapping cell–cell interactions and receptor–ligand interactions in patient tumors. The ability to spatially map the location of different cell types, expression of gene/protein biomarkers and metabolites will likely usher in a new age of digital pathology that will help shape clinical decision making.

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Tumor Microenvironment: Immune Cells and Immunosuppressive Functions of Carcinoma-associated Fibroblasts and Macrophages

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Introduction

The tumor microenvironment of pancreatic cancer (pancreatic ductal adenocarcinoma: PDAC) is complex and interactions between its components influence the progression of this cancer. Chapter 9 has described the role of pancreatic stellate cells on the proliferation and dissemination of cancer cells. This chapter focuses on how pancreatic stellate cells (PSCs; also known as carcinoma-associated fibroblasts: CAFs) and tumor-associated macrophages (TAMs) modulate the immune response to PDAC.

Compared to many other cancers, the tumor microenvironment (TME) of PDAC is particularly important as this cancer demonstrates a prominent stromal reaction [1] that has been shown to promote cancer progression.

In vitro and *in vivo* evidence indicates that the collagenous stroma facilitates cancer cell proliferation and invasion and decreases cancer cell apoptosis, thus promoting cancer cell survival [2,3]. In turn, cancer cells stimulate stromal cell proliferation, extracellular matrix (ECM) synthesis, and cell migration. The outcome of these interactions is a growth-permissive microenvironment for cancer cells [4]. Thus, opportunities for interactions between cancer cells and other components of the tumor play an important role in determining the progression of disease.

Another effect of the tumor stroma in PDAC is the promotion of an immunosuppressive state, allowing immune escape of cancer cells, known as the *cold immune microenvironment* [5,6]. The causes of this cold microenvironment are multifactorial and include the relative dearth of neoantigens compared to other solid tumors, as well as the interactions between CAFs, TAMs, and cancer cells. While other stromal cells, such as myeloid-derived suppressor cells (MDSCs), also contribute, these are outside the scope of this chapter, thus are not discussed in depth.

Key Players in PDAC Stroma

The simplified schema in Figure 123.1 shows the interactions between the key players within the tumor microenvironment, which lead to an immunosuppressive state. Note that this schema represents a gross generalization of the net effect of each cell type and does not consider heterogeneity within these cell types (see Section, *Heterogeneity of CAFS and TAMS*). It is also not an exhaustive schema, as there are many other stromal cells which interact with these cells as well.

Pancreatic Stellate Cells/Cancer-associated Fibroblasts

Cancer-associated fibroblasts are fibroblast-/myofibroblast-like cells within the PDAC stroma. These cells secrete ample amounts of collagen, fibronectin, etc., and are responsible for the extensive desmoplasia characteristic of PDAC. It is generally acknowledged that the predominant source of CAFs is PSCs (resident cells of the pancreas, described in detail in Chapter 9) [7]. Minor contributions to the CAF population may also come from a variety of extrapancreatic sources, such as pericytes, bone marrow-derived cells, and mesenchymal stem cells [8–11]. In the interests of simplicity, the terms PSCs and CAFs are used synonymously in this chapter.

In health, PSCs are in a *quiescent* state (identifiable by the presence of vitamin A lipid droplets in their cytoplasm)

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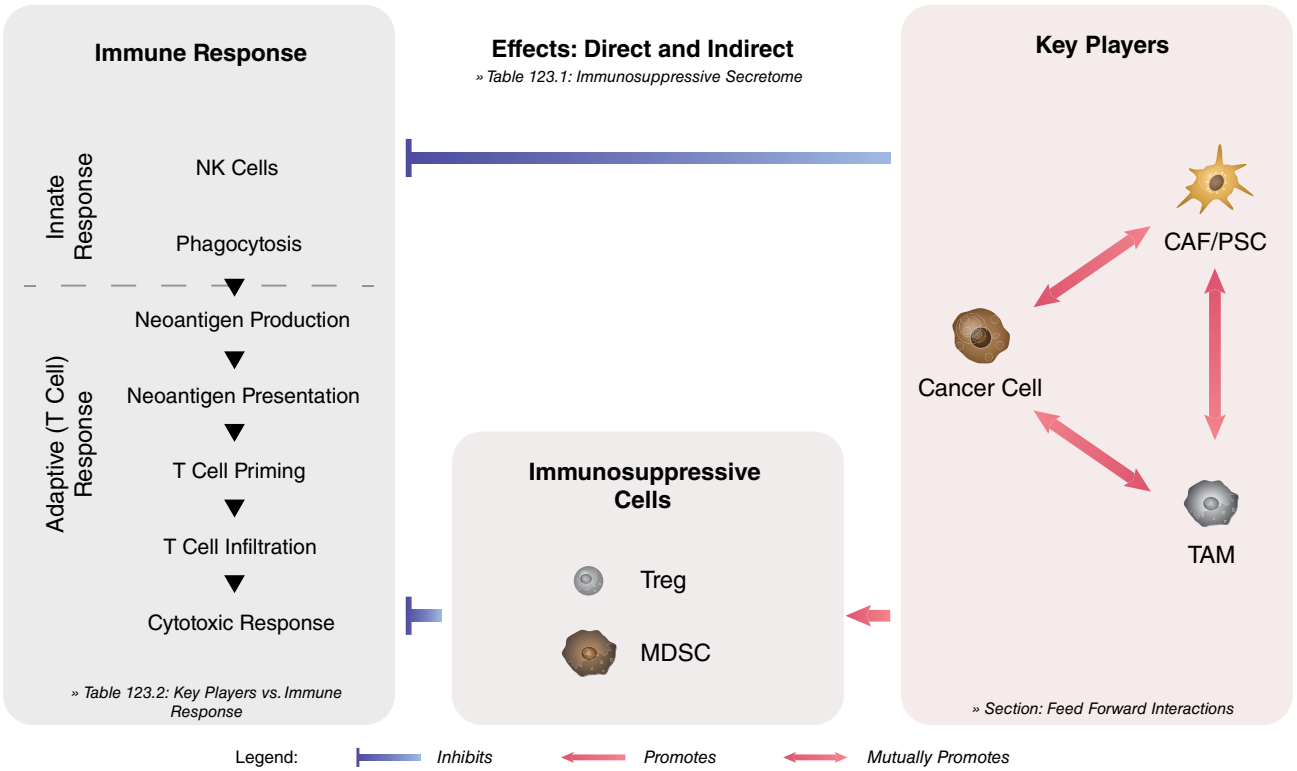


Figure 123.1 Simplified schema illustrating the effects of the key players (CAFs, TAMs, cancer cells) with the immune response (adaptive and innate). CAF, cancer-associated fibroblast; MDSC, myeloid-derived suppressor cell; NK, natural killer; PSC, pancreatic stellate cells; TAM, tumor-associated macrophage; Treg, tegulatory T cells.

and regulate ECM turnover through the secretion of metalloproteinases (MMP-2, -9, and -13) and their inhibitors, to maintain the architecture of the pancreas. PSCs are activated by cancer cells, and in this activated state (identified by activation marker α-smooth muscle actin [α-SMA] and a myofibroblast-like phenotype), PSCs synthesize excessive amounts of ECM proteins leading to the desmoplastic characteristic of PDAC [4,12]. CAFs/PSCs play an important role in the development of all stages of pancreatic cancer from being present around premalignant pancreatic intraepithelial neoplasms (PanINs) to advanced-staged PDACs [13]. Their role even extends to metastatic PDAC deposits [14].

Tumor-Associated Macrophages

Tumor-associated macrophages are macrophages in the tumor stroma. They may arise from tissue-resident macrophages or be recruited from bone marrow-derived monocytes [15]. Classically, TAMs are characterized as being on a spectrum between two polarities, M1 and M2 macrophages. M1 macrophages are proinflammatory and antitumoral, while M2 macrophages are anti-inflammatory and protumoral, although this dichotomy is generally considered an oversimplification [16]. In general, factors within the PDAC tumor microenvironment promote development into M2 phenotype macrophages, leading to protumoral and immunosuppressive effects (Table 123.1).

The protumoral effects of TAMs can broadly be classified into: (i) the promotion of progression from PanINs to PDAC, (ii) the promotion of metastasis, (iii) the development of chemotherapy resistance, and (iv) the inhibition of the host immune response to the tumor [17].

Pancreatic Cancer Cells

Pancreatic cancer cells are not themselves passive players but are central in the creation of the immunosuppressive TME [18]. Their actions can be direct, such as by modification of neoantigen presentation, or indirect, such as by providing signals to promote PSC activation and M2 polarization of TAMs.

Myeloid-derived Suppressor Cells

While not within the scope of this chapter, a key player in the immunosuppressive TME of PDAC is the myeloid-derived suppressor cell [19,20]. The proliferation and recruitment of these cells from bone marrow to tumor

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Table 123.1 Immunosuppressive secretome released by the key players in TME.

Cell type	Cytokines/chemokines	Overall functions	References
CAF/PSCs	FGF, HGF, TGF-β, CXCL8, CXCL12, and CCL7 IL-1, IL-4, IL-6, CXCL1, CXCL2, M-CSF, MCP-1, SDF-1, IL-8 and IL-10	• Increased proliferation, stemness and metastasis of cancer cells • Angiogenesis	[22, 57]
TAMs	IL-10 TGF-β IL-8 CCL17 CCL22	• Suppression of NK cell and CD8+ T-cell activity • Induce differentiation of Tregs • Angiogenesis	[23, 58]
Cancer cells	IL-8 IL-6 IL-1β TNF-α IL-10 PGE2 TGF-β MIF VEGF HIF	• Inhibition of antitumor CD8+ activity • Inhibition of NK cells • Fibrogenesis • Angiogenesis • Invasion • Increased EMT • Metastasis	[23] [22, 58] [57]
MDSCs	ROS Arginase Reactive nitrogen species (RNS)	• Suppression of NK cell and T-cell activation	[23, 58]

CAF, carcinoma-associated fibroblast; EMT, epithelial mesenchymal transition; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; HIF, hypoxia inducible factor; IL, interleukin; MDSC, myeloid-derived suppressor cell; NK, natural killer; PGE, prostoglandin E; PSC, pancreatic stellate cells; TAM, tumor-associated macrophage; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

sites occur through cancer cell-derived factors, such as granulocyte- and granulocyte-macrophage colony-stimulating factor (G-CSF and GM-CSF). These cells exert their immunosuppressive effects both directly, by suppressing cytotoxic T-cell activity through cell–cell contact (e.g., PD-L1/PD ligation), and indirectly through the secretion of reactive oxygen species, arginase and inducible nitric oxide synthase (iNOS), and soluble factors (e.g., TGF-β, IL-10) [21,22].

Antitumor Immune Response

The above players create an immunosuppressive TME by modulating various steps in the tumor immune response. This section provides a brief overview of the relevant antitumor immune response to facilitate discussion of the mechanisms of immune suppression in PDAC.

The immune response can be divided into innate and adaptive parts. The key components of the innate response against malignancy include phagocytosis by macrophages and other cells, as well as the action of natural killer (NK) cells. The key component of the adaptive immune response against cancer involves the T-cell response (Figure 123.1).

Natural Killer Cells

Natural killer cells are cytotoxic immune cells in the TME with an inherent ability of identifying and killing tumor cells without affecting healthy cells. As part of the innate response, NK cells can recognize cancer cells without prior sensitization, through a variety of stimulatory and inhibitory "hard-wired" (germline-encoded) cell surface receptors. This mechanism ultimately leads to cytotoxic granule release. This germline-encoded response means that NK cells can react to cancer cells despite their immune evasion tactics; the latter are known to try to evade the T-cell response by downregulation of their major histocompatibility complex (MHC) class I expression, which reduces neoantigen presentation (a necessary step in the cytotoxic T-cell response, see below). NK cells also secrete an array of cytokines and chemokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and others, which potentiate the adaptive immune response [23,24].

T-cell Response

The T-cell response is the key host immune response to PDAC. It involves a series of steps, ultimately leading to the destruction of cancer cells by cytotoxic T cells (Figure 123.1).

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- *Production of neoantigens*: cancer cells produce neoantigens which will be the target of T-cell recognition. The production of neoantigens is a function of the mutational burden of the cancer [25].
- *Presentation of neoantigens*: activation of T cells requires presentation of the neoantigens by antigen-presenting cells (APCs) and macrophages after they phagocytize cancer cells containing neoantigens. These neoantigens are presented on MHC class II molecules on the surface of APCs.
- *T-cell priming*: T cells, circulating through the lymphatics and bloodstream, encounter APCs and bind to the MHC-antigen complex via specific T-cell receptors (TCR). This results in cytokine secretion and differentiation into cytotoxic T cells (CD8+ cells) or helper T cells (CD4+ cells).
- *T-cell migration and infiltration*: the cytotoxic T cells need to infiltrate into the tumor, as the effector cell cytotoxic effect on cancer cells (the next step) relies on direct contact.
- *T effector cell response*: like all nucleated cells, cancer cells present endogenous materials on HLA class I molecules. The tumor-infiltrating cytotoxic T cell will recognize antigens specific to its TCR, leading to a cytotoxic response against the cancer cell.
- *Modulation by regulatory cells and immune checkpoints*: the T-cell response is modulated by a variety of immunosuppressive cells (e.g., regulatory T cells [Tregs], MDSCs), through paracrine effects. Furthermore, processes which require TCR-antigen-MHC binding (T-cell priming and effector cell response) are modulated by coreceptors, both facilitatory and inhibitory, known as immune checkpoints.

Development of an Immunosuppressive Tumor Microenvironment

Using the above as a framework to understand the immunosuppressive TME, it can be noted that each of the key players exerts multiple immunosuppressive effects, albeit acting on different points of the host immune response (Table 123.2).

Cancer-associated Fibroblasts/Pancreatic Stellate Cells

Cancer-associated fibroblasts suppress the immune response by inhibiting the infiltration of T cells, impairing the effector function of cytotoxic T cells, recruitment of a variety of immune regulatory cells, and suppression of NK cells (see Table 123.2).

Cytokines such as TGF-β, CXCL12, MCP-1, SDF-1, IL-8, and IL-10 secreted by CAFs directly reduce CD4+ and CD8+ T cell numbers and decrease the M1/M2 macrophage ratio in the tumor [26]. Furthermore, through the action of CXCL12, CAFs reduce infiltration of CD8+ T cells into the tumor, reducing CD8+ cell access to, and thus killing of, cancer cells [27,28].

Cancer-associated fibroblasts also inhibit the cytotoxic T-cell response through physical alteration of the tumor microenvironment. CAFs are responsible for the desmoplasia of PDAC, which produces a poorly vascularized, hypoxic and acidic environment, which not only contributes to chemoresistance but also impairs immune cell infiltration and cytotoxic T-cell response [29].

Another mechanism of immune modulation is the recruitment of immunosuppressive cells and expression of inhibitory immune checkpoints. In other cancers, CAFs have been shown to facilitate the differentiation, recruitment, and proliferation of MDSCs, the differentiation of Tregs and the promotion of a TH2-mediated T-cell response [30,31].

Furthermore, CAFs can engage CD8+ T cells by the coexpression of neoantigen-MHC class I complex with inhibitory signals, such as programmed death ligand-2 (PDL2) and Fas ligand (FASL) [32]. Binding with CD8+ cells leads to antigen-selective deletion/inactivation of these cells.

PSCSs/CAFs have also been demonstrated to suppress the cytotoxicity of NK cells possibly by decreasing the production of IFN-γ, granzyme b and CD107, which further supports an immunosuppressive TME [33]

Tumor-associated Macrophages

Tumor-associated macrophages have wide-ranging immunosuppressive effects, including suppression of the T-cell effector response, induction of Treg differentiation, and inhibition of NK cells (see Table 123.2).

The effectiveness of the T-cell response is inhibited at multiple levels. A major mechanism by which TAMs exert their immunosuppressive effects is the secretion of a wide variety of immunosuppressive cytokines (particularly by M2 TAMs), including IL-10, TGF-β, IL-6, PGE, CCL2, CCL17, and CCL20. These serve to suppress the cytotoxic (CD8+) T-cell responses [6,34]. While not yet demonstrated in pancreatic cancer, TAMs in lung cancer have been shown to also reduce the infiltration of CD8+ T cells into the tumor, thus reducing their effectiveness [35]. It has also been shown that TAMs inhibit phagocytic activity against cancer cells through the expression of PD-1 (an inhibitory immune checkpoint) [36]. Such inhibition has two effects: impairment of phagocytosis as part of the innate immune response

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Table 123.2 The immunosuppressive effects of CAFs, TAMs, and cancer cells, classified according to the points of the immune process they inhibit.

Immune response	CAFs/PSCs	TAMs	Cancer cells
Adaptive			
Neoantigen production			• Low quantities of low-quality neoantigens
Neoantigen presentation[a]		• Inhibition of phagocytosis	• Reduced MHC class I expression leading to reduced neoantigen presentation
T-cell priming	• Reduce CD4+ and CD8+ T cells by variety of cytokines, e.g., TGF-β, CXCL12.		
T-cell infiltration	• Inhibits infiltration of CD8+ cells via CXCL12 • Inhibits migration and infiltration by excessive ECM	• Reduces infiltration of CD8+ T cells	
Effector cell response	• Inhibits cytotoxic response by hostile metabolic environment	• Inhibits T-cell response by variety of cytokines	• High intratumoral heterogeneity reduces effectiveness of specific T-cell response • Secretion of immunosuppressive cytokines and upregulation of inhibitory immune checkpoints
Modulation through immunosuppressive cells	• Recruitment of regulatory cells (Tregs, MDSCs) • Expression of inhibitory immune checkpoints • Antigen-selective deletion of CD8+ T cells by PDL2 and FASL	• Induces Treg differentiation through PD1 and PD-L1 and exosomes with miRNA cargo	• Facilitate recruitment of graulocytic MDSCs and immunosuppressive TAMs via chemokines, e.g., CXCL1 and CCL2 • Cancer cells facilitate recruitment of Tregs
Innate			
NK cell	• Suppress cytotoxicity of NK cells by IFN-γ, granzyme b and CD107	• Inhibits NK cell activation through a contact-dependent mechanism involving TGF-β	
Other[a]		• Inhibition of phagocytosis	

[a] Phagocytosis and neoantigen presentation are also part of the innate response, as it is an interaction point between innate and adaptive responses. However, as it is part of the chain of events in the T-cell response, we have included this in the adaptive response.
CAF, carcinoma-associated fibroblast; IFN, interferon; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; TAM, tumor-associated macrophage; TGF, transforming growth factor.

and reduction of presentation of neoantigens derived from phagocytosed necrotic tumor, thus impairing the adaptive immune response.

Tumor-associated macrophages induce the differentiation and maturation of Treg cells through various mechanisms, including the action of PD-1 and PD-L1 [37], and through exosomes which carry miRNAs, such as miR-29a-3p and miR 21-5 [38]. These Treg cells in turn suppress the effectiveness of the T-cell response.

Finally, TAMs have been demonstrated to inhibit NK cell cytotoxicity through a contact-dependent mechanism involving TGF-β [39].

Cancer Cells

It is important to recognise that pancreatic cancer cells are not passive players in developing the immunosuppressive TME. Cancer cells contribute to the immunologically cold TME through the quality and quantity of neoantigen production and presentation, as well as by facilitating the recruitment of immunosuppressive cells (see Table 123.2).

The sensitization of the adaptive immune system is based on the detection of neoantigens. Pancreatic cancer cells not only present low *quantities* of neoantigens, but the antigens presented are also of low *quality*. The former

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is due to the low number of mutations per patient, while the latter is due to the low degree of molecular differences between mutant and wild-type proteins [18]. Exacerbating the low tumor immunogenicity of PDAC is its high intratumoral heterogeneity. This can induce T-cell unresponsiveness and reduce the T-cell effector response, given that any specific T-cell clone can only target a small proportion of the tumor. Such impaired T-cell antigen dosing has been demonstrated in lung cancer and is associated with poorer patient outcomes [40]. This effect is further exacerbated by reduction in T cell–neoantigen interactions through the suppression of T-cell infiltration (such as by CAFs: see above); as well as reduced MHC class I expression in cancer cells (leading to reduced self-neoantigen presentation) [41]. Other immunosuppressive mechanisms of cancer cells include the secretion of immunosuppressive cytokines and upregulation of inhibitory immune checkpoints [42].

Similar to the effects of TAMs and CAFs discussed above, cancer cells themselves can also facilitate the recruitment of regulatory immune cells, further exacerbating the cold immune environment. Chemokine secretion, such as CXCL1 and CCL2, leads to increased recruitment of granulocytic MDSCs and immunosuppressive TAMs into the tumor [42,43]. Similarly, cancer cells also recruit Tregs into the TME.

Feed-forward Interactions

While each of the above cell types individually contributes to the immunosuppressive TME of PDAC, it should be noted that these effects are greatly amplified through positive feed-forward interactions amongst these cells (see Fig. 123.1).

Cancer cells activate resident PSCs/CAFs, promoting their proliferation and leading to the development of a protumoral phenotype. Cancer cells also secrete cytokines which recruit nonresident CAFs to the TME. In turn, PSCs/CAFs further promote cancer cell proliferation, invasion, angiogenesis, and metastasis [19]. Similarly, cancer cells promote an M2 polarity of TAMs. In turn, TAMs have been shown to promote epithelial mesenchymal transition (EMT), angiogenesis, and metastasis in PDAC [6]. Together, these protumoral effects of PSCs/CAFs and TAMs set up the conditions for further PSC/CAF activation and promotion of M2 TAM polarity.

Mutual stimulatory activity also occurs between CAFs and TAMs. CAFs have been shown to promote M2 TAM polarity while TAMs have been shown to activate PSCs [44].

Finally, PSCs/CAFs and TAMs further promote these feed-forward interactions through the conferral of treatment resistance of PDAC. PSCs secrete hyaluronan and other ECM proteins, leading to a dense fibrous stroma, impairing vascular function and reducing drug penetration [45]. TAMs induce resistance to gemcitabine by upregulation of cytidine deaminase and secretion of pyrimidine species which compete with gemcitabine [46,47]. PSCs have also been postulated to potentiate gemcitabine resistance by sequestering and activating gemcitabine within their cytoplasm, thus reducing availability of drug to cancer cells [48], and/or by secreting deoxycytidine which enters cancer cells through nucleoside transporters and competes with gemcitabine for the downstream phosphorylating enzyme deoxycytidine kinase, thereby reducing the activation of gemcitabine to its cytotoxic form [49].

Heterogeneity of CAFs and TAMs

There is significant heterogeneity within each cell type, such that subsets of these cells may exhibit antitumoral effects. While this does not negate the fact that the *net* effect is protumoral, the existence of such heterogeneity has important therapeutic implications.

Pancreatic Stellate Cells/Cancer-associated Fibroblasts

Even though PSC/CAFs morphologically represent myofibroblasts, their functions cross many physiologic and pathophysiologic areas. In addition to the function of ECM synthesis and degradation, these cells express Toll-like receptors 2, 3, 4, and 5 and exhibit phagocytosis, thus exhibiting an innate immune function. In response to inflammation and tumorigenesis, PSCs produce IL-6, 7, and 8, monocyte chemoattractant protein, CCL3, CCL11, and CXCL12, which can play roles in both proinflammation and immunosuppression [50].

While the *net* effect of CAFs/PSCs is widely accepted as protumoral, there are antitumoral effects at play also. For instance, a subset of CAFs, which express Meflin, suppress cancer progression, and knockout of this protein leads to poorly differentiated tumor in a murine model [51]. Also, earlier attempts at diminishing the protumoral stromal effects in PDAC by depletion of stroma appeared to worsen survival in stroma-depleted mice [52].

These observations indicate that there are distinct subpopulations of CAFs within PDAC. Two major classification systems have emerged in the last few years. The first was based on immunohistochemistry staining of fibroblast-activation protein (FAP), α-smooth muscle

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actin (α-SMA) (and MHC Class II expression) and was proposed by Öhlund et al. [53], and was then refined and validated using single cell RNA sequencing by Elyada et al. [54]. This classification divided CAFs into myofibroblast CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs). These subtypes displayed distinctly different gene expression, functions, and even intratumoral localization. The second system, proposed by Neuzillet et al. [55] and based on transcriptomic analysis, divided CAFs into four subtypes, which demonstrated distinct phenotypic features and differences in patient prognosis. It remains to be fully elucidated how these different subtypes of CAFs mediate the immunosuppressive and protumoral effects of CAFs.

Tumour-associated Macrophages

The heterogeneity of TAMS is classically captured by the concept of M1 and M2 macrophage polarities (see above). While an oversimplification [16], the relative proportions of these cell subtypes provide a convenient way of quantifying experimentally the overall antitumoral/protumoral effect of a population of TAMs. Many cytokines, growth factors, and pathways are known to influence this well-recognized dichotomy, and are being actively investigated as therapeutic targets [6].

Further heterogeneity relates to cell origin and temporal relationship to tumor development. TAMs could originate from both local macrophages in the pancreas and the bone marrow. The transcriptional profile of the subtypes suggests that they play different roles, with bone marrow-derived TAMs functioning as APCs, while locally derived TAMs function more as myofibroblasts [15].

Another source of heterogeneity relates to the temporal relationship of the cells with tumor development, with early macrophages, associated with PanINs, being proinflammatory and facilitating cancer cell growth. Later TAMs, found in established PDAC, appear to play a more immunosuppressive role [19]. Such heterogeneity adds complexity but also provides opportunities for therapeutic manipulation.

Therapeutic Implications

It is clear from this chapter that many interrelated and redundant processes drive the immunosuppressive TME in PDAC. The same cell types mediating immunosuppression also have other protumoral effects, and multiple redundancies feed into positive feed-forward loops. It is believed that all these factors contribute to the poor prognosis and treatment resistance of PDAC.

Together, these factors mean that a finessed approach aiming to "adjust the equilibrium" to favor antitumoral subpopulations rather than a blanket obliteration of these cells is required. Simultaneously, treatments targeting different steps of the immune response, and combination immunotherapy with cytotoxic chemotherapy may help overcome the cold immune TME. Such treatments can be provided either concurrently or sequentially (so-called *therapeutic sequencing*) [43].

At the time of writing, there were 48 interventional clinical trials of immunotherapy for pancreatic cancer still recruiting patients (www.clinicaltrials.gov/). About two-thirds of these trials were investigating PD-1/PD-L1 either as sole treatment or in combination with other therapies, such as chemotherapy, targeted therapy, cytokine, chemokine, vaccine and radiation therapy.

A non-exhaustive but broad overview of possible approaches is as follows. Focusing on TAMs, drugs can be divided into those with the aim of activating TAMs toward M1 (e.g., CD40 agonists, TLR agonists), away from M2 (e.g., Tie2 inhibitors, anti-CD47), and those aiming to deplete the TME of TAMs (e.g., anti-CSF-1, anti-CSF-2, anti-CD11b). Against CAFs/PSCs, drugs can be divided into those aimed at reduction of myofibroblast CAF activity (e.g., targeting IL-1 and LIF/JAK/STAT pathway, targeting TGF-β, stimulating pathways that mediate PSC quiescence such as PPARg and nuclear vitamin D receptors), inhibition of inflammatory CAF activity (e.g., targeting IL-6, receptor and pathway), depletion of CAFs (e.g., targeting Shh signaling), and inhibition of specific downstream effects of CAFs (e.g., targeting CXCL12-CXCR4). For T-cell-based treatments, those which generate tumor-reactive T cells (e.g., CAR-T cell therapy), augment the T-cell response (e.g., agonists for costimulatory receptors), and overcome specific immune escape responses (e.g., recruitment of NK cells against downregulation of MHCI molecules in cancer cells) are all therapeutic options. These approaches and their rationales have been reviewed by other authors [6,43,56].

Conclusion

Cancer cells, TAMs, CAFs, and other cells conspire to create an immunosuppressive environment. This likely contributes to the poor prognosis and treatment resistance of PDAC. A multipronged treatment approach targeting multiple mechanisms of immunosuppression is likely required for treatment success.

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Familial Pancreatic Cancer

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Introduction

Pancreatic cancer, like all cancers, is fundamentally a genetic disease driven by both acquired and inherited genetic changes. Having a family history of pancreatic cancer is one of the strongest risk factors for the development of pancreatic cancer [1,2].

Familial Pancreatic Cancer

Familial pancreatic cancer (FPC) is defined as a kindred in which a pair of first-degree relatives have been diagnosed with pancreatic cancer (i.e., a parent and child or a pair of siblings). Observational studies suggest that having at least one single family member with pancreatic cancer increases the risk of pancreatic cancer 1.5–13-fold [1,3–11]. Prospective studies within the National Familial Pancreatic Tumor Registry have shown that first-degree relatives of familial pancreatic cancer patients (individuals with at least two family members with pancreatic cancer) have a 6.79-fold (95% confidence interval [CI] 4.54–9.75) increased risk of pancreatic cancer [1].

Unlike other inherited cancer syndromes in which there is a profound difference in the mean age of onset between the familial and sporadic forms of the disease, the age of onset of pancreatic cancer in patients with a family history of pancreatic cancer is at most six years younger than those with sporadic disease [12,13], with other studies showing no age difference [9,14].

In addition to higher pancreatic cancer risk, relatives of familial pancreatic cancer patients have a higher risk of other cancers. They have a significantly increased risk of dying from breast (weighted standardized mortality ratio [wSMR] 1.66, 95% CI 1.15–2.34), ovarian (wSMR 2.05, 95% CI 1.10–3.49), and bile duct cancers (wSMR 2.89, 95% CI 1.04–6.39). Relatives of sporadic pancreatic cancer patients are at higher risk of bile duct cancer (wSMR 3.01, 95% CI 1.09–6.67) [15]. Other studies also showed pancreatic cancer patients are more likely to report a family member with prostate cancer (odds ratio [OR] 1.45, 95% CI 1.12–1.89) [11] or liver carcinoma (standardized incidence ratio [SIR] 2.70, 95% CI 1.51–4.46) [16].

Pathology of Familial Pancreatic Cancer

The pathologic phenotype of cancers that develop in individuals with a hereditary cancer syndrome can differ from the phenotype of cancers that develop in patients with apparently sporadic disease, such as mismatch repair deficient cancers among Lynch syndrome patients [17,18], or an excess of triple-negative breast cancers among *BRCA1* pathogenic variant carriers [19]. In contrast, familial and apparently sporadic pancreatic cancers appear remarkably similar. A review, blinded to family history, of 519 familial and 651 sporadic pancreatic cancers [20] reported no statistically significant differences in histologic subtypes between familial and apparently sporadic invasive pancreatic cancers. Additionally, among resected tumors there were no significant differences in mean tumor size, location, perineural invasion, angiolymphatic invasion, lymph node metastasis, or pathologic stage. The somatic genetic profile of familial pancreatic cancer does not differ from that of apparently sporadic cancer [12]. In combination, these data further support the finding that the etiology of familial and sporadic pancreatic cancer is very similar.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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In contrast, there is evidence supporting an increased prevalence of pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia in the pancreata of individuals with familial pancreatic cancer compared to those with sporadic disease. Familial pancreatic cancer patients had a significantly higher rate of PanIN per square centimeter 2.75 (95% CI 2.05–3.70, adjusted for age) than patients with sporadic pancreatic cancer. The precursor lesions observed in familial patients were more advanced than those observed in patients with sporadic disease (relative rate of PanIN-3 lesions 4.20; 95% CI 2.22–7.93) and the observation of high-grade IPMN was limited to familial cases [21].

Predisposition Genes

The ability to understand the inherited genetic variation that increases risk of pancreatic cancer is hindered by its underlying genetic heterogeneity [22]. Advances in both genotyping and sequencing technology have led to the identification of several new high-penetrance genes associated with pancreatic cancer risk [22–24] and common genetic variation associated with an increase in pancreatic cancer risk [25–28]. However, pathogenic variants in the high-penetrance genes that are firmly associated with pancreatic cancer explain only about 20% of the familial clustering of pancreatic cancer and the underlying genetic basis has yet to be identified in ~80% of familial pancreatic cancer kindreds. Recent studies have demonstrated that 5–10% of all pancreatic cancer patients, unselected for family history, are also found to have pathogenic variants in high-penetrance cancer susceptibility genes [29–31].

Knowledge of the precise genetic variants can guide therapeutic decisions for those who develop pancreatic cancer and early detection screening choices for at-risk relatives. Examples include early detection screening clinical trials using imaging techniques for patients who have a strong family history of pancreatic cancer and/or carry germline pathogenic variants in established familial pancreatic cancer genes [32–36], increased sensitivity of *BRCA2*- or *PALB2*-deficient cancers to PARP inhibitors (PARP) or mitomycin C [37–40], and improved survival of pancreatic cancer patients with a family history of breast, ovarian, or pancreatic cancer when treated with platinum-containing agents [41] and clinical trials of PARP inhibitors in BRCA-deficient pancreatic cancer have shown survival benefits [42]. In addition, while very rare, patients with mismatched repair deficient pancreatic cancer, which is associated with germline pathogenic variants in *MSH2*, *MLH1*, *MSH6,* and *PMS2,* benefit from treatment with immunotherapy [43–44].

BRCA2

In individuals who undergo germline genetic testing of pancreatic cancer, pathogenic variants in *BRCA2* account for the largest proportion of individuals with an identifiable genetic basis [45]. Pathogenic variants in the *BRCA2* gene are best known for predisposing to breast and ovarian cancers yet carriers are also at increased risk of prostate and pancreatic cancer. The first report of an increased frequency of *BRCA2* pathogenic variants in pancreatic cancer was by Goggins et al., who reported deleterious *BRCA2* variants in 7% of pancreatic cancer patients, unselected for family history [46]. *BRCA2* pathogenic variant prevalence has been shown to vary somewhat by family history with prevalence estimates as high as 16% for pancreatic cancer patients reporting three or more family members with pancreatic cancer [47], 12% in German pancreatic cancer patients from families with a least two pancreatic cancers [48], and 6% among US and Canadian pancreatic cancer patients with a first- or second-degree relative with pancreatic cancer [49].

Like the initial report by Goggins et al., more recent studies have also demonstrated that a substantial fraction, up to 1.9–3.6%, of pancreatic cancer patients, unselected for family history, carry pathogenic variants in *BRCA2* [50]. While some families found to have deleterious *BRCA2* variants report a family history of breast and/or ovarian cancer, many do not [31,51,52]. Deleterious *BRCA2* variants have also been reported in 4.6% of resected Ashkenazi Jewish pancreatic cancer patients, irrespective of family history of cancer [51]. Studies of the lifetime risk of pancreatic cancer among *BRCA2* carriers are limited to families ascertained based on a history of breast/ovarian cancer, and suggest a 3.51–5.79-fold increased risk of pancreatic cancer [52,53].

BRCA1

Individuals who carry pathogenic variants in *BRCA1* have also been shown to be at increased risk of pancreatic cancer. However, risk of pancreatic cancer in *BRCA1* carriers is thought to be less than that of *BRCA2* carriers. Studies of the lifetime risk of pancreatic cancer in *BRCA1* carriers are limited to families ascertained based upon a history of breast and/or ovarian cancer. Risk estimates range from 2.26- to 4.11-fold [53,54]. While not all studies report an excess of *BRCA1* pathogenic variants among patient with pancreatic cancer [51,55], some studies have reported a prevalence of 1.2% in patients with familial pancreatic cancer [45]. As with *BRCA2*, the lack of a reported family history of breast and/or ovarian cancer does not rule out the presence of a pathogenic variant in *BRCA1*.

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PALB2

Pathogenic variants in the *PALB2* gene, a binding partner of *BRCA2*, have also been associated with pancreatic cancer risk. While the initial reports suggested that up to 3% of FPC patients carry pathogenic *PALB2* variants [23], subsequent studies suggest the prevalence may be closer to 1% or lower [45,56,57].

ATM

Recently, pathogenic variants in the DNA repair gene *ATM* have also been associated with familial pancreatic cancer. Approximately 2.6–3.4% [22,24] of patients with familial pancreatic cancer harbor deleterious variants in *ATM*. Pathogenic variants in *ATM* have also been reported in apparently sporadic pancreatic cancer patients [58], and in a large-scale study of over 3000 pancreatic cancer patients, not selected based on family history, 2.3% of patients had pathogenic variants in the ATM gene. The lifetime risk of pancreatic cancer among individuals with pathogenic ATM variants has been estimated to be 9.5% by age 80 (59).

CDKN2A

Germline *p16/CDKN2A* pathogenic variants have been reported in up to 2.5% of patients with familial pancreatic cancer [45] and 0.3% of patients unselected based upon family history. Pathogenic variants in CDKN2A have been associated with a 38-fold increased risk of pancreatic cancer [60] with a lifetime risk of pancreatic cancer of approximately17% [61,62].

Lynch Syndrome

Individuals with Lynch syndrome, due to pathogenic variants in the DNA mismatch repair genes *MSH2*, *MLH1*, *MSH6,* and *PMS2,* have been shown to have a 3.68% (95% CI 1.45–5.88) risk of pancreatic cancer by age 70 [63]. Immune checkpoint inhibition, specifically PD-1 blockade, increases both overall survival and progression-free survival of patients with mismatch repair deficient cancers which includes but is not limited to mismatch repair deficient pancreatic cancers. Many clinical trials are underway exploring combinations of cytotoxic and immune therapy for pancreatic cancers [43,44].

Peutz–Jeghers Syndrome

Individuals with Peutz–Jeghers syndrome have a remarkably high risk of 11–32% [64] of developing pancreatic cancer [65,66].

Hereditary Pancreatitis

The risk of developing pancreatic cancer is extremely high among individuals with hereditary pancreatitis; the risk by age 70 is 30–40% [67,68]. Individuals with hereditary pancreatitis who smoke develop the disease 20 years prior to nonsmokers [68]. A portion of patients with hereditary pancreatitis have inherited pathogenic variants in the *PRSS1* genes [69–71]. In addition, variation in genes associated with an increased risk of pancreatitis or endoplasmic reticulum stress-inducing variants in pancreatic enzymes, including *CTRB2*, *CPA1*, and *CPB1*, have also been associated with an increased risk of pancreatic cancer [72–75].

Common Genetic Variants

In addition to pathogenic variants in high-penetrance genes, several recent genome-wide association studies have identified common variants in the following regions as also significantly associated with pancreatic cancer. Large-scale studies have been conducted in European ancestry populations, Chinese populations, and Japanese populations. Associations at 1q32.1, 1p36.33, 2p13.3, 3q29, 5p15.33, 7p14.1, 8q21.11, 8q24.21, 9q34.2, 13q12.2, 13q22.1, 16q23.1, 17q12, 17q25.1, 18q21.32, and 22q12.1 reached significance criteria when controlling for genome-wide statistical tests in the European populations [25–28,75] whereas regions on 6p25.3, 12p11.21, 7q36.2, 13q12.2, 13q221, and 16p12.3 were statistically associated with pancreatic cancer risk in the Japanese, and 21q21.3, 5p13.1, 21q22.3, 22q13.32, and 10q26.11 in Chinese ancestry populations [76–78]. Individually, these variants have only a small effect on pancreatic cancer increase, with per-allele odds ratios ranging from 1.1 to 1.3.

Many of these same variants have also been shown to have a similar association with familial pancreatic cancer [79]. Combining the effects of these variants into polygenic risk scores (PRS) has been examined as a way of identifying populations at increased risk of pancreatic cancer. However, to date these PRS scores alone are limited in their ability to discriminate between high-risk and moderate-/low-risk subgroups [80,81].

Conclusion

Inherited genetic variants play an important role in pancreatic cancer risk. Individuals with a family history of pancreatic cancer have been shown to be at increased risk of developing pancreatic cancer as well as other

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cancers. The genetic underpinnings of the familial clustering of pancreatic cancer are highly heterogeneous. However, an understanding of the causative genetic variants can inform early detection screening in at-risk individuals and treatment decisions for those who do develop pancreatic cancer.

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125

Pathology of Exocrine Pancreatic Tumors

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Introduction

The bulk of the normal pancreas is composed of acinar cells, yet most neoplasms of the pancreas have ductal differentiation. The classification of exocrine neoplasms of the pancreas is based on more than a century of integrating gross and microscopic findings with patient outcome. The recent introduction of molecular genetics and gene expression technologies has supported this gross and histological classification: most pathologically defined neoplasms of the pancreas have distinct genetic and gene expression profiles [1,2].

The purpose of this chapter is to describe the pathologic features of exocrine neoplasms of the pancreas, with emphasis on clinical correlates.

Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC), commonly known as "pancreatic cancer," is defined as a malignant gland-forming epithelial neoplasm of the pancreas [3]. Although the overall five-year survival rate has finally risen to 10%, the overall incidence of pancreatic cancer appears to be rising as the population ages [4–6]. The high mortality rate from PDAC is due in large part to widespread local and metastatic disease at the time of diagnosis combined with the poor response of most PDACs to existing therapies [7].

Endoscopic ultrasonography can be used to define the local extent of disease and to biopsy lesions by fine needle aspiration (FNA), a technique that has a high sensitivity for diagnosis of PDAC when performed by experienced endoscopists [8]. Because only 15–20% of PDACs are considered surgically resectable at diagnosis, FNA is often the only way for most patients to receive a definitive diagnosis prior to treatment [7].

Gross

Pancreatic ductal adenocarcinomas are grossly white or gray sclerotic lesions that form firm, ill-defined masses that subtly infiltrate the normal soft, lobulated yellow pancreatic parenchyma (Fig. 125.1). These carcinomas often invade and obstruct the common bile duct, the main pancreatic duct, or both, which results in upstream dilation of the affected duct and fibrous atrophy of the pancreatic parenchyma (see Fig. 125.1). The majority of PDACs occur in the pancreatic head, followed by the body and tail; there are even rare case reports of PDACs arising in heterotopic pancreas [3,9].

Careful gross examination of pancreaticoduodenectomy (Whipple) specimens is critical for margin assessment and for accurate grading and staging of the tumor. Margins to investigate include the common bile duct (usually taken parallel to the margin as a "shave" section), the pancreatic neck/distal pancreatic margin (shave), the proximal and distal bowel margins, and the uncinate/retroperitoneal/superior mesenteric artery margin (radial). The pancreatic neck and retroperitoneal margins are important in distal pancreatectomies. These margins are important because patients with no residual tumor (R0) have a better prognosis than those with microscopically positive margins (R1) [10,11]. Adequate sampling of the primary tumor is important for grading of the carcinoma because overall grade depends on the highest grade component of the tumor.

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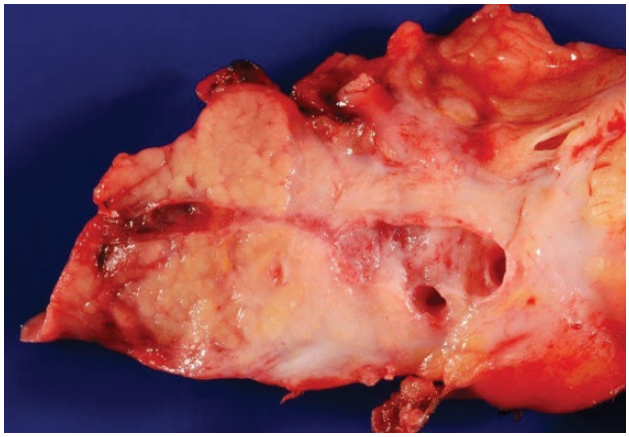


Figure 125.1 Cross section of a distal pancreatectomy for pancreatic cancer. Note the normal pancreatic duct (left), the infiltrative white mass narrowing the duct (center), and the upstream ductal dilatation (right).

Finally, assessment of at least 12 pancreatic lymph nodes is required for adequate staging, although in general, the more lymph nodes that can be examined, the more accurate the prognosis given to the patient [12,13].

Histology

Pancreatic ductal adenocarcinomas are characterized by haphazardly arranged glands and duct-like structures embedded in dense desmoplastic stroma (Fig. 125.2a). The cells forming the glands may be cuboidal or columnar and often have intracytoplasmic mucin.

Two histologic features stand out in PDAC. First, the neoplastic cells are extremely infiltrative. Perineural and intravascular invasion are present in practically all cases (Fig. 125.2b). The perineural invasion may explain some of the pain experienced by patients with PDAC, and nerves also serve as pathways for neoplastic spread beyond the pancreas [14]. Vascular invasion often leads to widespread dissemination of the neoplastic cells to other organs, particularly the liver. PDACs can grow into the lumina of vessels in a very distinctive way. Instead of forming a tumor thrombus, the neoplastic cells of PDACs can flatten out and grow along the endothelial surface of a vessel, mimicking the appearance of a duct (Fig. 125.2c) [15]. PDACs can also grow into preexisting pancreatic ducts in a similar fashion. This extension of the malignancy along a preexisting duct is referred to as "cancerization" of a duct. An abrupt transition from benign to malignant cytology favors cancerization (Fig. 125.2d) [16].

A second striking feature of PDAC is the dense, desmoplastic stroma. This stroma explains the firm consistency of PDAC, and it has been suggested that the stroma may impede the delivery of chemotherapy to the neoplastic cells [17–19].

Histologic grading of PDAC takes into account both cytologic and architectural features of the malignancy. PDACs that resemble normal pancreatic ducts are designated as "well-differentiated" while those that do not form glands, or which form poorly formed glands, are designated as "poorly-differentiated." When more than one grade is present in a tumor, the highest/worst grade should be given; this grade drives prognosis [20,21].

Well-differentiated PDAC can be quite bland by histology with well-formed ductal structures and relatively uniform nuclei. Well-differentiated PDACs can be histogically distinguished from the reactive glands of chronic pancreatitis using "architectural" features: loss of normal lobular architecture, incomplete glands, and the presence of ducts next to muscular arteries. Other helpful features include necrosis within glandular lumina, perineural invasion, and vascular space invasion [22]. A particularly tricky histologic variant of well-differentiated PDAC is the "large duct" variant, which can mimic cystic neoplasms grossly and histologically. The glands of the large duct variant form irregular dilated structures lined with a mucinous epithelium. Again, clues to the diagnosis of an invasive PDAC are primarily architectural: loss of lobular organization and large ducts that dissect through a desmoplastic stroma [23].

When compared to well-differentiated cancers, moderately-differentiated PDAC has greater variation in cytologic appearance and increased numbers of mitotic figures. Poorly-differentiated PDAC is defined by the presence of solid sheets and/or individual neoplastic cells that range in morphology from small cells with scant cytoplasm to larger, bizarre cells with abundant eosinophilic cytoplasm. Histologic grading is important because the prognosis of a poorly-differentiated PDAC is worse than that of a well or moderately differentiated one [3,21].

Gene expression in PDAC is important for multiple reasons. First, the protein products can be interrogated for diagnostic purposes. These include keratins 7 and 19, carcinoembryonic antigen (CEA), mesothelin, and mucin 1 (MUC1). In addition, expression studies may be useful for separating out subsets of pancreatic cancer with predictive and prognostic implications [24].

Histologic Variants of Ductal Adenocarcinoma

Several morphologic variants of PDAC with distinct clinical features have been described.

Adenosquamous Carcinoma

Adenosquamous carcinoma is, as the name suggests, an adenocarcinoma with a significant component with

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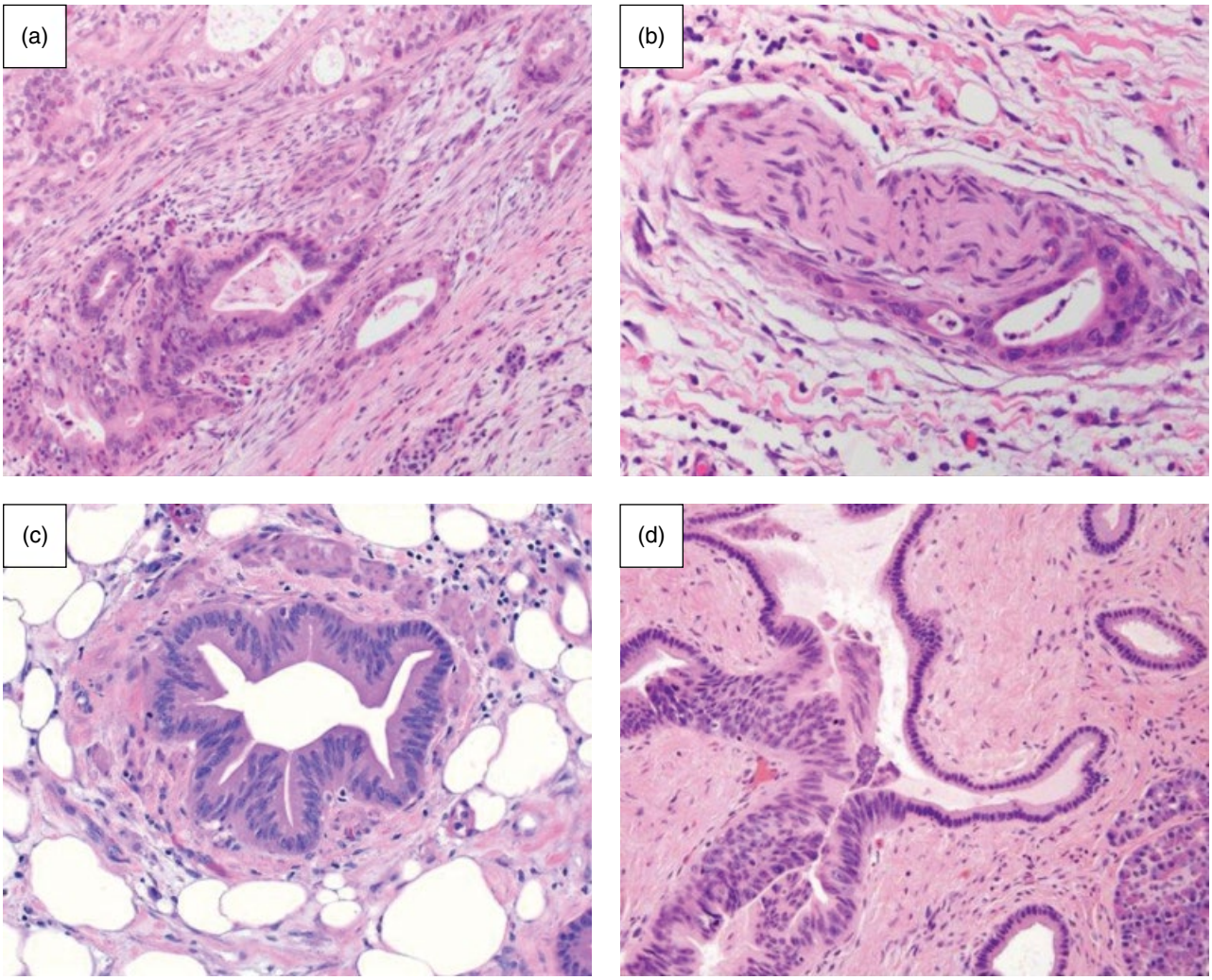


Figure 125.2 Infiltrating ductal adenocarcinoma. a) haphazardly arranged glands embedded in dense desmoplastic stroma. b) Perineural invasion. c) Venous invasion with the neoplastic cells replacing the endothelial cells and mimicking pancreatic intraepithelial neoplasia. d) Cancerization of a duct with the cancer (lower left) invading a preexisting pancreatic duct (center).

squamous differentiation (at least 30%). If no adenocarcinoma component can be found on extensive sampling, a metastasis from a primary squamous cell carcinoma from another organ must be considered. Patients with adenosquamous carcinoma of the pancreas have a worse prognosis compared to patients with PDAC, but recent studies have reported that some adenosquamous carcinomas respond to platinum-containing chemotherapies [25,26].

Colloid Carcinoma

Colloid, or mucinous noncystic, carcinoma is a variant of PDAC associated with intestinal-type intraductal papillary mucinous neoplasms (IPMNs, discussed below). In this subtype, pools of mucin dissect through stroma, and associated mucin-producing neoplastic epithelium either lines the mucin pools or floats within the mucin. Care must be taken not to overcall a ruptured cyst with mucin extruded into the stroma with a truly invasive colloid carcinoma. Malignant epithelium must be seen with the stromal mucin for a diagnosis of invasion [27].

Medullary Carcinoma

Like its counterpart in other organs, this variant is characterized by the syncytial growth of poorly differentiated epithelioid neoplastic cells with large nuclei. Medullary carcinomas also have "pushing" rather than infiltrating borders, and there is often a brisk inflammatory infiltrate of predominantly lymphocytes surrounding and infiltrating into the tumor, but fibrous stroma is scant [28].

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Medullary carcinomas are important to recognize for three reasons. First, despite their poor differentiation, they are associated with a good prognosis [29,30]. Second, patients with a medullary carcinoma are more likely to have a family history of cancer [28]. Third, medullary carcinomas are more likely than ductal adenocarcinomas to have the genetic change of microsatellite instability (mismatch repair defect) [31]. Not only may these mismatch repair deficient PDACs be the first presentation of Lynch syndrome [32,33], but new treatment options such as PD-1 inhibitors may be effective in mismatch repair deficient malignancies [34].

Undifferentiated Carcinoma

Undifferentiated carcinomas are composed of predominantly spindled cells or bizarre large cells without a clear direction of differentiation. A lower grade component of conventional PDAC can often be found in these neoplasms, but the histologic grade and prognosis are defined by the undifferentiated "grade 4" component [3,35]. Undifferentiated carcinomas are less cohesive than typical PDAC, a feature that can be demonstrated by loss of e-cadherin expression and that may contribute to the extremely poor prognosis of this variant: the mean survival is less than one year [36]. Undifferentiated carcinomas with rhabdoid features are important to recognize because they may harbor distinct somatic mutations [37,38].

Undifferentiated Carcinoma with Osteoclast- like Giant Cells

Undifferentiated carcinoma with osteoclast-like giant cells is a distinctive neoplasm characterized by the presence of numerous intratumoral multinucleated nonneoplastic giant cells. Admixed with these giant cells are undifferentiated spindled or bizarre malignant cells which often, but not always, label with antibodies to keratins by immunohistochemistry. The giant cells express histiocytic markers, such as CD68. Genetic analyses of single cells microdissected from these carcinomas have shown that the multinucleated giant cells are not neoplastic, but that the undifferentiated cells in between the giant cells are [39]. As is true for undifferentiated carcinomas, the prognosis of patients with an undifferentiated carcinoma with osteoclast-like giant cells is poor, with mean survival of less than one year [40,41].

Uncommon Variants

The hepatoid and signet ring cell variants of PDAC are unique in that they can resemble metastases from other organs to the pancreas. As the name suggests, the hepatoid variant consists of polygonal eosinophilic cells that mimic a hepatocellular carcinoma and that may even label with hepatocyte antigens, such as Hep-Par and α-fetoprotein [42,43]. Metastasis to the pancreas from the liver must be ruled out before a diagnosis of primary hepatoid PDAC is rendered [3].

The signet ring variant of PDAC is characterized by cells that contain intracytoplasmic mucin with indented and displaced nuclei. The neoplastic cells grow as single, infiltrating cells rather than in well-formed glands or sheets [44]. This carcinoma most closely mimics lobular breast carcinoma or diffuse gastric carcinoma, both of which should be considered in the differential for a malignancy of this morphology.

Ductal Malignancies with Mixed Differentiation

Carcinomas of the pancreas can rarely have multiple different directions of differentiation. These include mixed ductal-neuroendocrine carcinoma and mixed ductal-neuroendocrine-acinar carcinoma. Diagnosis of a "mixed" carcinoma requires that at least one-third of the malignancy be composed of each neoplastic component. The prognosis for patients with a mixed carcinoma is generally driven by the worst component, in most cases the PDAC [45,46].

Staging

The staging of PDAC and its variants by the WHO and the American Joint Committee on Cancer, 8th edition, takes into account the size of the malignancy, regional lymph node involvement, and distant metastases (the TNM system) [3,47]. The extent of local tumor spread is no longer the dominant criterion for determining pathologic T stage.

Cystic Neoplasms

Intraductal Papillary Mucinous Neoplasm

The intraductal papillary mucinous neoplasm (IPMN) is a mucin-producing, duct-based, usually papillary neoplasm that, by definition, is greater than 1.0 cm [16,48]. IPMNs may arise in the main pancreatic duct or within a branch duct. Main duct IPMNs are more likely to be symptomatic and to progress to invasive carcinoma [49]. IPMNs are often multifocal, and patients are at risk for synchronous and metachronous disease. Genetic analyses have suggested that these multifocal lesions are often genetically distinct, but intraductal spread of neoplastic cells can also occur [50]. Because of this multifocality, patients who undergo partial pancreatectomy for IPMN

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remain at risk for additional neoplastic cysts and even PDAC in their remnant pancreas [51]. Endoscopic ultrasound (EUS)-guided biopsy with sampling of cystic fluid for cytology and molecular studies can be important for preoperative diagnosis and planning [52,53].

Gross

Main duct IPMNs diffusely dilate the main pancreatic duct. Long finger-like papillae can often be seen projecting into the duct, and the duct typically contains thick, tenacious mucin. Branch duct IPMNs, by contrast, more often appear as a small group of cysts, often compared to a cluster of grapes, adjacent to but not involving the main duct. Many IPMNs are mixed and involve both main and branch ducts [48]. Foci of dense sclerosis adjacent to an IPMN suggest the possibility of an associated invasive adenocarcinoma. For this reason, and because invasion can be focal, the general rule for pathologic examination of IPMNs is very extensive, if not complete, submission for histology [54].

Histology

Histologically, the enlarged dilated ducts of IPMNs are lined by columnar mucin-producing neoplastic epithelial cells that may have intestinal, gastric, biliary, or pancreatobiliary type differentiation (Fig. 125.3). A single IPMN may have mixed differentiation, making the correlation between subtype and prognosis all the more complicated [48].

Intestinal-type IPMNs have interspersed goblet cells, typical of intestinal epithelium, and immunolabel with antibodies to MUC2, MUC5AC, and CDX-2 [48]. Of interest, many intestinal-type IPMNs have been found to harbor *GNAS* gene mutations [55]. Early somatic *GNAS*

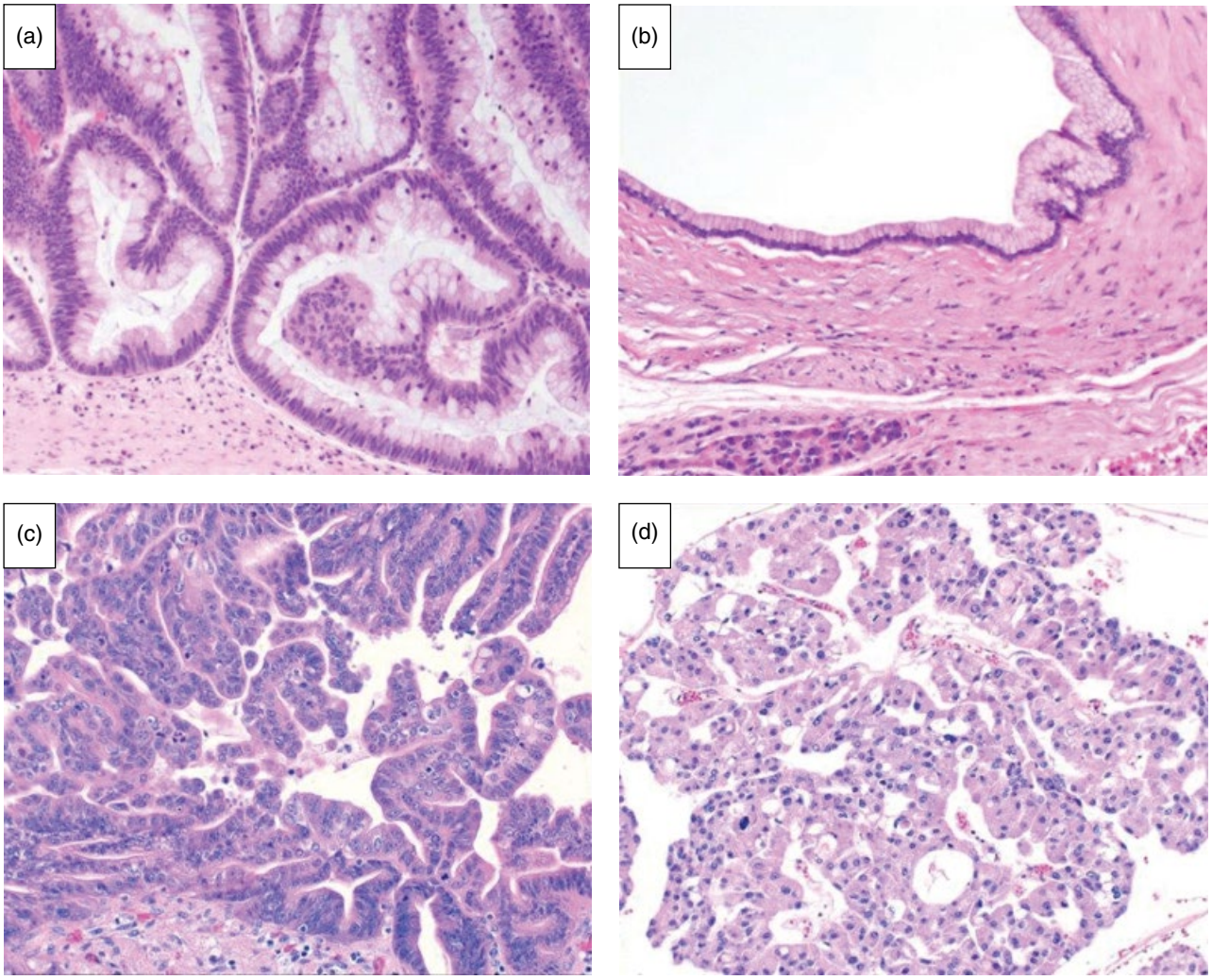


Figure 125.3 Intraductal papillary neoplasms. a) Intraductal papillary mucinous neoplasm- intestinal type. b) Intraductal papillary mucinous neoplasm- gastric type with low-grade dysplasia. c) Intraductal papillary mucinous neoplasm- pancreatobiliary type with high-grade dysplasia. d) Intraductal papillary oncocytic neoplasm.

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mutations are the underlying genetic defect in McCune–Albright syndrome, and IPMNs are known to be associated with this disorder [56].

Gastric-type IPMNs have small nuclei with an apical, eosinophilic mucin cap similar to foveolar cells of the stomach, and these IPMNs label with antibodies to MUC5AC. Pancreatobiliary type IPMNs are composed of cuboidal cells with increased nuclear:cytoplasmic ratio and minimal intracytoplasmic mucin, and they immunolabel with antibodies to MUC1 and MUC5AC.

Intraductal neoplasms with oncocytic differentiation are designated intraductal oncocytic papillary neoplasms (IOPNs). IOPNs are composed of an eosinophilic, multilayered epithelium with large nuclei and prominent nucleoli; this variant immunolabels with antibodies to MUC6. Despite the marked atypia in oncocytic IPMN, invasive carcinoma is not common in this subtype [54]. IOPNs have been found to have unique gene fusions involving *PRKACA* and *PRKACB* that are not found in other pancreatobiliary lesions, and IOPNs are therefore now classified as distinct neoplasms (not as a subtype of IPMN) [57].

Intraductal papillary mucinous neoplasms are graded as having low- or high-grade dysplasia based on the degree of architectural and cytologic atypia. Low-grade dysplasia is defined as a single layer of cells with small, uniform nuclei growing along cyst walls with well-formed papillae. High-grade dysplasia is characterized by loss of nuclear polarity with nuclear hyperchromasia and pleomorphism along with architectural irregularities including irregular papillae and cribriform growth. Most gastric IPMNs are low-grade, while pancreatobiliary and oncocytic IPMNs are usually high-grade. Intestinal-type IPMNs may have low- or high-grade dysplasia [48,49].

Approximately one-third of surgically resected IPMNs have an associated invasive PDAC. The risk is greater with main duct IPMNs, if a mural nodule is present, and with increasing grades of dysplasia. High-grade intestinal-type and pancreatobiliary-type IPMNs are the most likely to have an associated invasive adenocarcinoma of colloid (mucinous noncystic) and tubular type, respectively [54]. Genetic analyses have shown that the carcinomas that are in direct anatomic association with the IPMN usually arose from the IPMN [58].

Mucinous Cystic Neoplasm

Mucinous cystic neoplasms (MCNs) are mucin-producing epithelial neoplasms of the pancreas that typically do not involve the duct system, and which, by definition, have a characteristic ovarian-type stroma (Fig. 125.4a). MCNs, like IPMNs, also can progress to invasive adenocarcinoma. MCNs are most often located in the tail of the pancreas, and the vast majority arise in women [3].

Gross

Gross examination of MCN shows a well-demarcated multilocular cystic lesion. The cysts can be filled with mucin or in some instances blood-tinged fluid. The cysts can have a smooth lining or papillary projections may protrude into the lumina. The latter finding often corresponds to high-grade dysplasia and increased risk for invasive carcinoma. In contrast to IPMNs, the cysts do not communicate grossly with the duct system.

Histology

Histologically, MCN is lined by columnar mucin-producing epithelium that may have intestinal or gastric differentiation with varying degrees of dysplasia that is graded similarly to IPMN as low or high-grade. The key diagnostic feature for MCN is the specialized "ovarian-type"

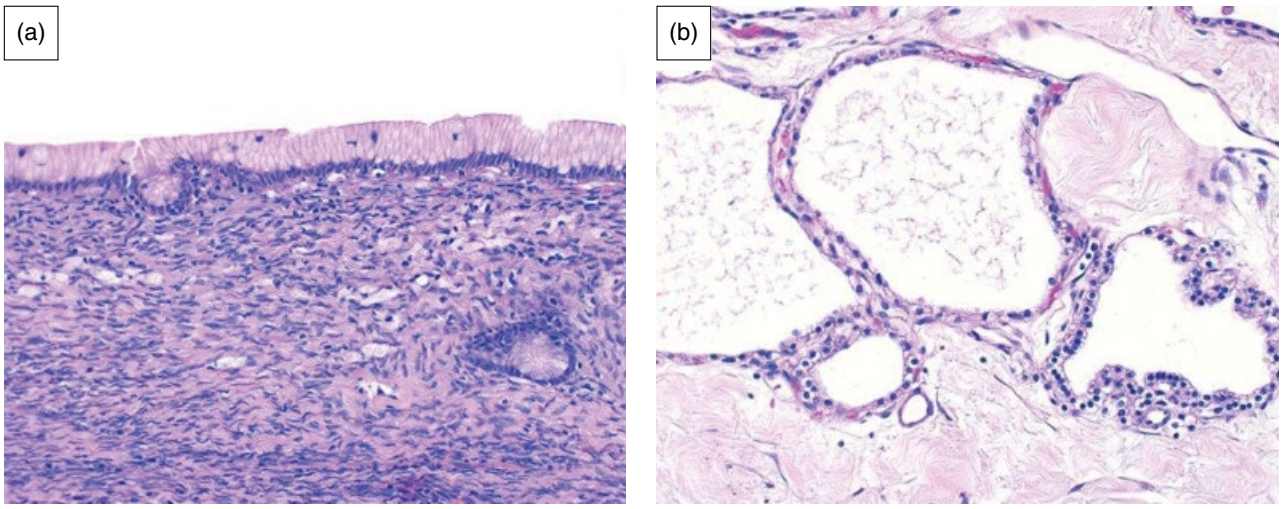


Figure 125.4 a) Mucinous cystic neoplasm with low-grade dysplasia. Note the characteristic ovarian-type stroma. b) Serous cystadenoma. Note the uniform cuboidal cells with clear cytoplasm.

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spindle cell stroma seen underlying the epithelium. Immunohistochemical stains for inhibin and progesterone receptor can be used to highlight the ovarian stroma [59].

Because MCNs are unifocal lesions, surgical resection of an MCN without invasive carcinoma is considered curative; however, up to 30% of MCNs have an associated invasive adenocarcinoma. The invasive component is usually a typical PDAC rather than a colloid carcinoma [59]. The depth and extent of invasion of the carcinoma are important prognosticators [60].

Serous Cystadenoma

Serous cystadenomas (SCAs) are cystic neoplasms of the pancreas composed of multiple cysts lined by glycogen-rich cells (Fig. 125.4b). The cyst fluid is watery or serous rather than mucinous.

Gross

The most common form of SCA is the microcystic SCA. Microcystic SCAs have innumerable small (millimeter) cysts, often surrounding a central scar. The macrocystic variant of SCA consists of one or at most a few large cysts. This latter variant can mimic an IPMN or MCN on imaging. Multiple SCAs throughout the pancreas suggest the von Hippel–Lindau (VHL) syndrome, as do mixed serous-neuroendocrine tumors [61]. The solid serous adenoma is a variant of SCA that, as the name suggests, grossly appears to be solid. Because solid serous adenoma remains well circumscribed, the differential diagnosis on both imaging and gross examination includes a neuroendocrine tumor [62].

Histology

All SCA variants are lined by a serous epithelium made up of cuboidal cells with clear to eosinophilic cytoplasm and small, centrally placed uniform nuclei. Transformation to a malignant serous cystadenocarcinoma (as defined by the presence of metastatic disease) is vanishingly rare; therefore, asymptomatic patients usually do not require surgery. In symptomatic cases, surgical resection of an SCA is considered definitive therapy [3,63,64].

Solid-Pseudopapillary Neoplasm

The solid-pseudopapillary neoplasm (SPN) is a neoplasm of uncertain histogenesis and low malignant potential [65,66]. SPNs occur with equal frequency in the pancreatic head, body, and tail.

Gross

On imaging and gross examination, SPNs are often large and heterogeneous but well demarcated. On cross-section, the tumor may be predominantly solid or cystic, and is often filled with hemorrhagic and necrotic material (Fig. 125.5a).

Histology

By light microscopy, SPNs are composed of loosely cohesive monomorphic epithelial cells with clear cytoplasm and round to oval grooved nuclei growing in pseudopapillae (Fig. 125.5b and 125.5c). Touch preparations at the time of intraoperative consultation can beautifully demonstrate the branching vascular architecture, cellular uniformity, and poor cohesion of the neoplastic cell population (Fig. 125.5d). Hyaline globules are often seen within the epithelial cytoplasm, and foreign body giant cells may be present. SPNs label with β-catenin (nuclear), which reflects the underlying β-catenin gene mutation in this neoplasm, and with LEF1 and CD10 [65,67,68].

All SPNs are classified as malignant. Although the majority of SPNs are indolent and cured by resection, cases of widespread metastatic disease are reported [69,70].

Acinar Cell Lesions

Acinar Cell Cystadenoma

This lesion is the subject of case series due to its rarity, and the reactive vs neoplastic nature is disputed because these lesions have not been found to harbor clonal mutations commonly associated with pancreatic neoplasia [71,72]. On gross examination, the cysts are well circumscribed and filled with clear, nonmucinous fluid. Histologic examination reveals an epithelial lining composed of cells with acinar differentiation and granular two-toned cytoplasm. There have been no reports of malignant transformation of this lesion, and the entity has therefore been renamed "cystic acinar transformation." [71].

Acinar Cell Carcinoma

Acinar cell carcinoma (ACC) of the pancreas is also quite rare, making up less than 2% of resected pancreatic neoplasms. ACCs have been reported in children as well as adults [73,74], and this malignancy usually harbors a high number of mutations [75].

Gross

Acinar cell carcinomas are well-circumscribed but bulky, fleshy, and often hemorrhagic neoplasms that may resemble the more common pancreatic neuroendocrine tumor (PanNET).

Histology

Histologic review shows a predominantly cellular neoplasm composed of a monomorphic population of

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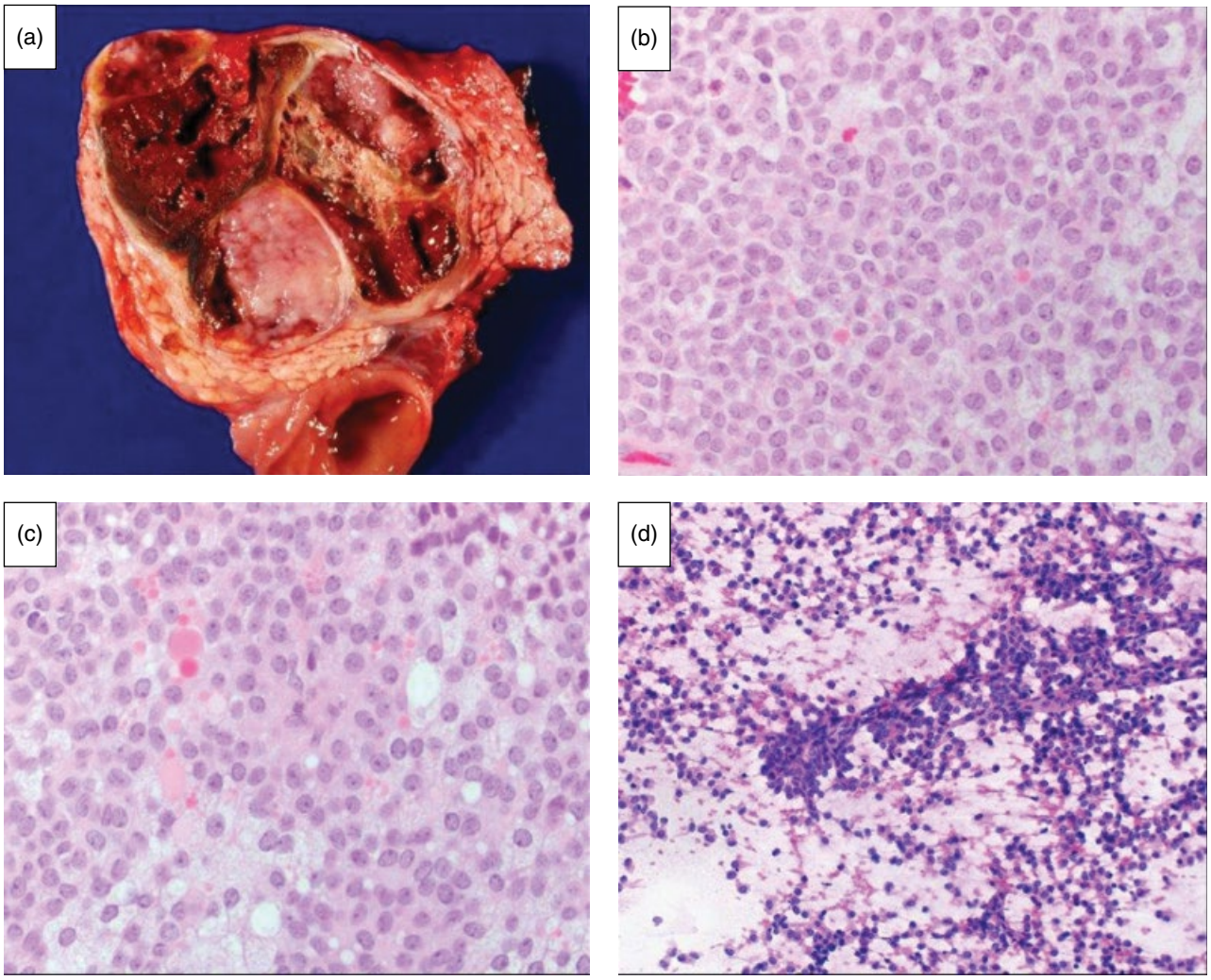


Figure 125.5 Solid pseudopapillary neoplasm. a) Grossly, some cysts contain viable tumor with a vaguely papillary architecture (center), while others (top) contain hemorrhagic debris. b) The nuclei of the neoplastic cells often have grooves. c) Hyaline globules are frequently found. d) A touch preparation helps highlight the delicate vessels and the poorly cohesive nature of the neoplastic cells.

cells with granular cytoplasm, large nuclei, and single prominent nucleoli (Fig. 125.6a). Several architectural patterns can be seen, from the formation of well-defined acini to solid sheets of cells. Desmoplastic stroma is not a prominent feature of ACC [74].

Ancillary stains are usually necessary to definitively diagnose an acinar cell carcinoma. Immunolabeling with antibodies to the pancreatic enzymes trypsin and chymotrypsin will highlight the cells, although a simple periodic-acid Schiff with diastase (PAS-D) can also highlight the enzymatic granules [74]. Some antibodies to BCL-10 cross-react with carboxyl ester hyrodrolase, and we find immunolabeling for BCL-10 to be particularly useful in identifying acinar differentiation [76]. Up to one-third of acinar cell carcinomas will show patchy labeling with neuroendocrine markers, specifically chromogranin A [74]. To diagnose a true mixed acinar cell/neuroendocrine carcinoma, however, at least 25–30% of the neoplastic cells need to have definitive neuroendocrine differentiation in addition to the cells with definitive acinar differentiation [77]. These neoplasms are given the unwieldy designation "mixed neuroendocrine–nonneuroendocrine neoplasm" (MiNEN). Mixed acinar/ductal adenocarcinomas have also been described [46].

The prognosis in mixed tumors is driven by the most aggressive component [46,77]. In pure acinar cell carcinoma, the prognosis is better than that of stage-matched PDAC, with a 25–50% five-year survival rate. Staging of acinar cell carcinoma follows the rules of PDAC [3].

Pancreatoblastoma

The pancreatoblastoma is one of the most common pancreatic malignancies of childhood [78,79]. Although most are nonsyndromic, pancreatoblastomas have been reported in infants with Beckwith–Wiedemann

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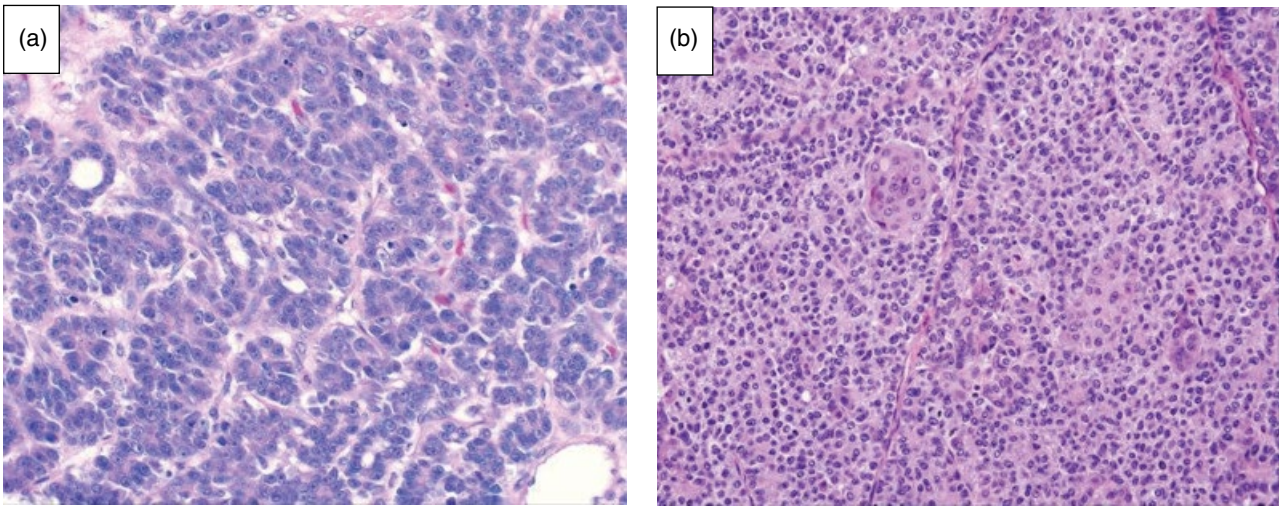


Figure 125.6 a) The neoplastic cells of acinar cell carcinomas form small lumina, and the nucleoli characteristically have single prominent nucleoli. b) Pancreatoblastomas, by definition, have squamoid nests (center).

syndrome and in older children/young adults with familial adenomatous polyposis [80–82]. Cases in adult patients can occur, but with even less frequency than in children [83,84].

Gross

On gross examination, fleshy lobules of tumor, fibrosis, necrosis, and calcifications may all be present in a single neoplasm [85].

Histology

On histologic review, pancreatoblastomas are composed of neoplastic cells with acinar cell differentiation admixed with squamoid nests (Fig. 125.6b). Squamoid nests are aggregates of cells with spindled to epithelioid morphology. Squamoid nests differentiate pancreatoblastoma from pure acinar cell carcinoma. Cells with neuroendocrine differentiation are also usually present, and rarely heterologous elements or small cell features may be seen within a pancreatoblastoma [73,86].

Like an acinar cell carcinoma, pancreatoblastoma is reactive for PAS-D, trypsin, chymotrypsin, and BCL-10, and scattered neuroendocrine markers may be expressed across the tumor. Abnormal, often patchy, nuclear labeling with antibodies to β-catenin is seen in a subset of pancreatoblastoma.

Surgical resection is considered the first line of treatment, and patients with nonresectable disease have a dismal prognosis. Even with resection, the five-year survival rate for pancreatoblastoma is only 65% [79,87].

Conclusion

Exocrine malignancies of the pancreas include benign lesions as well as some of the deadliest malignancies known. The importance of accurate pathologic diagnosis and staging for patient prognosis and treatment cannot be overstated, especially when dealing with the complicated area of cystic neoplasia. A new understanding of the molecular drivers of pancreatic neoplasia supports the current gross and histologic classification presented here. We hope that this chapter has provided the tools for confident gross examination and histologic diagnosis of exocrine pancreatic lesions.

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Pancreatic Cancer: Precancerous Lesions

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Introduction

Different precursor lesions can give rise to pancreatic ductal adenocarcinoma (PDAC). The basis for the current classification of these lesions was established in an international consensus meeting in 1999 [1]. Since then, additional consensus meetings have been held [2,3].

At present, five precursor lesions are recognized: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), intraductal oncocytic papillary neoplasm (IOPN), intraductal tubulopapillary neoplasm (ITPN), and mucinous cystic neoplasm (MCN) [4]. These noninvasive precursors exhibit a unique multistep morphologic and genetic progression to invasive carcinoma [5–7]. Histologically, these changes are reflected by different grades of dysplasia. By convention, the highest degree of atypia determines the histologic grade of the lesion. The previous three-tiered grading system has been replaced by a two-tiered system for PanINs, IPMNs, and MCNs and now distinguishes between low-grade and high-grade (occasionally referred to as "carcinoma in situ") lesions [3].

Pancreatic Intraepithelial Neoplasia

Clinical Features

Pancreatic intraepithelial neoplasia (PanIN) is the most common precursor lesion of PDAC and it is believed that most PDACs arise from PanINs. Hulst (Boerhaave Laboratory, Leiden, The Netherlands) was the first to describe this microscopic lesion a century ago as a lesion in between ("Zwischenform") normal tissue and invasive carcinoma [8]. These lesions were shown to be more common in pancreata with an invasive carcinoma than in pancreata without cancer [9]. PanINs were found in 82% of pancreata with PDAC, in 60% of pancreata with chronic pancreatitis, and in 16% of normal pancreata. Both sexes are equally affected and the incidence tends to increase with age [10]. In patients with a strong family history of pancreatic adenocarcinoma, PanINs are more frequently found and show a higher degree of dysplasia and multifocality [11,12].

Pancreatic intraepithelial neoplasia are not associated with specific clinical signs or symptoms and are typically found incidentally in resection or biopsy specimens. PanINs are more frequently located in the head of the gland than in the tail [9]. Because of their small size, PanINs are macroscopically invisible and cannot be diagnosed on imaging. However, nonspecific findings such as lobular atrophy and fibrosis can suggest their presence [11,13]. Some PanINs may present with obstruction or stricture and subsequent retrograde ductal dilation [14–16].

Pathologic Features

Pancreatic intraepithelial neoplasia are microscopic (usually <0.5 cm in diameter), noninvasive epithelial neoplasms. They are characterized by cuboid-to-columnar cells with varying amounts of apical cytoplasmic mucin and varying degrees of cytologic and architectural atypia. The epithelium almost always shows gastric-foveolar differentiation and has a flat or (micro)papillary architecture [3,4].

Since the first classification of the precursor lesions in 1999, three grades have been discriminated in the progression of PanIN, based on the increasing degree of epithelial atypia and architectural complexity: PanIN-1, PanIN-2, and PanIN-3 [1]. PanIN-1 lesions were characterized by minimal nuclear atypia, inconspicuous nucleoli,

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and absent mitotic figures and could be further subdivided into flat (PanIN-1A) and micropapillary types with slight nuclear stratification (PanIN-1B). Because of the absence of nuclear atypia and presence of mucin, which is not normally observed in pancreatic ductal cells without histochemical staining, these lesions had been previously designated as "mucinous metaplasia" or "mucous cell hypertrophy." Moderate nuclear atypia, pseudostratification, loss of polarity, hyperchromasia, and rare mitotic figures were features of PanIN-2. Features of PanIN-3 lesions were marked atypia, (atypical) mitotic figures, loss of polarity, and a papillary, micropapillary, or occasionally flat architecture. Cribriform structures, necrosis, and budding of epithelial cells into the lumen could be present.

Poor interobserver agreement between PanIN-1 and PanIN-2 as well as the very limited progression of both PanIN-1 and PanIN-2 to PDAC led to the recommendation from an expert panel to replace this traditional three-tiered grading system [3]. The new two-tiered grading system distinguishes between low-grade PanIN (former PanIN-1[A/B] and PanIN-2) and high-grade PanIN (former PanIN-3) and is now commonly adopted (Fig. 126.1) [4].

High-grade (HG) PanIN is almost exclusively found in association with invasive PDAC [9]. This association is so striking that in pancreata without PDAC, a HG-PanIN lesion may raise strong suspicion for invasion at a different part of the organ [3]. When PDAC is present, HG-PanIN is very hard to differentiate from the infiltrating carcinoma growing into preexisting pancreatic ducts and ductules (i.e., "intraductal spread of invasive carcinoma," "cancerization of the duct," or "colonization"). Signs indicative of this phenomenon frequently observed in PDAC

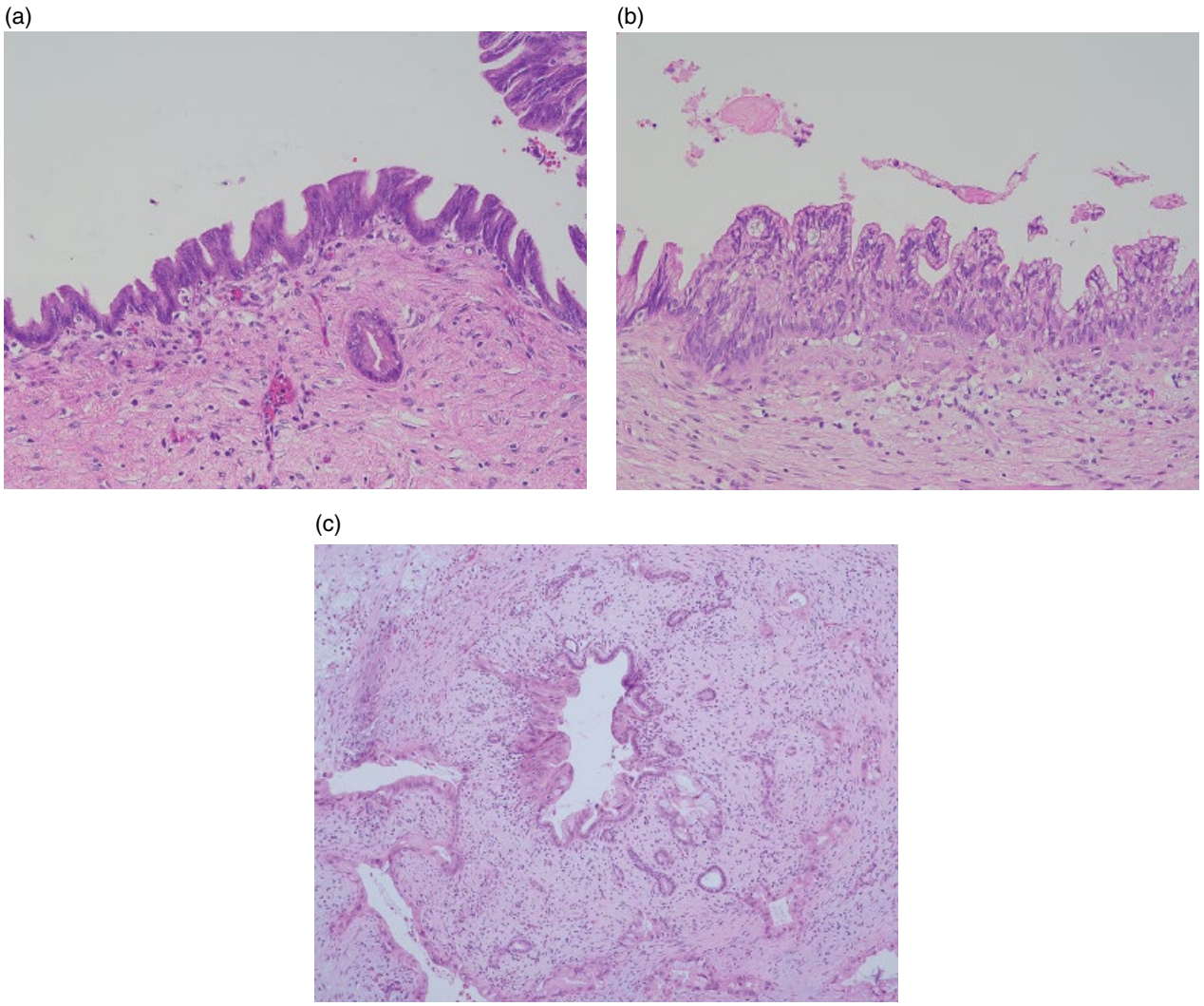


Figure 126.1 Dysplastic grades of PanIN. (a) Low-grade PanIN (formerly PanIN-2) shows moderate atypia and pseudostratification. (b) High-grade PanIN shows irregular nuclei and micropapillary architecture. This grading is reserved for the most severe nuclear and architectural atypia. (c) Cancerization of duct. Histomorphologic signs indicating ductal cancerization are the presence of normal-appearing ductal epithelium together with high-grade dysplasia within a single duct with abrupt transition. In addition, adjacent invasive carcinoma infiltrating the stroma favors the diagnosis of ductal cancerization.

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specimens are an invasive carcinoma immediately adjacent to the intraductal lesion with histologic similarity and an abrupt transition from highly atypical epithelium to normal duct epithelium within the same duct [4,17]. Distinguishing HG-PanIN from ductal cancerization has clinical relevance as the presence of an intraductally growing PDAC at the surgical resection margin may impact outcomes, whereas the presence of PanIN of any grade at the surgical margin in patients resected for PDAC does not influence survival and no additional resection is required [17,18]. Genetic analysis for alterations in *SMAD4* or *TP53* or immunohistochemical staining for the corresponding proteins may be helpful to distinguish ductal cancerization from HG-PanIN [16,17,19].

Some morphologic variants of PanIN have been described in the literature: foamy gland type, intestinal type, and oncocytic type [20,21]. However, the latter two could be early manifestations of IPMN or IOPN, respectively. PanINs lack MUC2 expression, but usually show expression of EMA/MUC1, MUC4, and MUC5AC [4]. MUC6 positivity may be seen in low-grade PanIN.

Molecular Features

The lowest grade PanIN lesions with minimal cytologic atypia were not originally regarded as neoplastic, but instead were interpreted as hyperplasia. After finding activating *KRAS* mutations, these lesions were considered neoplastic and the term "pancreatic intraepithelial neoplasia" was proposed [1,22–24]. A recent study confirmed the high prevalence of *KRAS* mutations in PanINs, with >90% positivity in both LG and HG lesions [19]. Telomere shortening has been observed as an almost universal feature in PanINs, including in PanIN-1A, indicating that this is a very early genetic event [25].

In a subset of PanINs, activating *GNAS* mutations were found, which may even precede *KRAS* alterations in some cases [19,26]. However, *GNAS* mutations are a genetic hallmark feature of IPMNs, so that presence of *GNAS* mutations in early PanIN could indicate a later development to IPMN [27–29]. Further in the progression of PanIN, genetic and epigenetic inactivation of *CDKN2A/p16* is seen [19,30]. *TP53* and *SMAD4* mutations are considered late events in the progression of PanIN; however, the latest research suggests that especially *SMAD4* mutations may only be seen after progression to invasive PDAC has occurred [16,17,19].

Intraductal Papillary Mucinous Neoplasm

Clinical Features

In 1936, György Habán described a pancreatic lesion with "aneurysma-like" cyst formation, papillary growth of the epithelium, and mucin production, which is considered to be the first description of what is today known as intraductal papillary mucinous neoplasms (IPMN) [31,32]. The term itself was first proposed by Morohoshi et al. in 1989 and later in the 1990s and early 2000s became the consensus name for a defined type of pancreatic lesion, previously referred to by various names [2,33].

Initially, IPMN was considered a disease of older, cigarette-smoking men. However, a metaanalysis showed that there are geographic differences in the gender of patients with an IPMN [34]. In Asia, main duct and branch duct-type IPMNs affect more men than women. In the United States and Europe, main duct-type IPMNs affect more men, while branch duct-type IPMNs affect more women. Patients diagnosed with IPMN are usually in their mid-60s, regardless of geographic region or type of duct involvement [34,35]. The mean age of patients diagnosed with IPMN with invasive carcinoma is a few years higher than the mean age of patients diagnosed with noninvasive IPMN, suggesting a window for interference with an advancing tumorigenic process [36,37].

A recent study based on genetic data estimated that the progression interval between high-grade IPMN and invasive carcinoma is over three years, with notable interpatient variability [5]. Once the lesion has advanced to PDAC, survival rates decrease significantly (five-year survival after resection: 94% HG-IPMN vs 31% invasive IPMN) [38]. Although early-stage IPMN-associated carcinomas have a relatively favorable prognosis and contribute to the better overall survival of IPMN-associated carcinomas as compared to resected standard PDAC (i.e., without preceding IPMN), the prognosis can be equally poor when IPMN-associated carcinoma is diagnosed at a late stage [39]. In fact, when adjusted for tumor stage or adverse pathologic characteristics (e.g., nodal involvement, perineural/vascular invasion), the survival difference between IPMN-associated carcinoma and conventional PDAC can vanish, indicating a similarly aggressive tumor biology [38,40]. These findings highlight the critical role of noninvasive IPMNs for early detection and intervention to improve survival.

Beyond invasive carcinomas that arise directly from IPMN ("IPMN-associated carcinoma" or "PDAC derived from IPMN"), invasive carcinomas can also develop independently from an IPMN within the same specimen ("IPMN with concomitant invasive carcinoma" or "PDAC concomitant with IPMN") [3,41–43]. Measuring the distance between invasive carcinoma and IPMN, complete histologic examination of the intervening tissue, and genetic analyses may aid in assessing the relationship and origins of the invasive carcinoma. However, the exact differences between these two entities, their specific mechanisms of tumorigenesis, and the clinical implications of their distinction are not fully understood yet.

Intraductal papillary mucinous neoplasms are seen more frequently in patients with a family history of

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pancreatic cancer, Peutz–Jeghers syndrome, familial adenomatous polyposis (FAP), Lynch syndrome, Carney complex, and McCune–Albright syndrome. In addition, an increased prevalence of extrapancreatic malignancies has been observed in patients diagnosed with IPMN, potentially indicating an overall increased risk for neoplasia in these individuals [44,45].

Due to the widespread implementation of cross-sectional abdominal imaging techniques, macroscopic pancreatic cysts are relatively common findings. Epidemiologic studies show great variety in the prevalence of pancreatic cysts due to the use of different imaging techniques and different study populations. In asymptomatic cohorts undergoing cross-sectional imaging, pancreatic cysts were detected in more than 2% of patients [46–48]. Of these incidentally discovered cysts, more than 80% were radiologically diagnosed as IPMN. Both, the prevalence of pancreatic cysts overall and the prevalence of IPMN, increased with age, reaching up to 13.5% and 12.2%, respectively, in patients over 80 years of age.

Despite their macroscopic appearance and radiographic visibility, patients diagnosed with IPMN are frequently asymptomatic [35,49]. However, unspecific abdominal symptoms, such as pain or discomfort, can be present. Some patients present with more objective symptoms like jaundice, weight loss, or acute pancreatitis. On endoscopy, a patulous papilla extruding mucus can be seen in some patients with IPMN. This so-called "fish-mouth" appearance is virtually diagnostic for the presence of an IPMN (Fig. 126.2a).

Intraductal papillary mucinous neoplasms are most frequently located in the proximal pancreas (i.e., pancreatic head, uncinate process) [35,38]. Based on the involvement of the pancreatic duct system, IPMNs are classified as main duct type, branch duct type, or mixed type. The rationale behind this classification is that lesions with main duct involvement harbor a significantly higher risk of malignancy. Pooled data from multiple studies showed that invasive carcinoma is present in 43.6% of main duct-type, 16.6% of branch duct-type, and 45.3% of mixed-type IPMNs [50]. However, there can be considerable discrepancy in the assessment of duct involvement between radiologic and histopathologic examination. For example, imaging studies may fail to accurately diagnose minimal main duct involvement of IPMNs that primarily affect the branch ducts [51]. Therefore, distinction of IPMNs according to their duct involvement (i.e., main-, branch- or mixed-type) is primarily an imaging classification and not a pathologic criterion. However, it plays a key role in the clinical management of patients with suspected IPMN [4].

Based on preoperative imaging, clinical presentation, and cyst fluid analysis, surgical resection is recommended in a subset of IPMN patients at high risk for malignant progression [52–55]. However, even if invasion is absent in final pathology, recurrence in the remnant pancreas in the form of a new IPMN or PDAC has been reported in up to every fifth patient, indicating that surgical intervention should be seen as risk reduction rather than definitive cure and demands ongoing postoperative surveillance [56–60]. Recurrence following resection of noninvasive IPMN along with molecular studies suggest that IPMN may be a multifocal disease affecting the entire gland in some patients ("field cancerization/defect"), placing them at risk for malignant neoplasia [42,58,59].

Pathologic Features

Intraductal papillary mucinous neoplasms has been defined in consensus meetings as: "*grossly visible, predominantly papillary or rarely flat, noninvasive mucin-producing epithelial neoplasm arising in the main pancreatic duct or branch ducts*" [1–3]. This definition incorporates the two hallmark features of IPMN: papilla formation and mucin production. The diameter of IPMN is usually ≥1.0 cm, highlighting its macroscopic visibility. An intraductal neoplastic precursor lesion larger than a PanIN (≥0.5 cm) but smaller than a typical IPMN (<1.0 cm) can be either a large PanIN or a small IPMN.

Features that occur predominantly in the setting of an IPMN, like the differentiation towards intestinal-type epithelium or a mutation specific for IPMN (such as an activating *GNAS* mutation), are clues for a small IPMN [28]. If one of these features is present, the lesion can be called "incipient IPMN" [3,4]. Gastric-type differentiation can be seen in both PanIN and IPMN, making it a nondistinctive feature. Gastric-type lesions of at least 0.5 cm but smaller than 1.0 cm lacking features of incipient IPMN should be documented descriptively. Of note, during surgical resection or tissue processing, the lesions' size may be reduced from its original *in situ* size, so that combination with radiographic data for size assessment can be helpful to establish the correct diagnosis.

Similar to PanINs, a consensus meeting recommended replacing the three-tiered with a two-tiered grading system [3]. The former "IPMN with low-grade dysplasia" and "IPMN with intermediate-grade dysplasia" are now "IPMN, low-grade" while the former "IPMN with high-grade dysplasia" is now "IPMN, high-grade".

Histologically, IPMNs can be subtyped by their direction of differentiation as gastric, intestinal, or pancreatobiliary [4,61]. Gastric-type IPMN is characterized by cells that resemble the foveolar epithelium of the stomach and is the most common IPMN subtype. Gastric-type IPMNs typically involve the branch ducts [62]. The epithelium consists of a monolayer of columnar cells with basally oriented nuclei and abundant mucinous cytoplasm (Fig. 126.2b). Gastric-type IPMNs are usually low-grade dysplastic and commonly show mutations in *KRAS* and *GNAS* [29]. Moreover, they have the lowest risk for invasion compared to other subtypes. IPMNs containing

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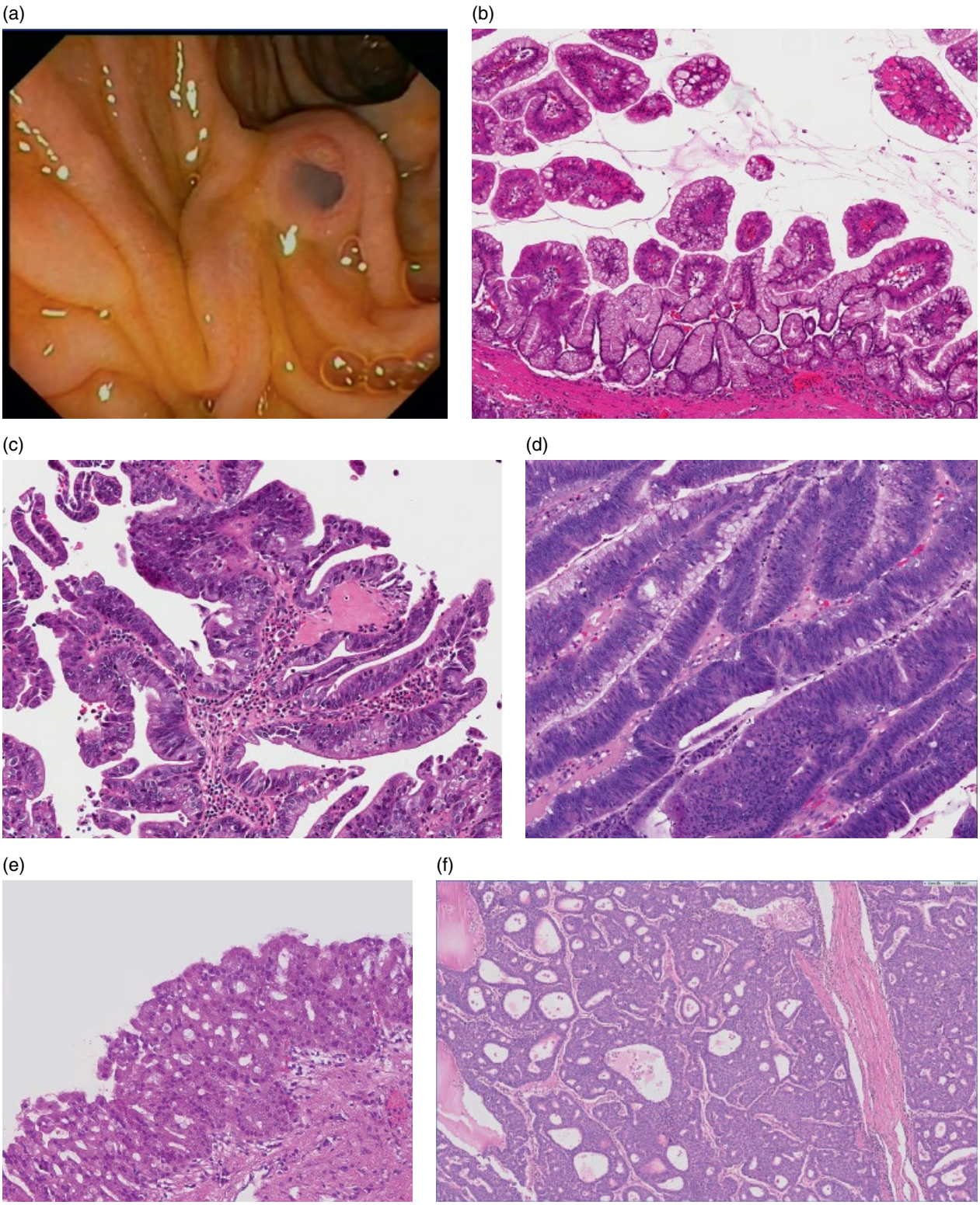


Figure 126.2 IPMN, IOPN, ITPN. (a) Fish-mouth papilla. Mucinous extrusion from the papilla seen in endoscopy is highly suggestive of the presence of IPMN within the pancreas. (b) Gastric-type IPMN with a flat architecture and a single layer of gastric foveolar-type epithelium. (c) Pancreatobiliary-type IPMN lined by cells with marked atypia and prominent nucleoli. (d) Intestinal-type IPMN. Pseudostratified appearance with cigar-shaped nuclei and scattered goblet cells. (e) IOPN. Multilayer of cuboidal epithelium, composed of cells with abundant eosinophilic cytoplasm, reflecting the accumulation of mitochondria, and prominent nucleoli. (f) ITPN. Nodules of glands arranged back-to-back with a tubular-predominant morphologic pattern. Uniform cuboidal neoplastic cells lack relevant amounts of intracellular mucin and show atypical nuclei.

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an admixture of morphologic subtypes often show gastric-type epithelium along with either pancreaticobiliary or intestinal epithelium [63].

It has been proposed that gastric-type IPMNs are an early type of lesion from which other subtypes may emerge. Traditionally, gastric-type IPMNs have been linked to precede the pancreaticobiliary type; however, a recent study suggested an evolutionary linkage between gastric- and intestinal-type IPMN [64,65]. The growth pattern of gastric IPMNs can be flat, papillary, or tubular. The tubular growth pattern can sometimes predominate. The tubular-predominant, gastric-type IPMN (formerly "intraductal tubular adenoma, ITA") needs to be distinguished from intraductal tubulopapillary neoplasm (ITPN; formerly "intraductal tubular carcinoma, ITC"), with high-grade cytonuclear features in the latter being a clue for their distinction.

The pancreatobiliary-type IPMN is least frequently seen and lined by mucin-depleted cells with nuclei with marked variation in size and shape. These nuclei have irregular contours and prominent nucleoli (Fig. 126.2c). Pancreaticobiliary-type IPMNs are predominantly graded as high-grade dysplastic and are the subtype most frequently associated with invasion [62].

The intestinal-type IPMN is morphologically similar to a colonic villous adenoma. The papillae are typically long and occasionally branching. The nuclei of the cells are hyperchromatic, elongated ("cigar-shaped"), and show some degree of pseudostratification. The cells contain variable amounts of mucin and dispersed goblet-cells can be observed (Fig. 126.2d). This subtype typically shows high-grade dysplasia and is predominantly found in the main duct [61,62].

The 2019 World Health Organization classification of tumors of the digestive system provided an immunohistochemical aid for subtyping these IPMNs based on mucin glycoprotein-stains [4]. All IPMNs stain positive for MUC5AC. In addition, intestinal-type IPMNs show positivity for MUC2 and CDX2, whereas the pancreatobiliary type is positive for MUC1/EMA. However, definitive assignment to one of the histologic subtypes may not be possible in a considerable proportion of IPMNs due to uncharacteristic morphology, mixed epithelial subtypes, or discordant immunohistochemistry [63]. In addition, moderate interobserver agreement has been reported [66]. Given these limitations in subtyping of IPMNs, the associations between subtype and prognosis may be even stronger than previously indicated [62,63,67]. Alternatively, the differences in prognosis between the various subtypes of IPMN may mainly reflect inherent differences in the grades of dysplasia between subtypes.

Intraductal papillary mucinous neoplasms can progress into tubular carcinoma or colloid carcinoma. Tubular carcinomas are associated with gastric- and, especially, pancreatobiliary-type IPMNs [62]. They resemble conventional PDAC, both histologically and in terms of survival [68]. Similar to conventional PDAC, *KRAS* mutations were the predominant genetic alterations in this tumor type [29]. In contrast, colloid carcinomas are associated with intestinal-type IPMNs, show a more favorable prognosis than tubular or conventional PDACs, and harbor frequent *GNAS* mutations [29,62,68].

Molecular Features

Whole-exome sequencing of IPMNs revealed an average of 26 mutations per IPMN [69]. *KRAS* and *GNAS* are the most commonly mutated genes, each reported to be altered in 50–80% of IPMNs [27,69]. Primary locations of the mutations are at codon 12 and 201, respectively [69]. In almost all IPMNs, either a *KRAS* or *GNAS* mutation can be found and co-occurrence of these alterations within the same lesion is frequently observed [27,70]. The overall third most prevalent somatic mutation in IPMNs is *RNF43,* reported to be altered in 14–75% [69–72]. *CDKN2A/p16* is another gene commonly mutated in IPMNs. Alterations in *TP53* can be found in high-grade dysplasia and *SMAD4* mutations are usually not observed until invasion is present [70,71]. In turn, mutations in *KLF4*, a member of the Krüppel-like transcription factor family, show a high prevalence in low-grade dysplasia [71]. Beyond the degree of atypia, the histologic subtype affects the prevalence of somatic mutations in IPMNs [73].

Recent analyses of somatic driver gene mutations revealed significant genetic heterogeneity within IPMN lesions, especially with respect to mutations in *KRAS*, *GNAS*, and *RNF43*. Along with computational modeling, this suggests an evolutionary development, in which selection, expansion, and progression of multiple subclones eventually lead to emergence of an invasive subclone that has accumulated a distinct set of mutations in various driver genes. It has been proposed that this clonal selection incites with multiple subclones that arise independently from each other at a very early stage of tumorigenesis (*polyclonal origin*) and that the subsequent clonal selection process may be different between individuals and driven by varying selective pressures at different time points [5,27,29,43,71,74].

Intraductal Oncocytic Papillary Neoplasm

Clinical Features

First described as an entity in 1996, intraductal oncocytic papillary neoplasms (IOPNs) were classified as oncocytic-type IPMNs until recently [75]. Emerging evidence of their distinct morphologic and genomic features as

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compared to other IPMN subtypes led to their classification as separate precursor lesions in the 2019 WHO classification of the digestive system [4]. This reclassification also appreciates the similarity of IOPNs to a group of other oncocytic tumors in various extrapancreatic organs (e.g., thyroid, kidney, salivary gland) [76–79]. Besides their oncocytic features, this heterogeneous group of tumors shares its rare occurrence and a usually more indolent course. Therefore, they are commonly classified separately from their respective conventional-type (i.e., nononcocytic-type) tumors.

Despite their relatively large size (reported mean 4.6–6 cm) [75,77,80,81], previous studies indicated a favorable biologic behavior of IOPNs with an excellent prognosis following surgical resection [76,82]. Although higher recurrence rates compared to other IPMN subtypes have been hypothesized, survival was excellent, even if an invasive component was present or recurrence occurred.

Intraductal oncocytic papillary neoplasms show a relatively equal sex distribution and about half of the resected cases were asymptomatic [76,82]. Approximately two-thirds of IOPNs are located in the pancreatic head and the lesions can resemble PDAC on preoperative imaging due to their complex composition [75–77,81,82]. Given the rarity of these lesions and their changing classification, larger cohorts are needed to allow for more robust analysis of their clinical behavior and prognosis. The most recent classification as a separate entity will likely aid in these efforts.

Pathologic Features

The growth pattern of IOPN is distinctive, consisting of arborizing papillae, lined by 1–5 layers of cuboidal epithelium. These epithelial cells are characterized by abundant eosinophilic cytoplasm due to the accumulation of mitochondria. The nuclei of these oncocytic cells contain a single, prominent, eccentric nucleolus. A specific feature is the punched-out spaces in the epithelium (Fig. 126.2e). Given the architectural complexity and nuclear atypia, IOPNs are typically regarded as high-grade dysplastic [4]. Of note, histopathologic observations that suggest invasion (e.g., growth along adjacent benign ducts, myxoid/edematous stromal changes simulating desmoplasia, complex architecture) are commonly present, but may frequently only mimic invasiveness (e.g., as a result of tangential sectioning), likely explaining the differing rates of cases with associated invasion described in the literature (12–61%) [76–78,81,82]. However, a dedicated analysis found predominantly local invasion (i.e., pT1 or pT2), if true invasion was identified [82]. If PDAC is found in association with IOPN, extracellular mucin accumulation, in which neoplastic cells are suspended, can often be seen and resembles colloid carcinoma [81].

Immunohistochemical staining for MUC5AC, MUC6, and HepPar-1 is typically positive in IOPNs [4,78]. Recently, CD117 expression has been proposed as an additional marker to distinguish IOPN from other differentials and the presence of hyalinized stroma may aid in establishing the diagnosis of IOPN [78,80,83]. Similar to the nomenclature in IPMNs, small lesions with a diameter between 0.5 and 1.0 cm can be called "incipient IOPN" when oncocytic differentiation is present [4].

Molecular Features

Genetic studies of IOPN have repeatedly confirmed the absence of established driver gene mutations commonly present in PDAC or other precursor lesions. IOPNs typically lack somatic mutations in *KRAS* and *GNAS*. Missense mutations and frameshift deletions in *ARHGAP26*, *ASXL1*, *EPHA8*, and *ERBB4* have been reported [77]. A recent study indicated that recurrent gene fusions, rather than isolated mutations in specific genes, may be the genetic drivers of IOPN [81]. *ATP1B1-PRKACB*, *DNAJB1-PRKACA*, and *ATP1B1-PRKACA* fusions were present not just in the lesion but also in their corresponding associated invasive carcinoma and preoperative cyst fluid analyses, the latter highlighting potential clinical utility for preoperative diagnosis.

Intraductal Tubulopapillary Neoplasm

Clinical Features

Intraductal tubulopapillary neoplasms ITPNs are rare intraductal neoplasms of the pancreas. Grossly, they are rather solid, noncystic lesions with intraductal growth and typically do not secrete mucin. They occur equally in men and women. About half of the patients are symptomatic and present with nonspecific gastrointestinal complaints, such as abdominal pain [84]. The lesions are distributed across the entire organ, with a slight predominance in the pancreatic head and with about a quarter of cases diffusely involving the gland [84]. Assessment of invasiveness and, if present, its extent can be challenging. In previous studies, up to 80% of patients had an invasive component, but nodal involvement was rarely seen [84,85]. The prognosis of an ITPN-associated invasive carcinoma is significantly better than the prognosis of conventional PDAC.

Pathologic Features

Extracellular mucin production is not prominent and cyst formation is less evident than in IPMN. ITPN is characterized by densely packed tubules that frequently lie back-to-back, forming large sheets. Tubulopapillary

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growth is sometimes seen, with focal papilla formation present in about a third of ITPN cases [84]. Overall, ITPNs are relatively homogeneous in histologic appearance (Fig. 126.2f) [4]. The cells are cuboidal with modest amounts of eosinophilic cytoplasm and do not contain apparent mucin. There is nuclear atypia and increased mitotic activity and the lesions are usually graded as high-grade dysplastic. Necrosis is frequently observed in the nodules, presenting with a comedo-like pattern [84].

In contrast to IPMN and IOPN, immunohistochemistry for MUC5AC is typically negative in ITPNs [84,86]. EMA/MUC1 is almost always positive and MUC6 is positive in about two-thirds of cases. MUC2 is consistently negative, indicating a closer relatedness to gastropancreatic than intestinal epithelial lesions [85]. ITPN has formerly been called "intraductal tubular carcinoma" (ITC).

Molecular Features

Intraductal tubulopapillary neoplasms usually lack the driver gene mutations frequently found in IPMNs or PDAC, such as *KRAS*, *GNAS*, *RNF43*, *TP53*, or *SMAD4*. Genetic alterations in *CDKN2A* or the PI3K pathway (e.g., *PIK3CA*) were identified in about a quarter of ITPNs each [85,87]. Mutations in chromatin remodeling genes (e.g., *MLL* family) have been found in about a third of cases. In addition, *FGFR2* fusions have been reported and *MCL1* amplifications were commonly found.

Mucinous Cystic Neoplasms

Clinical Features

Although mucinous cystic neoplasms (MCNs) were first described by Compagno and Oertel in 1978, it was not until 2006 that the presence of ovarian-type stroma was adopted as an obligate criterion for their diagnosis [88,89]. In addition to this hallmark feature, the lack of communication with the pancreatic duct system aids in the discrimination between MCNs and IPMNs. MCNs predominantly occur in female patients at perimenopausal age in the distal part of the pancreas (i.e., body or tail) in the form of solitary lesions. Morphologically, they commonly show a "cyst-in-cyst" growth pattern by the formation of septae. It has been previously hypothesized that MCN has its origins in embryology [90]. A recent study highlighted the striking clinical, histomorphologic, and molecular similarities between pancreatic MCNs and mucinous ovarian tumors [91].

Elias *et al.* indicated that MCNs may originate from tissue of primordial germ cells that get stuck in the pancreatic body or tail during their physiologic descent to the gonads in embryogenesis. This concept could also potentially explain the existence of similar, MCN-like lesions in the liver or kidney or mixed epithelial stromal tumors (MEST) of the kidney, if cells remain at other sites during their caudal migration. However, the exact mechanisms, including the role of hormonal influences or other potential triggers like smoking, are yet unknown.

Patients with noninvasive MCN are significantly younger than patients with invasive carcinoma, with an age difference of about 10 years (44 versus 55 years) [92]. This link between increased patient age and presence of an invasive component, as well as the observation of different dysplastic grades within one lesion, suggest an adenoma-to-carcinoma-like progression pattern in MCNs. The majority of surgically resected patients presented with symptoms and with median radiographic sizes of 3.5–5 cm (range 0.5–20.0 cm), the size range highlighting the immense potential for voluminous growth in these lesions [92,93].

Surgical resection of noninvasive MCNs is curative and without recurrence [92–95]. Presence of an associated invasive carcinoma has been reported in 6–25% of resected MCNs and is associated with a five-year disease-specific survival of 57–79.6% [92–96]. Recurrence following surgical resection has been reported in more than a third of patients with an invasive component, occurs commonly early, and leads to rapid death [92,96]. However, these findings in invasive MCNs indicate a significantly better overall prognosis following resection than for conventional PDAC or IPMN with invasive carcinoma. This difference may be partially explained by the lower rate of lymph node involvement in invasive MCNs, which is only present in up to one-third of these patients at surgical resection [92–95,97].

Despite a correlation of increased cyst size with the risk for malignancy, recent studies indicate that size may be less accurate in distinguishing between noninvasive and invasive MCNs [93,97]. Instead, radiographic features (e.g., solid component/mural nodule, duct dilation) [95], elevated serum levels of CA19-9 [93,95,96], weight loss [93], location in the pancreatic head [95], male sex [93,95,97], and high age [92,96,97] suggest presence of an invasive component. In addition, radiographic evidence of splenic vein thrombosis has been reported to be strongly associated with invasiveness [94].

Pathologic Features

Mucinous cystic neoplasms are defined as having two components. The cyst is lined by neoplastic, mucinous, columnar epithelial cells, surrounded by a nonneoplastic, ovarian-type stroma. The epithelial dysplasia is graded in a two-tiered fashion, as recommended by the latest consensus meeting [3]. "MCN, low-grade" comprises the former "MCN with low-grade dysplasia" and "MCN with

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intermediate-grade dysplasia" and is contrasted against "MCN, high-grade" (formerly "MCN with high-grade dysplasia"). Coexistence of low- and high-grade epithelium within one lesion, eventually located in different loculues of the MCN, is common [98]. In addition, denudation of the epithelial layer is seen in many cases and can be extensive. Therefore, histologic examination of the entire MCN is required, which can be laborious in large lesions, to properly assess the highest dysplastic grade within the MCN and reliably exclude invasion.

Irrespective of the histologic grade, morphology and mucinous quantity of the epithelium can vary from flat or cuboidal cells without significant intracytoplasmic mucin to tall, columnar cells with abundant supranuclear mucin (Fig. 126.3). Although a mix of mucin-rich and mucin-depleted epithelial cells is common within a single lesion, MCNs that have predominantly mucin-rich epithelium are more frequently associated with high-grade dysplasia or invasion [99–101].

Ovarian-type stroma is mandatory for diagnosis of MCN but may be only focally present or not obvious due to fibrosis, hyalinization, or hypocellularity, which can impede the correct diagnosis [102]. Sometimes, nests of epithelioid cells are seen in the stroma, suggesting luteinization. The cells of the ovarian-type stroma frequently express progesterone and estrogen receptor, α-SMA, and luteinized cells, if present, are positive for inhibin [98]. These stains can be useful in establishing the diagnosis of MCN.

The invasive carcinoma typically associated with an MCN is a tubular adenocarcinoma; however, other tumor types, such as adenosquamous or undifferentiated carcinoma, have also been reported [98].

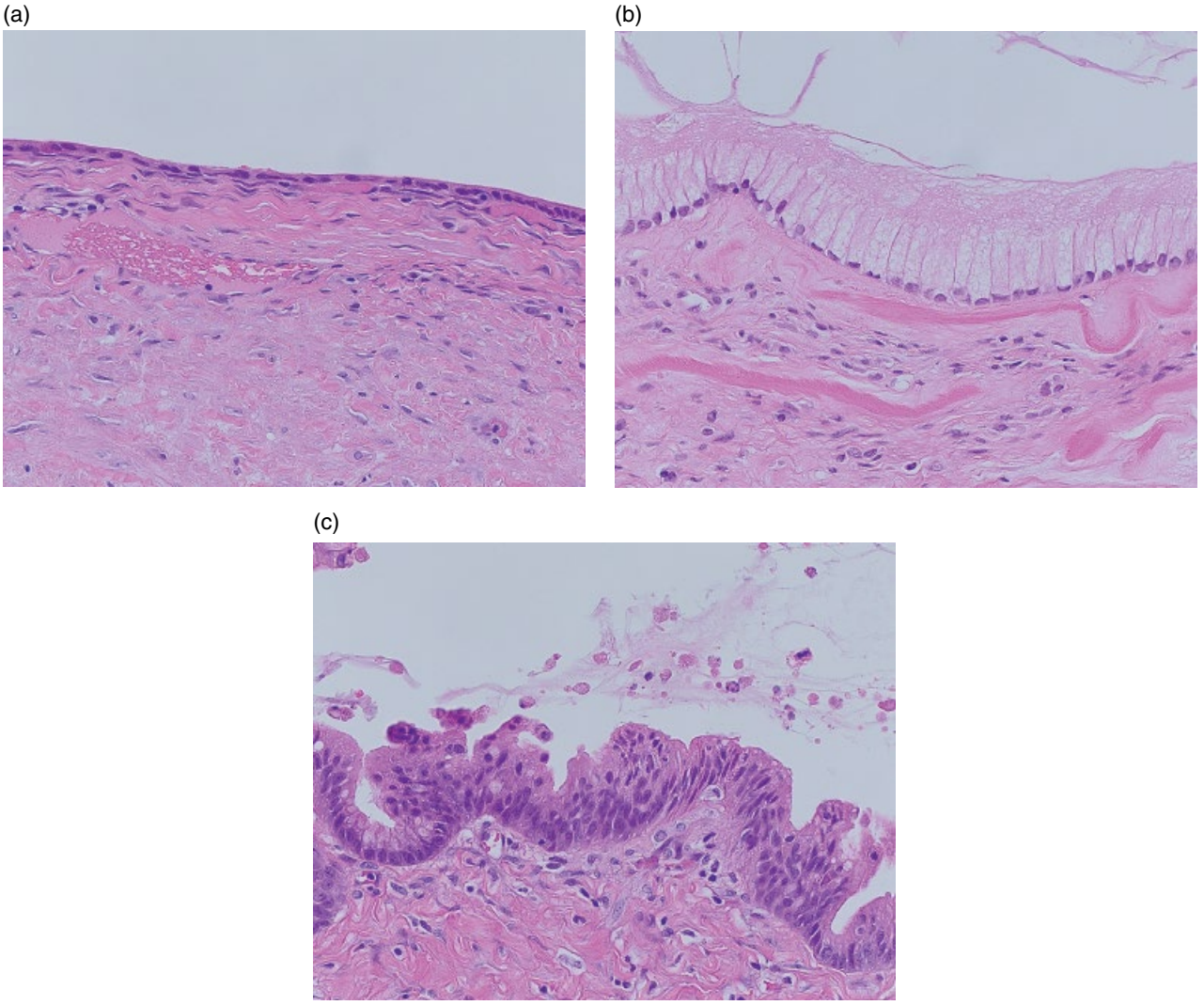


Figure 126.3 MCN with characteristic, spindle-shaped ovarian-type stroma covered by an epithelial monolayer. (a) Low-grade MCN with flat epithelium and little to invisible intracytoplasmatic mucin. (b) Low-grade MCN with tall columnar cells and abundant supranuclear mucin. (c) High-grade MCN with marked architectural atypia.

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Molecular Features

Whole-exome sequencing of MCNs showed on average 16 nonsynonymous somatic mutations and relatively few "loss of heterozygosity" events compared with IPMNs [69]. Alterations in *RNF43* have been described in low- and high-grade MCNs. Hotspot mutations in *KRAS* are a common finding in MCNs, particularly in lesions with high-grade dysplasia or invasion (up to 100%) and in lesions with predominantly mucin-rich epithelium [101,103,104]. Alterations in *TP53* and *CDKN2A* are frequent events in about half of high-grade or invasive MCNs and *SMAD4* has been reported in a small subset of MCNs with associated invasive carcinoma [104]. Of note, *GNAS* mutations are absent in MCNs and can serve as a useful genetic feature to distinguish MCN from IPMN [103,104].

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Clinical History and Risk Factors of Pancreatic Cancer

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Introduction

It does not matter which way you look at it or by what means you endeavor to access the extensive field of pancreatic carcinoma, whether as a nonspecialist but interested reader, an oncology expert, or even as an afflicted patient, and no matter the angle of view or the basic discipline you use to acquaint yourself with pancreatic carcinoma, whether by pathology, internal medicine, or surgery, the catchy introductory phrase is almost always followed by the stereotypical statement: "The diagnosis of pancreatic carcinoma most frequently implies an unfavorable prognosis." This monotonous introduction to pancreatic carcinoma is clear evidence of the lack of effective therapeutic options, especially in the case of an unresectable tumor.

There are multiple reasons for this but undoubtedly, the relatively long period of freedom from symptoms greatly contributes to the fact that only around one-fifth of patients are diagnosed early enough to consider a curative approach. Moreover, numerous widespread but rarely specific factors exist that often cannot be influenced but may increase the likelihood of developing pancreatic carcinoma. However, it should be noted that phenomena such as pancreatitis or diabetes tend to be part of the clinical appearance of the tumor disease rather than risk factors.

This chapter aims to make a connection between current knowledge in terms of relevant risk factors and the clinical appearance and symptoms of pancreatic carcinoma. Finally, by raising the reader's awareness, it is hoped to improve early detection and intervention as a basis for a more effective therapeutic approach and thus a better prognosis for the patient.

Clinical History of Pancreatic Cancer

Probably the greatest hindrance to the prompt diagnosis of pancreatic carcinoma is the lack of early disease-specific indicators. On the one hand, it is difficult to distinguish these from other nonspecific symptoms, and on the other hand, afflictions that possibly indicate malignant disease can often be explained otherwise and may be misinterpreted. Moreover, symptoms may vary significantly depending on the tumor's location in the pancreas.

Functional Impairment of the Pancreas

Increasing loss of exocrine function is one potential tumor-related symptom. The absence of important digestive enzymes in the functionally complex interaction of intestinal digestion causes inadequate fragmentation of carbohydrates, proteins, and fats. Therefore, resorption across the intestinal wall into the portal system is insufficient and the major portion of undigested fat remains in the gut, which causes so-called *fatty stools* (*steatorrhea*). This may lead to considerable *diarrhea*, *flatulence*, and *abdominal cramps*.

Furthermore, the tumor may noticeably compromise the endogenous function of the pancreas. Several studies have proved that *diabetes* frequently predates a diagnosis of pancreatic carcinoma [1,2]. A diabetic disorder caused by a pancreatic carcinoma is also called pancreatic cancer-related, pancreatic cancer-associated, or -induced diabetes. It is also categorized type 3c diabetic disease (pancreoprivic diabetes according to the American Diabetes Association) which includes diabetes due to both malignoma and other pancreatic conditions such as acute or chronic pancreatitis [3]. Chari et al. analyzed the medical histories of patients with pancreatic cancer and

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revealed new-onset diabetes in 52% of the patients prior to assessment and hyperglycemia in 80% of the cases at the time of detection of the disease [4].

It is therefore likely that the mechanism of diabetes development in pancreatic carcinoma is not only due to β-cell destruction because even pancreatic carcinomas that involve only small parts of the organ are already associated with diabetes. A recently published review emphasizes the impact of pancreatic stellate cells on possible modulations of β-cell function and peripheral insulin resistance [5]. Furthermore, metabolic changes (such as serum glucose levels) diagnosed only a few months before detection of pancreatic cancer support the hypothesis of a paraneoplastic phenomenon of this malignancy [6].

Invasion into Intra- and Extrapancreatic Nerve Plexus

Rapid *loss of body weight* and reduced general state of health in afflicted patients are frequently triggered by *pain symptoms* in the upper abdomen and the back. Pain in the upper abdomen can be found in approximately 70% of patients with pancreatic carcinoma. Symptoms usually start intermittently and after a distinct period of time develop into continuous pain. Inside the pancreas, nerves are altered and damaged as tumor cells invade intra- and extrapancreatic perineural structures. Perineural invasion is characteristic for pancreatic cancer and it occurs in almost all cases [7]. It is believed that the extent of perineural invasion is linked to the severe pain syndrome of pancreatic cancer patients. Noticeably, patients with severe abdominal pain show a higher degree of neural invasion and increased nerve hypertrophy compared with patients who are pain free [7,8].

Pancreatic cancer-associated pain has characteristics of *neuropathic pain*, as well as *nociceptive pain*, which is why it is considered to be of "mixed" type. The continuous spread of tumor cells and the consequent increased severity of neural invasion are independent prognostic factors for worse overall and disease-free survival. The development of neuropathic pain is affected not only by neurons but also by immune cells, Schwann cells, and glial cells of the central nervous system [9]. Current research is investigating the genesis of neuropathic pain with the aim of developing adequate pain management.

Tumor Cell Ingrowth into Adjacent Organs and Nearby Vessels

Whereas a tumor located in the head of the pancreas characteristically causes both pain-free *jaundice* and intra- and extrahepatic cholestasis, lesions in the pancreatic corpus and tail rarely give rise to these symptoms [10].

Jaundice of sclerae and skin and the accompanying troublesome *pruritus* are caused by intrapancreatic biliary obstruction with storage of bile acids and bilirubin in the tissue. The tumor causes constriction of the common bile duct that passes through the pancreatic head and then leads to the major duodenal papilla and the duodenum together with the pancreatic duct. With constriction of the pancreatic duct, *acute pancreatitis* may develop. Nevertheless, this phenomenon is rare due to the slow tightening of the pancreatic duct. Patients usually also report *discoloration of feces and urine*. As a consequence of impaired biliary excretion via the bowel, feces become light and clay-colored. The accumulated bilirubin in the serum is then compensatorily excreted by the kidneys, turning the urine brown.

Furthermore, local tumor growth and infiltration of adjacent organs may cause gastric emptying disorders or duodenal obstructions, resulting in *nausea*, *loss of appetite*, *a sensation of pressure in the upper abdomen*, and *increasing emesis*. Because of the close anatomic proximity of the pancreas to adjacent vessels (portal vein, celiac trunk, and superior mesenteric artery), even relatively small tumors may invade vessels. However, the so-called *paraneoplastic syndromes* (especially thromboses of the major femoral and lower leg veins with respective clinical appearance) are independent of local tumor growth.

Clinical Symptoms of Neuroendocrine Tumors of the Pancreas

Apart from the afore-mentioned nonspecific and sometimes nondirective symptoms of pancreatic carcinomas, neuroendocrine tumors (NET) of the pancreas often secrete hormones into the bloodstream. Various types of NET produce different hormones, which in turn may cause varying clinical symptoms. However, not all NET of the pancreas are hormonally active.

Gastrinomas are functionally active NET that produce the hormone gastrin, which causes increased secretion of gastric acid. Typically, gastric and intestinal ulcers resistant to medication develop in up to 95% of afflicted patients over time or rapidly reoccur after end of treatment. Subsequently, *intense abdominal pain* and/or *intestinal bleeding* may appear. A smaller number of patients (~60%) develop pathologic *gastroesophageal reflux* with *pyrosis* or *dysphagia*. Over 30% of patients suffer from *diarrhea* and/or *steatorrhea*.

Insulinomas are the most frequent type of functionally active NET of the pancreas. These tumors typically lead to elevated insulin levels, which depress blood glucose levels and provoke symptoms of *hypoglycemia* such as *trembling*, *ravenous appetite*, and *confusion*.

Glucagonomas may cause nonspecific *loss of capability* or *body weight*. Hyperglycemia caused by release of

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glucagon and *necrotizing dermatitis* are characteristic symptoms of glucagonomas.

Somatostatomas, ***vasoactive intestinal peptide-releasing tumors (VIPomas)***, and ***pancreatic polypeptide-producing tumors (PPomas)*** are rare hormone-producing NET. A list of specific and nonspecific symptoms is shown in Table 127.1, together with symptoms of the afore-mentioned tumors.

Risk Factors for Pancreatic Cancer

Malignancies typically develop by interaction of diverse factors but it is impossible to specify them for pancreatic cancer in every single case. However, large observational studies have defined risk factors that statistically foster development of pancreatic carcinoma. This implies that these risk factors cannot be found retrospectively in all patients with pancreatic cancer nor do all individuals with these factors inevitably evolve a pancreatic carcinoma.

Smoking

The etiology of numerous diseases can be attributed to inhalation of tobacco smoke. This mainly applies to the respiratory organs, cardiovascular system, and malignant tumors. Smoking is an unambiguous risk factor for development of pancreatic cancer. A metaanalysis of 82 cohorts and case–control studies reports a relative risk of 1.7 (95% confidence interval [CI] 1.6–1.9) for smokers and 1.2 (95% CI 1.1–1.3) for ex-smokers independent of gender and region. Investigation of cigar smokers and pipe smokers ascertained pooled risks of 1.5 (95% CI

Table 127.1 Clinical symptoms of pancreatic carcinoma.

By functional impairment of the pancreatic gland

Digestive difficulties (diarrhea, abdominal pain, flatulence)

Changes in stools

Development of diabetes

Loss of weight

By intra- and extrapancreatic nerval invasion

Pain in the upper abdomen and the back

By infiltrative tumor growth into adjacent organs and vessels

Jaundice

Nausea and vomiting

Inappetence

Sensation of pressure in the upper abdomen

Acute pancreatitis

Thromboses (including paraneoplastic syndromes)

By specific hormones of neuroendocrine pancreatic tumors

Type of tumor	Hormone	Symptoms
Gastrinoma	gastrin	Acid reflux, burning abdominal pain, excess fat in stool, weight loss
Glucagonoma	glucagon	High blood glucose, anemia, weight loss, swelling/irritation of skin
Insulinoma	insulin	Low blood glucose, perspiration, confusion, shakiness, accelerated heartbeat
Somatostatinoma	somatostatin	Nonspecific symptoms like diabetes, gallstones, diarrhea, weight loss
VIPoma	vasoactive intestinal peptide	Watery diarrhea, fatigue, nausea
PPoma	pancreatic polypeptide	Belly pain, enlarged liver, watery diarrhea

VIPoma, vasoactive intestinal peptide-releasing tumor; PPoma, pancreatic polypeptide-producing tumor.

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1.02–2.3) and 1.4 (95% CI 0.94–2.0), respectively [11]. The authors depict a linear trend for risk of carcinoma development with increasing smoking exposure. However, the correlation could not be proved in a metaanalysis by Zou and colleagues [12].

Another pooled analysis studied the impact of cigar and pipe tobacco and smokeless tobacco on pancreatic cancer risk. The results principally confirm an association between cigarette smoking (odds ratio [OR] 1.5, 95% CI 1.4–1.6) and cigar smoking (OR 1.6, 95% CI 1.2–2.3) and pancreatic carcinoma. However, any impact of pipe smoking on later occurence of pancreatic carcinoma could not be demonstrated [13]. Data on smokeless tobacco use (mainly snuff) are rare. Here the authors show results consistent with a metaanalysis, which does not indicate any excessive risk of pancreatic carcinoma in several case studies [14]. Conversely, another metaanalysis refers to an association between smokeless tobacco and pancreatic carcinoma [15]. However, the consumption of smokeless tobacco in particular has not been proven to be a distinct risk factor because of the marked heterogeneity of ingredients.

Recent data from a comprehensive European case–control study confirm a 72% increased risk for pancreatic carcinoma in current smokers versus never-smokers. A positive, nonlinear correlation could be revealed for length of exposure to cigarette smoke, intensity, and increased levels of cumulative dose [16]. The elevated risk of pancreatic cancer diminishes after complete cessation of smoking. Due to the high prevalence of smoking worldwide, experts assume that as many as 25% of pancreatic carcinomas can be attributed to cigarette consumption [17].

Diabetes Mellitus

As stated in the introduction to this chapter, risk factors and early symptoms of pancreatic cancer can be difficult to distinguish. A comprehensive study revealed a threefold increased risk of pancreatic cancer in patients with type 2 diabetes (OR 3.22, 95% CI 3.03–3.42) [18]. These results can be supported by data from an earlier metaanalysis that also identified diabetes type 2 as a risk factor for pancreatic carcinoma (OR 1.82, 95% CI 1.66–1.89) [19]. The authors hint at the fact that in a majority of the included studies, there was no distinction between type 1 and type 2 diabetes. Nevertheless, it could be assumed that most individuals had type 2 diabetes as it is the predominant type of diabetes in the elderly [19]. Therefore, these study populations do not allow for a transfer of results to individuals suffering from type 1 diabetes.

It remains unclear whether these patients are at risk for developing pancreatic malignancies. In a metaanalysis of three cohorts and six case–control studies, the investigators took this factor into account and analyzed 39 patients with type 1 diabetes and juvenile-onset diabetes (interpreted as type 1). Type 1 diabetes could be identified as a risk factor for pancreatic carcinoma with a relative risk of 2.00 (95% CI 1.37–3.01) but the authors urgently call for confirmation by further studies because of the low number of patients [20]. In a large international study, the incidence of pancreatic cancer in patients with proven type 1 diabetes was compared to the incidence in the nonaffected population. An increased risk for pancreatic cancer could be revealed in this way. However, interestingly, individuals with new-onset diabetes showed a higher risk of tumor disease within the first year compared to patients with a long-term diagnosis of diabetes [21]. These findings again support the hypothesis of a bidirectional relationship of diabetes and pancreatic carcinoma, as recent-onset diabetes may be an early symptom and therefore the manifestation of pancreatic cancer (as outlined in the earlier section "Functional impairment of the pancreas"), whereas a longer time of diabetes disease is a risk factor for this malignancy.

Other factors associated with disturbed glucose metabolism may possibly trigger an increased risk for pancreatic cancer. A prospective cohort study was initiated to determine the independent association between postload plasma glucose concentration and the risk of pancreatic cancer development among patients without self-reported diabetes. After an observation period of 25 years and after adjusting for age, race, cigarette smoking, and body mass index (BMI), the relative risk of pancreatic cancer mortality was 1.65 (95% CI 1.05–2.60, for postload plasma glucose levels between 6.7 and 8.8 mmol/L) [22]. Another study reported a positive association between pancreatic cancer and elevated baseline fasting serum concentrations of glucose and insulin, and insulin resistance, respectively [23].

Overweight and Obesity

The World Health Organization (WHO) defines overweight and obesity by use of the body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. Thereby, underweight (BMI <18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.5 kg/m^2), and obese (30 kg/m^2 and above) can be differentiated. In several cohort studies and case–control studies, an up to three-fold increased risk for development of pancreatic carcinoma was found for overweight individuals. Next, it was shown that overweight (OR 1.67, 95% CI 1.20–2.34) and obese individuals (OR 2.58, 95% CI 1.70–3.90) had an elevated risk for pancreatic carcinoma independent of concomitant diabetic

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disorders [24]. One aspect of this study was the finding that overweight and obesity during early adulthood (between 20 and 49 years) increased the risk of developing pancreatic cancer and that it usually develops 2–6 years earlier than average. This was an important report of an association between excess body weight across the life span and the risk of pancreatic cancer, which emphasizes the importance of these findings with regard to public health. Moreover, it was shown that there is an increased risk of obesity-associated pancreatic cancer in males [24]. These results were confirmed in a pooled analysis of 20 prospective cohort studies which determined an association between increased pancreatic cancer mortality and BMI during early adulthood in individuals who are overweight or obese [25].

The question arises whether those (rather few) individuals who manage to reduce their body weight significantly and approach normal weight during their life can thereby reduce the risk of pancreatic cancer development. Therefore, an important prevention measure is body weight control at younger ages.

Pancreatitis and Consumption of Alcohol

The positive correlation between chronic pancreatitis and development of pancreatic carcinoma was proven in a precedent-setting cohort study [26]. Including 2000 patients with chronic pancreatitis, the authors demonstrated an increased lifetime risk of nearly 4% in this population group in terms of development of pancreatic carcinoma. Population-based prospective surveys assume a standardized incidence ratio of 4.8, which approximates to a risk of 0.6% after 20 years. Amongst around 1500 patients who were observed for a period of at least two years, the percentage distribution of pancreatitis was alcohol induced in 77%, idiopathic in 17%, hereditary in 1.9%, and of different origin in 4.1%. Even though the relation may have turned slightly towards a higher rate of hereditary pancreatitis during the last two decades, this study identified chronic pancreatitis to be a risk factor, which is independent of age, region, and underlying origin.

Numerous other reports suggest that chronic pancreatitis is a risk factor for pancreatic carcinoma; however, the relative risk varies considerably in the literature (range 2.3 [27] to 18.5 [28]). Most likely, these variations can be attributed to methodologic concerns and the retrospective design of many studies. In a prospective analysis of 373 patients with proven chronic pancreatitis and a follow-up of at least two years, a significantly increased risk for pancreatic cancer was found compared with the general population [29].

Recent investigations also indicate an increased risk of pancreatic carcinogenesis in cases of acute pancreatitis and recurrent pancreatitis. A comprehensive cohort study based on data from the Swedish National Registry identified an episode of acute pancreatitis in nearly 70% of patients who later developed pancreatic cancer. The risk was especially increased within the first years after diagnosis of acute or recurrent pancreatitis but decreased to the common population risk level after a period of 10 years [30]. These data are in line with a Danish nationwide, population-based, matched cohort study including more than 41 000 patients with proven acute pancreatitis. A two-fold increased risk for pancreatic carcinoma after five years (95% CI 1.57–2.61) was demonstrated even though the incidence decreased over the course of time [31].

The true impact of alcohol as a direct risk factor for pancreatic cancer is under debate and different mechanisms are postulated. Inducing different cascades of inflammation, alcohol might indirectly induce carcinogenesis via both chronic pancreatitis and diabetes [32]. However, one point of criticism of the partially inconsistent studies is the fact that analyses were performed without considering the relationship of doses and pattern of alcohol exposure. Heavy alcohol consumption was associated with an increased risk for development of pancreatic cancer in males in a population-based study. According to dose, duration, and pattern of alcohol abuse, the OR was increased 1.5–6-fold [33].

Environmental Factors

A range of environmental factors has been identified as having a possible association with pancreatic carcinoma development. Table 127.2 gives a list of these triggers. Aromatic amines seem to be the substrate of the

Table 127.2 Risk factors for pancreatic adenocarcinoma.

Demographic factors	
Age	[34]
Black race	[35]
Blood group	[36]
Environmental factors	
Smoking	[11]
Alcohol	[37]
Aromatic amines (cooked meat, cigarette smoke)	[38]
Obesity, high-fat diet	[39]
Occupations (chemists, petrochemical worker, etc.)	[40]
Preexisting diseases	
Chronic pancreatitis	[26]
Diabetes mellitus	[18]
Insulin resistance	[23]
Gastrectomy	[41]
Helicobacter pylori infection	[42]
Genetic factors	
Positive family history	
Tumor predisposition syndromes (see Chapters 124 and 130)	

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carcinogenic effect of both smoking and consumption of cooked meat and fish. The same applies to occupations with comparatively high exposure to these amines.

Hereditary Factors

A positive family history of pancreatic carcinoma has repeatedly been shown to be a risk factor. These aspects and the respective tumor predisposition syndromes are the subject of Chapters 124 and 130.

Conclusion

The identification of early symptoms of pancreatic cancer and the subsequent timely start of diagnostics in daily clinical practice remain highly demanding. Several specific and nonspecific risk factors for pancreatic carcinoma have been identified with more or less certainty, which can be proved by respective studies. If possible, abstinence and avoidance should be practiced to the greatest extent to prevent development of pancreatic cancer. However, with regard to numerous predisposing factors and especially a positive family history, this cannot be performed satisfactorily. An early diagnosis is the only possibility to improve patient survival. Therefore, every worrisome finding should be investigated and resected in case of doubt.

Finally, particular attention must be drawn to the group of cystic pancreatic tumors with their numerous different entities and distinct clinical and morphologic characteristics. These neoplastic and nonneoplastic, mucinous, and serous cystic lesions can be detected even earlier and at a smaller stage because of continuing improvements in imaging methods. Nowadays, these tumors can be investigated by highly precise risk stratification, which results in distinct therapeutic recommendations. Based on several clearly defined criteria, pancreatic cystic tumors should be either observed or resected. This strategy allows for early resection of precancerous lesions or even pancreatic cancer with the chance of cure.

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The Role of Endoscopic Ultrasonography in the Diagnosis and Differential Diagnosis of Neoplastic Lesions

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Introduction

A wide range of neoplastic lesions occur in the pancreas, roughly divided into solid tumors and cystic tumors. Transabdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and other imaging modalities are available for diagnosis of pancreatic neoplastic lesions. The malignant potential of pancreatic ductal adenocarcinomas (PDACs) is particularly high compared to other pancreatic neoplastic lesions, with the five-year survival rate reported to range from several percent to 10% [1,2]. There are some reports that the five-year survival rate is about 80% in the case of pancreatic carcinomas ≤10 mm [3]. Endoscopic US (EUS) is superior to US, CT, MRI, and other imaging modalities in its ability to qualitatively diagnose focal lesions and local progression of a lesion, and it allows diagnosis of small pancreatic neoplastic lesions that are difficult to detect with US, CT, and MRI. In addition, cytologic and histologic diagnosis of the target are possible (EUS-guided fine-needle aspiration [biopsy]: EUS-FNA[B]).

As is the case with other organs, a paradigm shift is currently under way from one-size-fits-all cancer therapy regimens to mutant gene-based cancer genomic medicine for cancers of the pancreas. Tissue collected via EUS-FNA(B) is becoming more and more important as a specimen source for comprehensive genomic profiling (CGP) as opposed to simple histologic diagnosis.

In this chapter, we will first discuss the latest characteristics of EUS. We will then discuss the role of EUS in the differential diagnosis of solid tumors and cystic tumors of the pancreas. Lastly, we will discuss the current status of EUS-FNA(B) in CGP.

Characteristics of Endoscopic Ultrasonography

Endoscopic ultrasonography is the most popular endoscopic technique used to diagnose and evaluate pancreatic masses. High-resolution images of the pancreas can be generated by placing a high-frequency probe in close proximity to the pancreas [4].

Endoscopic ultrasonography equipment includes probes for various imaging procedures (Fig. 128.1): radial probes allow 360° imaging perpendicular to the long axis, and convex probes allow imaging along a plane parallel to the long axis of the instrument (Table 128.1). The former allows only diagnostic imaging, whereas the latter was developed for fine-needle aspiration (biopsy) (FNA[B]) [5,6]. Pancreatic masses can be detected by EUS with 93–100% sensitivity and a negative predictive value approaching 100%, particularly when combined with FNA [7]. Small masses (<2 cm) that can be detected by EUS may be identified as occult according to other imaging modalities and in patients with previous indeterminate findings.

The National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma state that patients without a pancreatic mass evident on cross-sectional images should undergo further evaluation with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP) as clinically indicated [8]. Another advantage of EUS is that pancreatic masses can be detected and characterized without intravenous contrast, which is of particular importance when patients have renal dysfunction or other contraindications.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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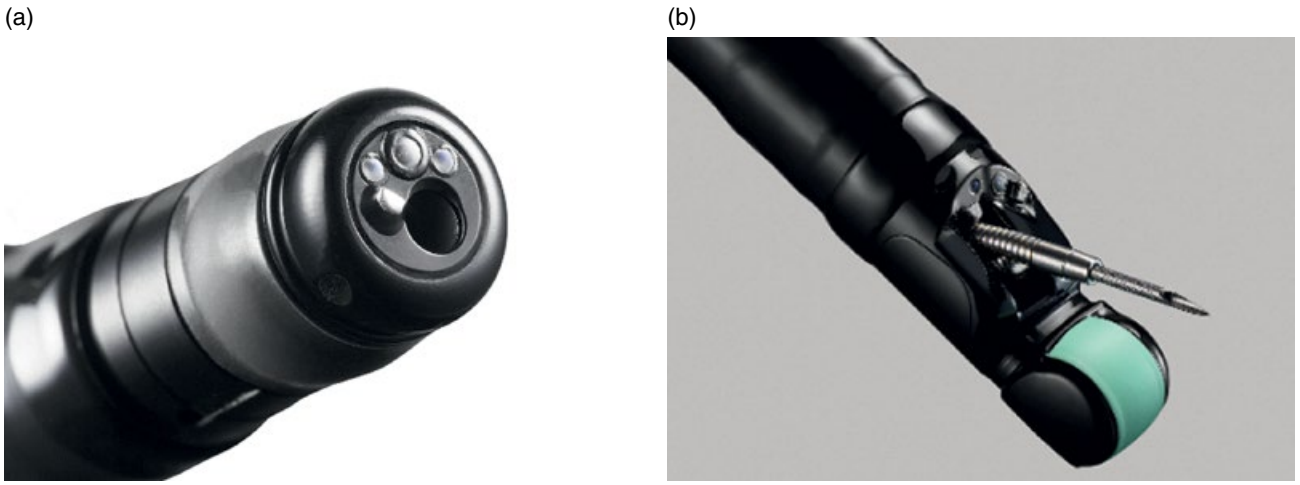


Figure 128.1 (a) The tip of a radial endosonoscope. The radial EUS image is 360° perpendicular to the long axis. (b) The tip of a convex endosonoscope with FNA needle. The convex EUS image is parallel to the long axis of the instrument.

Table 128.1 Advantages and disadvantages of EUS imaging modalities.

	Radial scope	Convex scope
Advantages	• Scanning range is 360°	• Histologic diagnosis is possible
	• Pancreas is easily seen as a longitudinal and continuous image	• Junction between the pancreatic head and body can be seen from the stomach
Disadvantages	• Histologic diagnosis is impossible	• Scanning range is 150° to 180°
	• Operator-dependent	• Images of the body and tail of the pancreas become cross-sectional images

Potential of Radial Scope with Forward-viewing Optics

Radial scopes with forward-viewing optics are commercially available. In addition, radial scopes with forward-viewing optics developed by the Fujifilm Corporation have 190° upward bending capability and a 2.8 mm working channel, which may offer a screening program of the pancreas as well as the esophagus, stomach, and duodenum at the same time, and some facilities, including our university hospital, are interested in this program to detect the early stages of pancreatic cancer in Japan.

Various Imaging Modalities Used with EUS

An endoscope is used for EUS, but it relies on US diagnostic imaging technologies. Representative diagnostic imaging technologies are outlined below [4,9,10].

The most fundamental diagnostic imaging technology is B-mode imaging, which is the first step to detecting and diagnosing a lesion; we cannot find any intrinsic value in EUS without improvement of B-mode images. The first technology developed for EUS was mechanical radial scanning. The quality of B-mode imaging markedly improved thereafter, which led to the incorporation of electronic scanning in the early 2000s [11–13]. Current EUS B-mode imaging may be approaching its completed form with the addition of tissue harmonic imaging technology.

Color Doppler and power Doppler imaging were subsequently incorporated into EUS, which greatly improved its diagnostic ability by providing the characteristic hemodynamic information of a target lesion in addition to B-mode information.

Moreover, after the development of US contrast agents that can be administered intravenously, diagnosis with color Doppler and power Doppler imaging in combination with US contrast agents, as well as contrast-enhanced EUS using harmonic imaging techniques developed for use with US contrast agents, began to show their usefulness. Many pancreatic tumors exhibit characteristic hemodynamics, making use of contrast agents indispensable in the diagnosis using CT and MRI. However, CT and MRI are useless in patients in whom they are contraindicated, such as those with renal dysfunction and those allergic to contrast agents. On the other hand, US contrast agents can be used in many cases (excluding patients with egg allergy) even when CT and MRI contrast agents cannot be used. It can be said that EUS, which allows evaluation of hemodynamics by using a US contrast agent in combination with clear B-mode images, is useful for the diagnosis of pancreatic tumors [14–16] (Figs 128.2 and 128.3).

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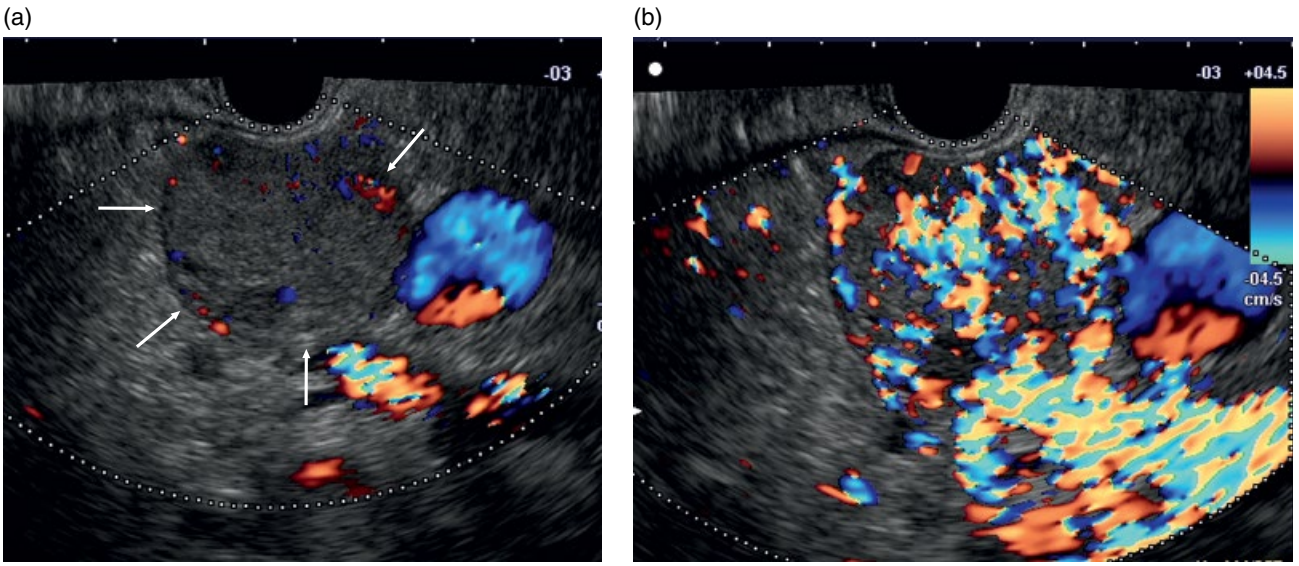


Figure 128.2 Intraductal papillary mucinous carcinoma. (a) Color Doppler imaging revealed the subtle vasculature inside the papillary growth-like structure. (b) After intravenous injection of ultrasound contrast agent (Sonazoid®, GE Healthcare), blood flow was seen inside the papillary growth, resulting in the diagnosis of IPMC.

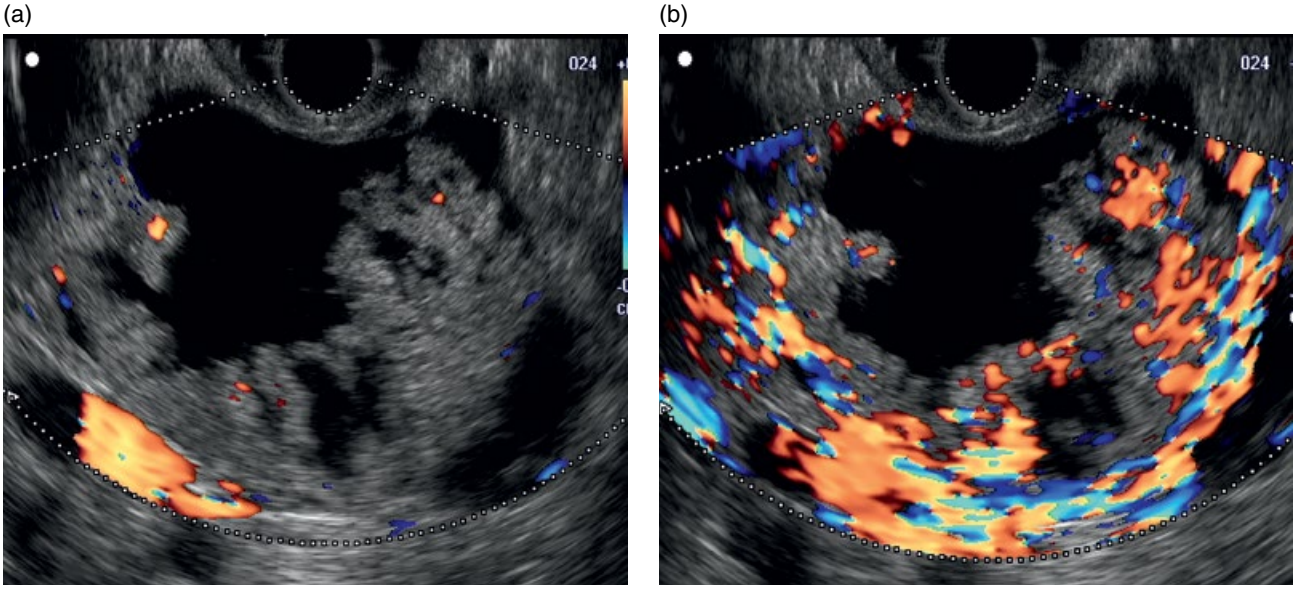


Figure 128.3 Pancreatic neuroendocrine neoplasm. (a) Plain color Doppler imaging demonstrated a hypoechoic tumor with a smooth contour (arrow). (b) After intravenous injection of ultrasound contrast agent (Sonazoid), blood flow was seen inside the tumor. The findings of both B-mode imaging and hypervasculature resulted in the diagnosis of pancreatic neuroendocrine neoplasm.

Lastly, we will discuss elastography. Elastography is a diagnostic imaging modality that can be used to qualitatively or quantitatively evaluate the stiffness of a target lesion. There are two types of elastography: strain and shear wave. Only strain elastography was available in early EUS elastography units, but shear wave elastography became available very recently [17,18]. With strain elastography, stiffness is evaluated by measuring the degree of strain (displacement) in response to deformation of the target by cardiovascular pulsation or manual compression. The degree of strain is small in the case of hard lesions and large in the case of soft lesions.

With shear wave elastography, acoustic radiation force impulse (ARFI) is applied to the target. Shear waves propagate in every direction from the point in the target where ARFI is applied. What is measured is shear wave speed. It is known that higher shear wave speeds indicate a greater degree of stiffness, resulting in the following

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relationship. The shear wave speed is displayed in meters per second or kilopascals through Young's modulus E = 3 (Vs2ρ), where E is Young's modulus, Vs is the shear wave velocity, and ρ is the tissue density; that is, stiffer tissue corresponds to faster shear wave velocity. While strain elastography is qualitative, stiffness can be quantitatively evaluated with shear wave elastography.

A more accurate diagnosis can be made by acquiring hemodynamic information with color Doppler and power Doppler imaging in addition to the base information from B-mode imaging (plus tissue harmonic imaging). Additionally, a more detailed hemodynamic evaluation is possible by adding a US contrast agent to color Doppler and power Doppler imaging, and to harmonic imaging. It is also possible to add information on the stiffness of the target by using elastography. It is our opinion that neglecting diagnostic imaging and relying on EUS-FNA(B) alone should be avoided.

Solid Pancreatic Tumors

The types and histopathologic characteristics of solid pancreatic tumors are described in detail in another section. The main purpose of this section is to describe the differential diagnosis of pancreatic tumors using EUS.

In terms of solid tumors, the differentiation of pancreatic ductal adenocarcinomas (PDACs) and pancreatic neuroendocrine neoplasms (PNENs) seems to be of particular importance. Here, we will discuss the characteristics of PDACs, which are the most important pancreatic cancer, and PNENs, which we need to differentiate from PDAC. As mentioned above, we describe the differential diagnosis of PDACs and PNENs from the stance that we should not purely rely on EUS-FNA(B).

Pancreatic Ductal Adenocarcinomas

Pancreatic ductal adenocarcinomas are epithelial malignant tumors that arise from the pancreatic duct (pancreatic duct branches). They are characterized by being more hypovascular than PNENs.

First, we will discuss EUS B-mode imaging of PDACs. In terms of the echogenicity of PDACs, most are hypoechoic. On B-mode imaging, the contour is distinct and the border irregular. When the tumor is located in the head or body of the pancreas, the caudal main pancreatic duct is occluded and stenosed, and dilation of the main pancreatic duct is found in most cases. Obstructive pancreatitis occurs to one degree or another on the caudal side of the tumor due to an increase in pressure in the caudal pancreatic duct. The border on the caudal side of the tumor sometimes becomes slightly indistinct as the border of the area of inflammation becomes slightly indistinct [19].

With color Doppler or power Doppler imaging alone, the sensitivity is generally not sufficient to detect blood flow; therefore, there are few cases where the tumor is seen as hypovascular compared with the surrounding pancreatic parenchyma. It has been reported that it is possible to diagnose 90–95% of PDACs by studying the hemodynamics using a combination of a US contrast agent and color Doppler or power Doppler imaging and simultaneously combining it with B-mode imaging. In addition, the accuracy of contrast-enhanced harmonic imaging, which combines harmonic imaging and a US contrast agent, has been reported to be 95–98% [4,7–10].

Next, we will discuss elastography for PDACs. Strain elastography is an index of the relative stiffness in the region of interest (ROI). In the case of PDACs, the value of strain elastography as add-on information to B-mode imaging and blood flow information is considered to be high as the tumor tissue is harder than the pancreatic parenchyma. In fact, there are reports that accuracy in diagnosing PDACs is further improved by adding elastography information to B-mode and harmonic imaging. On the other hand, there are some shortcomings, e.g., the elastography pattern differs when the size of the ROI is changed, due to the fact that strain elastography provides the relative stiffness in the ROI. In addition, it is difficult to compare different cases [20–22].

A parameter called *strain ratio* has been put forward based on the hypothesis that the stiffness of peripancreatic connective tissue is likely almost constant in individuals [23,24]. That is, when the strain ratio is set at S1/S0, with the stiffness of the target regarded as S1 and the stiffness of the surrounding connective tissue designated S0, it is possible to compare different S1s with each other as S0 is constant. Based on our investigations, we are skeptical of strain ratio as the value being sought is not determined by what site we designate as S1 within the selected ROI, i.e., it lacks reproducibility.

As for shear wave elastography, objective comparison of different targets seems to be possible as it yields the actual speed at which the waves propagate through a target. More evidence for this modality needs to be gathered going forward [17,18].

Pancreatic Neuroendocrine Neoplasms

Neuroendocrine neoplasms (NENs) are tumors that originate from the diffuse neuroendocrine system (DENS), which is distributed throughout the body, and NENs that occur in the pancreas are called PNENs. While PDACs grow in an invasive manner, PNENs are generally considered to grow in an expansive manner, although this depends on the degree of malignancy. They are also generally considered to be hypervascular tumors.

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Due to these characteristics, they exhibit EUS imaging findings that differ from those of PDACs.

On EUS B-mode imaging, the echogenicity of PNENs is generally hypoechoic, but it is often slightly more hyperechoic than PDACs. In addition, the contour is distinct and the border is regular. PDACs have an irregular border, and this is a major indicator when making the differential diagnosis on B-mode imaging. Furthermore, PNENs about 20 mm in size often do not have dilation of the main pancreatic duct on the caudal side of the tumor. The main pancreatic duct is displaced at the tumor portion because it does not exhibit invasion-induced stenosis or occlusion [19].

Pancreatic neuroendocrine neoplasms are often observed as hypervascular on color Doppler or power Doppler imaging without use of a contrast agent. In the case of enlarged tumors with hemorrhagic necrosis in the central portion, the said portion becomes anechoic or hyperechoic (which indicates fresh bleeding), and a blood flow signal is not observed at such areas. Contrast-enhanced harmonic imaging often shows similar findings.

Pancreatic neuroendocrine neoplasms are generally soft tumors, with EUS strain elastography often showing stiffness comparable to that of the surrounding pancreatic parenchyma.

We have described EUS diagnosis of pancreatic tumors that are often encountered as solid tumors in routine clinical practice [9,10,14,16].

Cystic Pancreatic Tumors

Detailed information on cystic pancreatic tumors has already been provided in another section. Here, we will describe the role of EUS in the diagnosis of intraductal papillary mucinous neoplasms (IPMNs), the cystic pancreatic lesion most commonly encountered in routine clinical practice.

Many IPMN-related clinical practice guidelines have been published [25–28], but here we will describe the role of EUS in the diagnosis of IPMNs based on "Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas" (2017). In short, the role of clinical practice guidelines is to ascertain as accurately as possible cases that require surgery and cases that can be referred to follow-up.

According to the 2012 International Association of Pancreatology (IAP) guidelines, although sensitivity increased, specificity remained relatively low. In the revised Fukuoka guidelines, the two-step (high-risk stigmata and worrisome features) method for predicting malignancy was revised. The size of enhancing mural nodules in high-risk stigmata was limited to ≥5 mm, while nonenhancing mural nodules were excluded from worrisome features. In addition, CA19-9 >37 ng/mL and enlargement ≥5 mm in two years were added. We will need to wait for the results of future investigations to determine whether or not the specificity of prediction of malignancy improves.

The diagnosis and treatment algorithm based on the 2017 IAP guidelines is shown in this paper. Surgery is recommended in cases with high-risk stigmata. Enhancing nodule ≥5 mm is in the high-risk stigmata category, and we assume that contrast-enhanced EUS would be necessary to actually diagnose this. In the absence of any high-risk stigmata, whether or not any worrisome features are observed is important, and EUS is recommended if even one worrisome feature is found. In terms of the role of EUS after finding a worrisome feature(s), EUS is recommended for confirming the presence or absence of any malignant cells in intracystic fluid collected using EUS-FNA, in addition to confirming the presence of an enhancing nodule ≥5 mm.

In the case of EUS-FNA(B), the frequency is unknown, but the possibility of tumor cell seeding has been pointed out even if a lesion is fundamentally a solid tumor. The possibility of tumor seeding occurring is even more likely with a cystic lesion than with a solid lesion. Therefore, careful judgment is necessary.

We described the role of EUS in the diagnosis of IPMNs, the cystic pancreatic tumor most commonly encountered in routine clinical practice.

EUS-FNA(B) and Comprehensive Genomic Profiling (CGP)

This section in the 3rd edition of this book was written based on the stance that EUS-FNA should be performed as a matter of course if its result would change or determine the treatment strategy. Seeding associated with EUS-FNA was thought to occur in only a small number of cases, if at all, and the above stance was regarded as the prevailing opinion with respect to performing EUS-FNA. Oddly enough, the essence of EUS, i.e., US diagnostic imaging, was left out of the discussion.

Later, reports that tumor seeding associated with EUS-FNA is seen at a frequency of 5–6% began to appear in the literature [29–32]. The frequency is statistically low, but if we put ourselves in the shoes of the patient and their family, we believe that we cannot ask the patient to undergo EUS-FNA based on a low frequency of tumor seeding.

There is an important point that needs to be made here. A paradigm shift is currently under way in the way cancers

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of every kind are treated, not just PDACs. A standard therapy is determined after a number of clinical studies have been conducted. However, we know that there are some PDAC patients who respond to the standard therapy and some who do not. In other words, there are cases where the standard therapy is not the best therapeutic approach for the patient. Performing oncogene panel testing in order to carry out cancer genomic medicine is on its way to becoming common practice [33–36]. There are ways to perform oncogene panel testing using a blood sample, etc., but the most common method currently is oncogene panel testing using a histologic specimen.

In many cases, PDACs are inoperable by the time they are detected. We have conventionally preferred to collect a histologic specimen using EUS-FNA rather than selecting cytology. In recent years, the terminology has changed from EUS-FNA to EUS-FNA(B), with EUS-FNA(B) being distinguished from EUS-FNA given that it is a method for collecting a histologic specimen. Submission of the tissue collected via EUS-FNA(B) for immunostaining or oncogene panel testing is now understood to be important.

When considering diagnosis of pancreatic lesions using EUS, whether or not it is possible to collect an

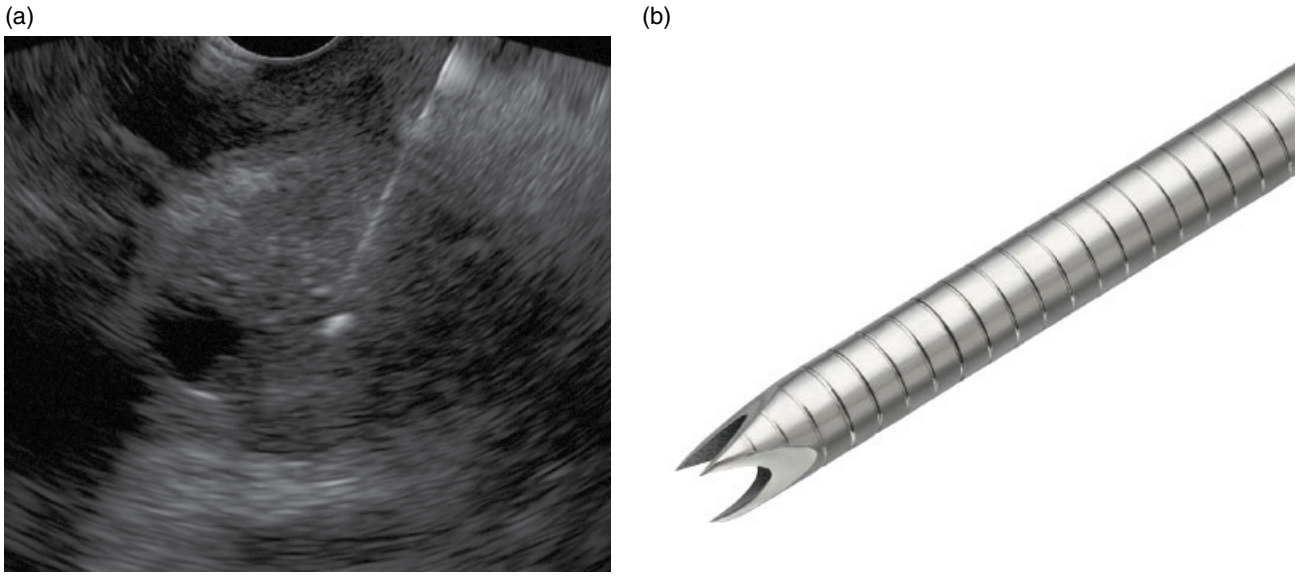


Figure 128.4 Pancreatic ductal adenocarcinoma. (a) EUS-FNA(B) was done to obtain both qualitative diagnosis and comprehensive genomic profiling. (b) The needle used was Acquire™ (22G Boston Scientific).

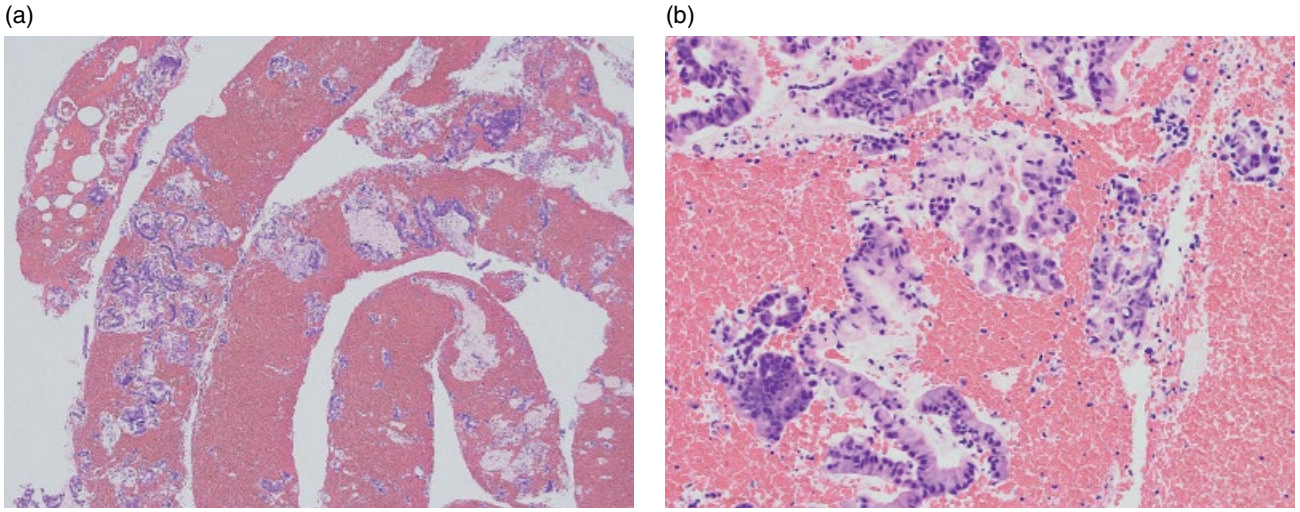


Figure 128.5 Specimens obtained by EUS-FNA(B) (the same case as Fig. 128.4). (a) Gross appearance of EUS-FNA(B) specimens. (b) More than 40% of tumor cells were found and comprehensive genomic profiling was possible.

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EUS-FNA(B) specimen suitable for CGP may become a major issue in the future. In our department, all the EUS-FNA(B) specimens collected using a 22 gauge puncture needle have been suitable for in-house oncogene panel testing to date. On the other hand, even if an abnormality is detected by oncogene panel testing, the likelihood of it actually leading to a druggable abnormality is no higher than several percent. However, performing EUS-FNA(B) to discover genetic mutations that match drugs currently in development is important. In the case of inoperable PDACs, it appears to be extremely important to perform EUS-FNA(B) to reliably obtain a specimen for CGP, in addition to actively making use of conventional diagnostic approaches (Figs 128.4 and 128.5). On the other hand, whether or not EUS-FNA(B) should be performed in the case of operable pancreatic cancers (in which case tissue is obtained during surgery) is admittedly an open question requiring further research.

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Radiologic Diagnosis of Pancreatic Cancer: CT, MRI

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Introduction

Pancreatic cancer is a relatively common malignancy, with an estimated 60 430 new cases in the United States in 2021 [1]. However, despite recent advances in the surgical and medical oncologic treatment of pancreatic cancer, it still carries an extraordinarily poor prognosis with a high mortality. It represents the fourth leading cause of cancer-related mortality in the United States, with an estimated 48 220 deaths in 2021 [1]. Fewer than 20% of patients are considered to be candidates for curative resection at the time of presentation, and unfortunately, even in patients considered to be candidates for curative resection, the overall survival rate is less than 15% [2,3].

Despite the poor prognosis, imaging plays an extraordinarily important role in the evaluation of patients with pancreatic cancer, particularly when surgical resection is still considered a potential option. Not only does modern imaging (particularly CT and MRI) play an important role in identifying these aggressive malignancies in their earliest stages (when they are still potentially resectable), it also plays a critical role in terms of properly staging these tumors. It provides the information necessary to determine whether a patient is truly capable of undergoing an R0 surgical resection (i.e., complete surgical resection with negative tumor margins) [2–4].

This chapter will describe the two most important imaging modalities in the preoperative evaluation of pancreatic cancer, namely multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI). MDCT is currently the most important as well as most commonly utilized modality for the evaluation of pancreatic cancer, playing a vital role in the initial identification of tumors, allowing optimal staging of a tumor's local extension (including vascular involvement) and identifying the presence/absence of distant metastatic disease. MRI, alternatively, may allow the identification of tumors in difficult cases where tumors may be small or isodense to the pancreatic parenchyma on CT (and thus not adequately visualized), and can also be helpful in terms of staging distant metastatic disease in equivocal cases, particularly when evaluating indeterminate liver lesions [5,6]. This chapter will discuss standard protocol options for both MDCT and MRI, the typical imaging findings of pancreatic cancer on each of these two modalities, and the strengths and weaknesses of each in terms of lesion identification and tumor staging. This chapter will also briefly discuss the novel three-dimensional visualization technique of cinematic rendering.

Multidetector Computed Tomography

Technique

Utilizing proper technique is essential to obtaining high-quality images required for the optimal evaluation of pancreatic cancer. Per National Comprehensive Cancer Network (NCCN) guidelines, the images should be obtained on a helical, multidetector row scanner, preferably 64-multidetector row scanner or more, with the thinnest possible slices, preferably submillimeter (0.5–1 mm) if available [7].

The administration of intravenous contrast is absolutely critical, as noncontrast images make adequate visualization of small tumors nearly impossible (with the vast majority of small pancreatic cancers appearing invisible

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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on noncontrast imaging). Typically, roughly 100–120 cc of intravenous contrast media are administered through a peripheral IV, and a small amount of water (neutral oral contrast), roughly 500–750 cc, is ingested by the patient immediately prior to the scan in order to distend the stomach and duodenum and allow the radiologist to distinguish duodenal or gastric pathology from a true pancreatic mass. Positive oral contrast is not recommended as it might interfere with three-dimensional and maximum intensity projection reformats [7].

Most standard pancreaticobiliary CT protocols employ a dual-phase technique, with the acquisition of both arterial and venous phase images. Per NCCN guidelines, arterial phase/pancreatic parenchymal phase images are typically acquired at roughly 40–50 seconds after contrast injection, often using bolus tracking software, while venous phase images are typically acquired at 60–70 seconds after contrast administration, typically using a fixed delay.

Noncontrast and delayed images have little utility in the evaluation of pancreatic cancer and are usually not acquired as a part of these protocols [2,3,7]. However, utilization of dual-energy CT allows for the creation of virtual noncontrast images without obtaining additional sequences, and may provide added value in difficult cases [8].

Images on the most recent generation of CT scanners can be acquired with extremely thin collimation (0.625–0.75 mm), and these thin collimation images can subsequently be reconstructed into thicker axial images (3–5 mm) for standard radiology review, and to facilitate the reconstruction of high-quality coronal and sagittal reformations directly at the CT scanner. In addition, the evaluation of pancreatic cancer is one instance where 3D reconstructions can be very helpful, particularly when evaluating vascular involvement by tumor. Thin collimation images are typically sent to an independent workstation where the radiologist can use advanced 3D visualization software to create 3D images in real time. The two most important 3D reconstruction algorithms being used widely today in clinical practice are maximum intensity projection imaging (MIP), a 3D technique that entails the acquisition of the highest attenuation voxels in a data set and their projection into a 3D image (a very important technique when seeking to evaluate a tumor's involvement of the adjacent vasculature), and volume-rendered imaging (VR), a complex computational algorithm that assigns a specific color and transparency to each voxel in a data set. Which of these two techniques is most useful will depend on the individual radiologist's preferences, the specific tumor being imaged, and the imaging feature being evaluated [2,3,9–13].

Cinematic rendering (CR) is an new 3D visualization technique which utilizes a novel global illumination model to create photorealistic images from standard volumetric CT data sets [14–16]. As a new technology, its clinical role remains under study, but it may prove valuable in the diagnosis, staging, and treatment of pancreatic cancer [17,18].

Diagnosis

Pancreatic adenocarcinoma appears as an infiltrative, hypodense, poorly marginated mass with frequent extension posteriorly into the retroperitoneum to involve critical vascular structures (Figs 129.1–129.4) [4,13,19–21]. The literature has shown that MDCT is an excellent modality for the identification of pancreatic cancer, with sensitivity rates well over 95%, and it is very likely that this underestimates the true sensitivity of CT, particularly given the rapid improvements in both temporal and spatial resolution seen with the most recent generation of CT scanners. In most cases, pancreatic cancer is most apparent in the arterial/pancreatic phase, when the pancreatic parenchyma is most enhancing, providing contrast to the hypoenhancing pancreatic tumor [4,19]. Accordingly, the acquisition of images using a dual-phase technique does improve sensitivity, particularly when seeking to identify subtle or small tumors [4,22–24]. Nevertheless, it is worth remembering that there are small subcentimeter tumors (probably representing less than 5% of all lesions) that are isodense to the pancreatic

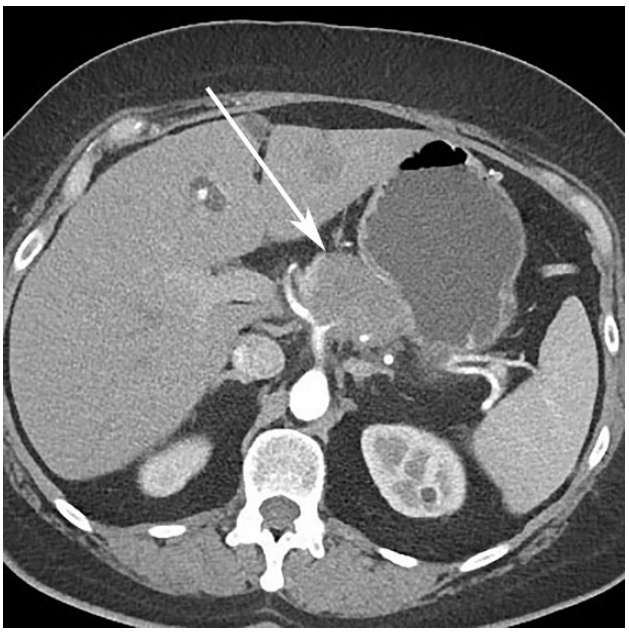


Figure 129.1 Axial contrast-enhanced CT image demonstrates a hypodense mass centered in the pancreatic body (arrow), with infiltrative, poorly defined margins, classic for pancreatic adenocarcinoma. Note that the tumor involves the celiac artery, hepatic artery, and splenic artery, and abuts the adjacent stomach.

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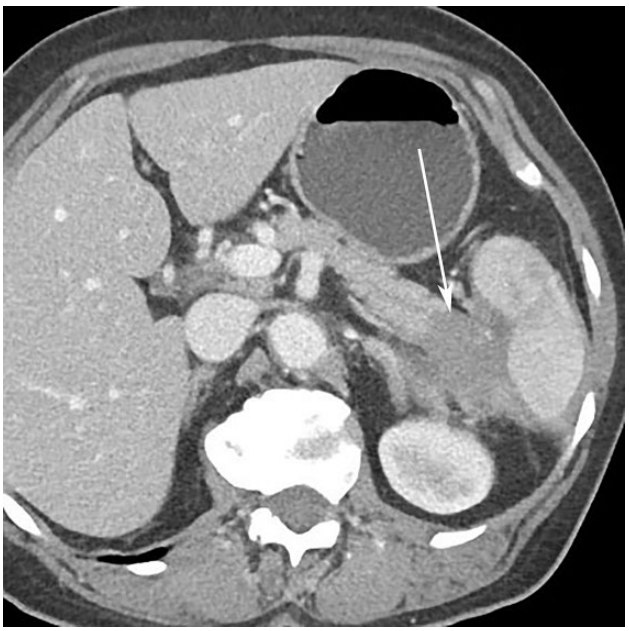


Figure 129.2 Axial contrast-enhanced CT image demonstrates a poorly defined hypodense mass (arrow) centered in the pancreatic tail, compatible with pancreatic adenocarcinoma. The tumor in this case is markedly infiltrative, not only involving the adjacent spleen but also extending to involve the adjacent left adrenal gland.

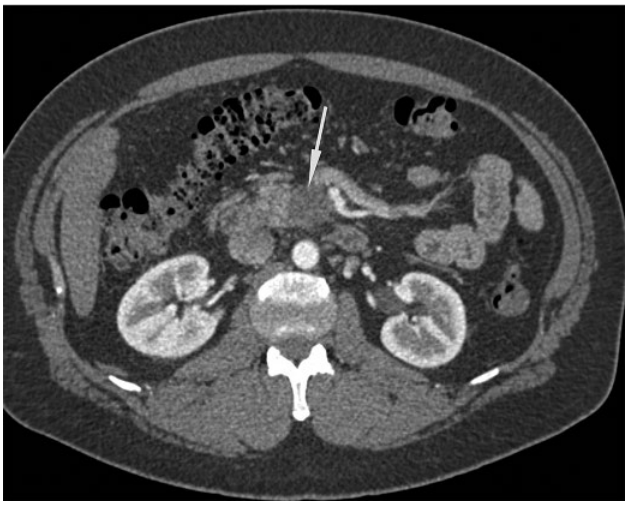


Figure 129.3 Axial contrast-enhanced CT demonstrates a subtle hypodense mass (arrow) in the uncinate process, a location in which pancreatic tumors are commonly missed on CT.

parenchyma on all phases of imaging, and can thus be very difficult to identify in the absence of secondary signs of malignancy [25].

Even if the primary tumor is not clearly visualized, secondary signs of malignancy can be extraordinarily helpful for identifying subtle or small lesions. In particular, the most important secondary signs of malignancy



Figure 129.4 Axial contrast-enhanced CT demonstrates a large hypodense infiltrative mass (arrow) involving nearly the entirety of the pancreas, found at resection to represent pancreatic adenocarcinoma.

include focal or upstream pancreatic atrophy, pancreatic ductal dilation/obstruction with abrupt cut-off of the pancreatic duct, biliary ductal obstruction (especially with pancreatic head malignancies), and an abnormal contour of the pancreas [26–28]. Of these secondary signs, by far the most important is the presence of a dilated pancreatic duct; a dilated pancreatic duct with abrupt cut-off should always be considered suspicious for an occult obstructing mass/tumor, even if the primary lesion is not clearly visible on CT, and should prompt further evaluation with another modality, usually endoscopic ultrasound (Figs 129.5 and 129.6) [28,29].

Staging

Computed tomography currently represents the best modality for the local staging of pancreatic adenocarcinoma, including a tumor's involvement of adjacent retroperitoneal vascular structures and other organs. In particular, tumor involvement of several critical retroperitoneal vascular structures plays a crucial role in determining whether a patient is capable of undergoing an R0 surgical resection. The five vessels that are most important in determining a patient's resectability are three major arteries (celiac artery, superior mesenteric artery [SMA], and hepatic artery), and two major veins (portal vein, superior mesenteric vein [SMV], and portal/SMV confluence) [7,8]. It should be noted that only these five major vessels are important in terms of dictating a

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Figure 129.5 Axial contrast-enhanced CT demonstrates a very subtle hypodense mass (arrow) in the pancreatic body segment, representing pancreatic adenocarcinoma. Noticeable is severe atrophy with a dilated pancreatic duct in the upstream pancreas, features that are highly suggestive of an underlying malignancy. The presence of a dilated pancreatic duct with pancreatic atrophy, even in the absence of a discretely visualized mass, should raise strong concern for an occult tumor.



Figure 129.6 Axial contrast-enhanced CT demonstrates a hypodense pancreatic mass in the body (arrow) resulting in severe upstream pancreatic atrophy and abrupt obstruction of a dilated pancreatic duct.

patient's resectability, while smaller vascular structures (such as the gastroduodenal artery or inferior mesenteric vein) do not have the same presurgical significance.

When evaluating the central mesenteric arterial vasculature using CT, tumoral involvement is typically stratified using a quantitative system, with tumoral involvement delineated as either involving <180° or >180° of the vessel circumference. The ability of CT to distinguish such subtle degrees of vascular involvement by tumor has become increasingly critical, as the line between "resectable" and "unresectable" tumors has increasingly become blurred. The NCCN currently describes three categories for resectability status: resectable, borderline resectable, and local advanced [7]. At one time, tumors that demonstrated *any* significant involvement of the celiac, SMA, or hepatic artery were considered "unresectable," while a tumor was considered "resectable" only if it did not involve any of these major mesenteric arteries. Increasingly, however, it is possible to have some degree of arterial involvement and be considered "borderline resectable," and still undergo surgical resection [8,30]. Placing the patient into this "borderline resectable" category requires very careful evaluation of tumoral involvement of the vessel, in order to make quite subtle distinctions between <180° and >180° involvement of the vessel, although these distinctions have become slightly easier given improvements in image quality on the latest generation of scanners (Figs 129.7–129.10).

Compared to the arterial vasculature, involvement of the central mesenteric venous vasculature has recently become less of a hindrance for complete surgical resection because of the increasing utilization of modern vascular surgical reconstruction techniques (such as interposition grafts or other vein reconstruction procedures). Accordingly, a strict numerical descriptor of tumoral involvement of the portal vein or SMV is less important than providing the surgeon with enough information to determine whether a surgical reconstruction of the vein is feasible (when involved by tumor). In other words, the radiologist's report should provide information regarding the length and degree of venous involvement and whether there is sufficient normal portal vein above or normal SMV below the tumor to allow an interposition graft to be placed (Fig. 129.11).

Metastatic Disease

The most common sites of distant metastatic disease in patients with pancreatic cancer include locoregional lymph nodes, liver, and peritoneum, with metastatic disease to the lungs and bone relatively less common. As with many other malignancies in the abdomen/pelvis, the assessment of peripancreatic and retroperitoneal

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Figure 129.7 Sagittal contrast-enhanced CT demonstrates a hypodense pancreatic mass, representing a pancreatic adenocarcinoma, resulting in 360° encasement of the superior mesenteric artery, a feature that makes this patient's tumor unresectable.



Figure 129.9 Axial contrast-enhanced CT demonstrates an infiltrative hypodense mass (arrow) arising from the pancreatic uncinate process resulting in 360° encasement of the celiac artery.

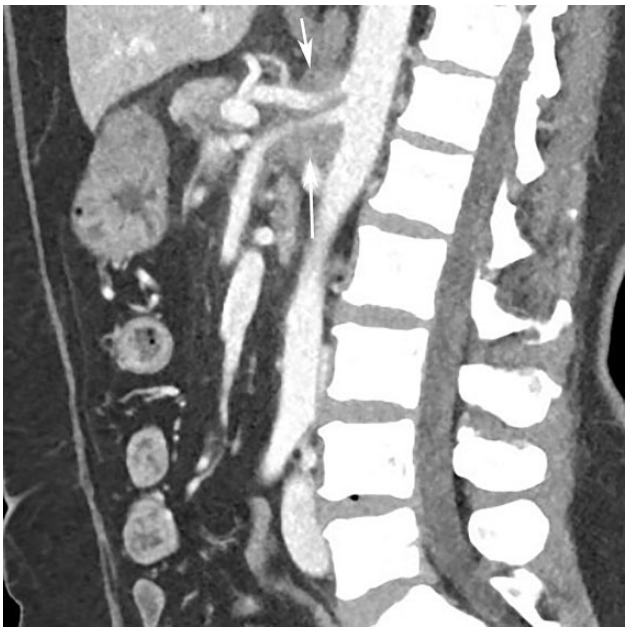


Figure 129.8 Sagittal contrast-enhanced CT demonstrates a poorly marginated hypodense pancreatic mass (arrows) resulting in 360° encasement of both the celiac artery and the superior mesenteric artery at their origins from the aorta.



Figure 129.10 Coronal contrast-enhanced CT demonstrates a hypodense infiltrative pancreatic mass (arrows) resulting in 360° encasement of the distal celiac artery and the hepatic artery.

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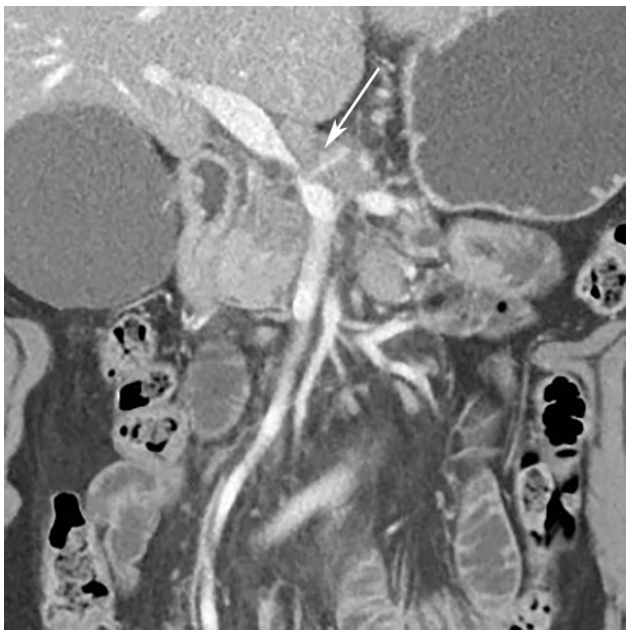


Figure 129.11 Coronal contrast-enhanced CT imaging of the venous phase demonstrates a hypodense pancreatic adenocarcinoma (arrow) resulting in narrowing of the distal main portal vein near the portal/SMV confluence.

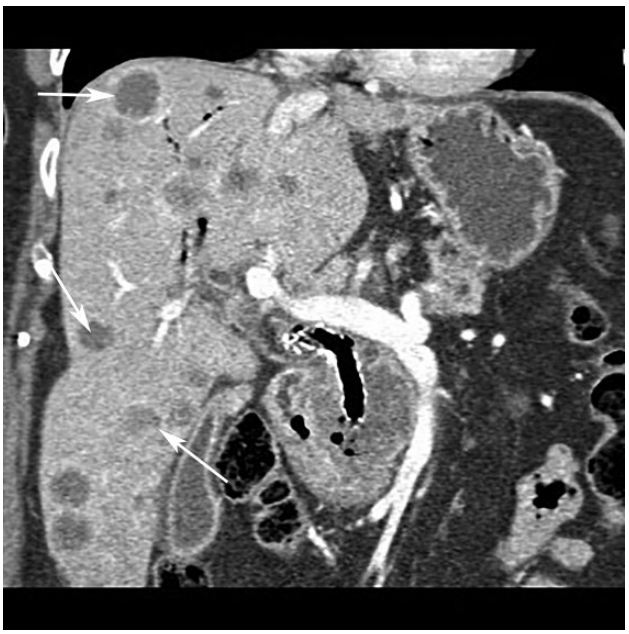


Figure 129.12 Coronal contrast-enhanced CT imaging in a patient with a pancreatic head adenocarcinoma demonstrates multiple hypodense lesions (arrows) in the liver, some of which demonstrate peripheral enhancement, compatible with extensive metastatic disease to the liver.

lymphadenopathy using CT is relatively limited, particularly given that CT relies primarily on size criteria when delineating a node as "normal" or "suspicious." However, normal-sized nodes can often harbor metastatic disease, while enlarged nodes may be reactive and be histologically normal on surgical resection [31,32]. Accordingly, several studies looking at the sensitivity and specificity of CT for metastatic lymphadenopathy have shown that CT is relatively limited, with accuracy rates under 60% [2,3,33]. Fortunately, the accuracy of MDCT for metastatic lymphadenopathy is not of significant consequence, as locoregional lymph node metastases do not typically preclude a patient from undergoing surgical resection.

However, distant metastatic disease is critical in determining the patient's resectability, as the presence of distant metastases (most often to the liver or peritoneum) precludes surgical resection, making radiation and/or chemotherapy the only palliative options. The liver is by far the most common site of distant metastatic disease in patients with pancreatic cancer, and in virtually all cases, is the first site of distant metastatic disease (prior to the development of peritoneal, lung, or osseous metastatic disease). While the arterial phase of imaging may have some utility in the identification of liver metastases (demonstrating peripheral hyperenhancement around a lesion or perfusion abnormalities near a metastasis), the venous phase images are the most critical for the identification of liver lesions (Fig. 129.12). The overall sensitivity of CT for liver metastases is relatively good for lesions that measure over 1 cm, with sensitivity rates ranging above 75%.

However, regardless of the type of primary tumor, the sensitivity of CT for smaller lesions (particularly lesions measuring under 1 cm in size) is relatively limited [34]. In particular, part of the problem when assessing small liver lesions is accurately differentiating small benign lesions (such as cysts or hemangiomas) from malignant lesions, as standard imaging criteria can be very difficult to utilize for tiny liver abnormalities which are too small to characterize. Nevertheless, the vast majority of these tiny nonspecific liver lesions (in the absence of clear morphologic features of malignancy) are benign, and MRI may be an additional helpful tool if it is necessary to further characterize these small lesions [35,36].

The second most common site of distant metastatic disease in patients with pancreatic cancer is peritoneal carcinomatosis. Regardless of the primary tumor, CT is well known to struggle in the identification of early peritoneal metastatic disease. The imaging appearance of peritoneal metastases can range from a subtle micronodular pattern (with tiny nodular foci in the omentum and adjacent stranding/induration) to the development of frank confluent omental soft tissue with an "omental caking" pattern. In most cases, peritoneal carcinomatosis is accompanied by the presence of ascites, so the presence of free fluid in a patient with pancreatic cancer

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should prompt a very careful, thorough search of the omentum and peritoneal cavity for tumor implants (Figs 129.13 and 129.14) [37]. FDG PET/CT can also prove advantageous in the detection of peritoneal carcinomatosis [38].

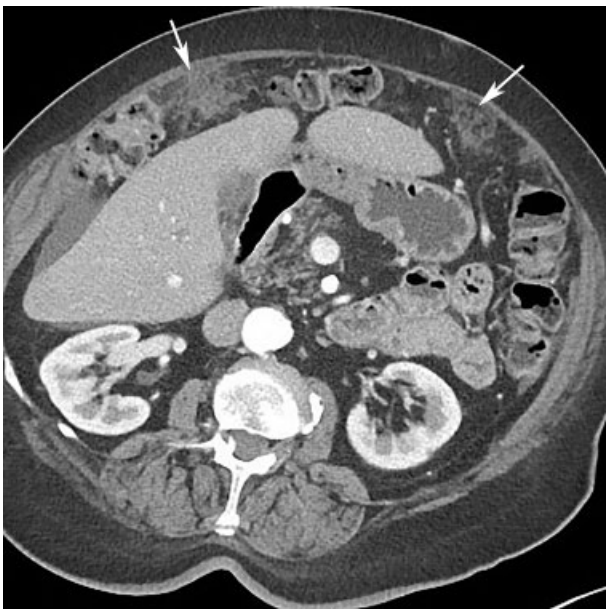


Figure 129.13 Axial contrast-enhanced CT imaging of a patient with known peritoneal carcinomatosis demonstrates a small amount of ascites, as well as ill-defined soft tissue and nodularity in the omentum (arrows), compatible with peritoneal carcinomatosis.

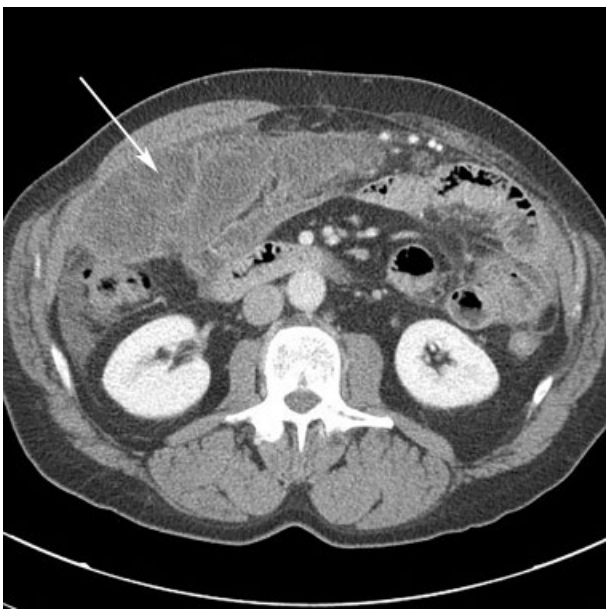


Figure 129.14 Axial contrast-enhanced CT demonstrates extensive hypodense soft tissue throughout the omentum, compatible with peritoneal carcinomatosis and "omental caking" in this patient with underlying pancreatic cancer.

Magnetic Resonance Imaging

Technique

While CT protocols for pancreatic imaging are relatively standardized across institutions, there is considerable variability in both the MRI protocols and field strengths of MRI scanners being utilized at different institutions. The NCCN recommends a protocol including coronal (with or without axial) T2-weighted single-shot fast spin-echo images, axial T2-weighted fat-suppressed spin-echo images, axial T1-weighted in-phase and opposed-phase gradient echo, coronal T2-weighted MR cholangiopancreatography (MRCP) images, axial diffusion-weighted imaging, and axial precontrast and dynamic gadolinium-enhanced 3D T1-weighted fat-suppressed gradient echo (pancreatic, portal venous, and equilibrium phases) [7,8]. One of the advantages of MR is that protocols can be tailored to the exact indication for the study with more sequences added as necessary.

Lesion Identification

In most of the organs of the abdomen, T2-weighted images are of critical importance, and often pathology will appear conspicuous as a result of its T2 hyperintensity. However, the pancreas is somewhat unique, given that its intrinsic T2 signal intensity can be quite variable depending on the age of the patient and the degree of fatty infiltration. This T2 signal variability in normal pancreatic tissue leads to pancreatic adenocarcinoma being relatively inconspicuous on standard T2-weighted images in many cases.

On T1-weighted images, the normal pancreas (in the absence of underlying chronic pancreatitis) is typically relatively T1 bright (roughly equal in signal intensity to the liver parenchyma) due to the large amount of acinar protein it contains. As a result, pancreatic cancers, which are usually relatively T1 hypointense and fibrotic, are often conspicuous when juxtaposed against the intrinsically T1 bright pancreatic parenchyma. T1-weighted images can therefore be relatively useful for lesion identification in patients who cannot receive gadolinium as a result of allergy. The pancreas upstream from the mass often appears atrophic and abnormally T1 hypointense as a result of fibrosis, and the upstream dilated/ obstructed pancreatic duct is often nicely accentuated on T2-weighted/MRCP images (Figs 129.15–129.18) [5,39–41]. The highly T2-weighted MRCP images nicely depict the ductal anatomy, which can aid in palliative techniques such as stent placement and biliary drainage [41].

Dynamic contrast-enhanced T1 imaging is also an essential component of the imaging protocol. Pancreatic adenocarcinomas are typically best seen on the arterial/

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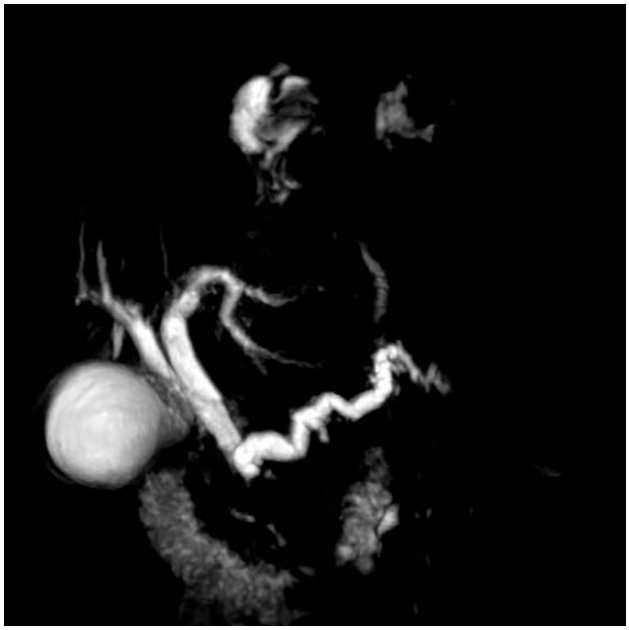


Figure 129.15 Coronal MRCP images with maximum intensity projection reconstruction demonstrates a classic double duct sign of pancreatic adenocarcinoma, with marked dilation of both the biliary tree and the pancreatic duct to the level of the pancreatic head, at the site of the patient's known pancreatic adenocarcinoma.

pancreatic parenchymal phase, when they appear hypointense to the avid pancreatic background parenchymal enhancement, as well as appearing poorly marginated and infiltrative [41,42].

While not reliably seen in all cases, many pancreatic tumors demonstrate restricted diffusion, offering another means of identifying subtle or small tumors that may be relatively inconspicuous on standard imaging sequences [5,39,43–48].

In most cases, MRI is not utilized for the initial screening or diagnosis of pancreatic tumors (although many sources suggest that it can be quite accurate when asked to do so), but rather as a troubleshooting tool to be used when a tumor is not adequately visualized on MDCT or there are indeterminate findings. In particular, MRI can be quite valuable in cases where a primary tumor is strongly suspected on the basis of secondary findings (such as a dilated duct), but where the tumor is not seen on MDCT because it is too small or isodense to the pancreatic parenchyma. MRI can also provide value in differentiating pancreatic adenocarcinoma from mimics, including focal chronic pancreatitis and autoimmune pancreatitis [41,49].

(a)



(b)

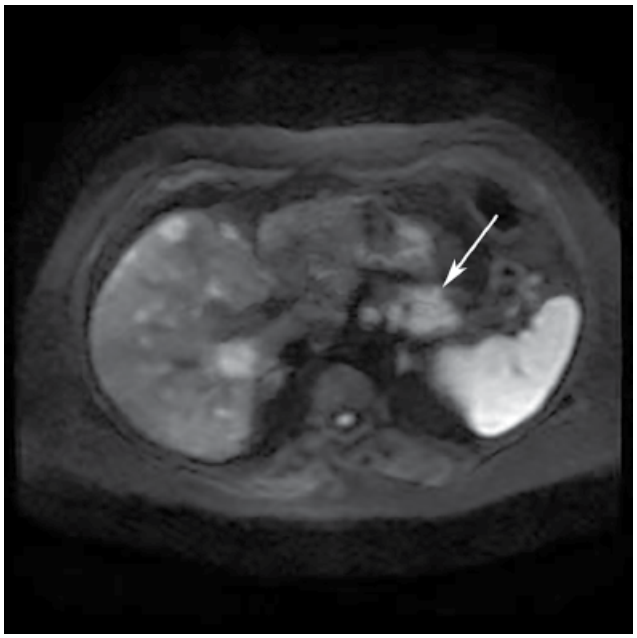


Figure 129.16 Axial postgadolinium T1-weighted image (a) and axial DWI (b) demonstrate a mass in the pancreatic tail (arrows), which demonstrates hypoenhancement on the postgadolinium image and demonstrates restricted diffusion (i.e., bright on the DWI image). Notice the multiple metastases in the liver, which also demonstrate hypoenhancement and restricted diffusion.

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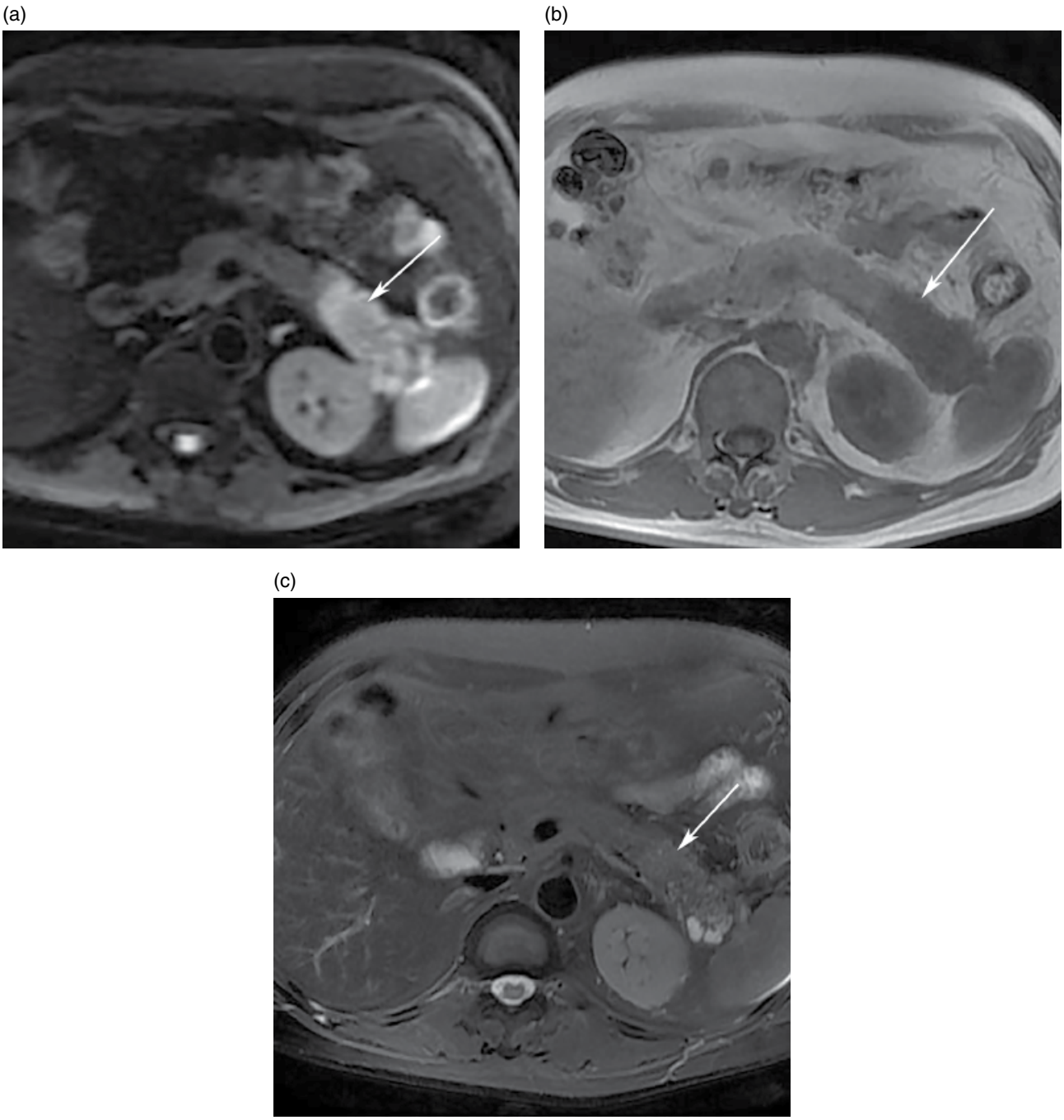


Figure 129.17 Axial DWI (a), axial T1 without gadolinium (b), and axial T2 FSE with fat saturation (c) demonstrate a pancreatic adenocarcinoma (arrow) in the tail. Notice how the mass is relatively conspicuous on the pregadolinium T1-weighted images, juxtaposed against the T1 bright pancreatic parenchyma, and is also quite conspicuous on the DWI images as a result of restricted diffusion. However, as with many pancreatic adenocarcinomas, the mass is relatively inconspicuous on the T2-weighted images.

Tumor Staging

Magnetic resonance imaging has generally been considered inferior to MDCT in the local staging of pancreatic adenocarcinoma, and in particular, in evaluating tumor involvement of the critical retroperitoneal mesenteric vasculature. In general, CT is better for evaluating involvement of the mesenteric arteries and veins because of its superior temporal resolution. CT images are much

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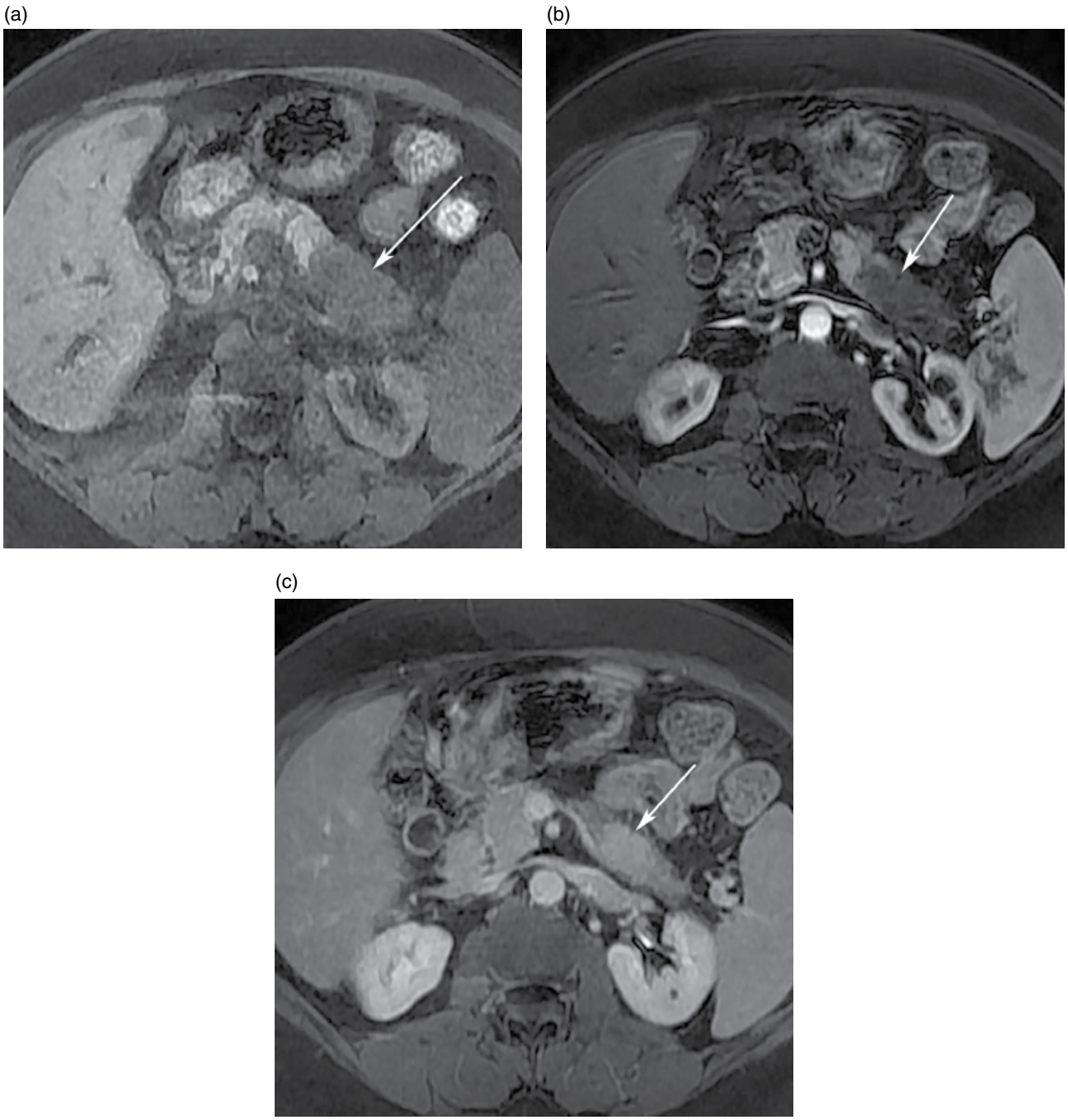


Figure 129.18 Axial T1 without gadolinium (a), axial T1 post gadolinium in the arterial phase (b), and axial T1 post gadolinium in the delayed phase (c) demonstrate a hypodense mass (arrows) in the pancreatic tail, conspicuous on both the pre- and postgadolinium images. The mass does demonstrate evidence of delayed enhancement, a relatively common feature with these tumors.

less likely than MRI to be plagued by motion artifacts or other technical artifacts that might make subtle determinations of vascular involvement difficult. Some authors have recently argued that technical advancement in MRI protocols and scanners may have made this gap less significant than was previously thought [50–53].

Magnetic resonance imaging suffers from many of the same problems as CT in terms of evaluating locoregional lymph nodes, as MRI also largely relies on size criteria for the differentiation of benign from malignant lymph nodes. In some cases, a lymph node can be delineated as abnormal based on morphologic characteristics (such as

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abnormal shape or central necrosis), but this is relatively comparable to CT. Unfortunately, while diffusion-weighted imaging was originally thought to hold promise in terms of differentiating benign from malignant lymph nodes, it is now clear that there is a significant overlap in the ADC values of benign and malignant lesions (including normal and abnormal lymph nodes), and the presence or absence of restricted diffusion within a lymph node is of little value in terms of making an absolute judgment as to whether or not a lymph node is infiltrated by tumor.

However, one area where MRI does have clear advantages over CT is in the evaluation of indeterminate liver lesions, in particular in terms of characterizing lesions under 1 cm in size [54–58]. Multiple MRI pulse sequences can be used in combination to make a more specific diagnosis such as tiny cysts (which demonstrate a fluid signal on T2-weighted images) or small hemangiomas (which also demonstrate marked T2 hyperintensity). MRI has been shown to identify liver metastases that are occult on CT, in one study altering management in 10% of patients [56,57]. MRI has also been shown to improve detection of peritoneal disease [59]. One recent study demonstrated that the addition of MRI to CT in patients with pancreatic ductal adenocarcinoma changed resectability status from resectable to unresectable in 14.4% of patients, due to the detection of liver metastases, vascular involvement, para-aortic lymph node enlargement, and peritoneal seeding [60]. While not every patient with pancreatic adenocarcinoma requires evaluation with MRI, MRI may be a helpful tool to determine surgical resectability.

Emerging Techniques: Cinematic Rendering

Cinematic rendering is a novel technique that creates photorealistic three-dimensional images from isotropic volumetric data, which is readily generated from modern CT scanners. While 3D imaging has often been used for pancreatic cancer staging, cinematic rendering takes three-dimensional visualization to another level. The improved anatomic detail and realism created by cinematic rendering may aid in detection of subtle pancreatic lesions (Figs 129.19–129.21) [17]. Cinematic rendering may also help delineate the relationship of the tumor to adjacent structures given its improved 3D visualization, and may also aid in surgical planning when vascular reconstruction and grafting may be required [18].

Conclusion

There is little doubt that MDCT is currently the most important imaging modality for the identification of pancreatic tumors, local tumor staging (including

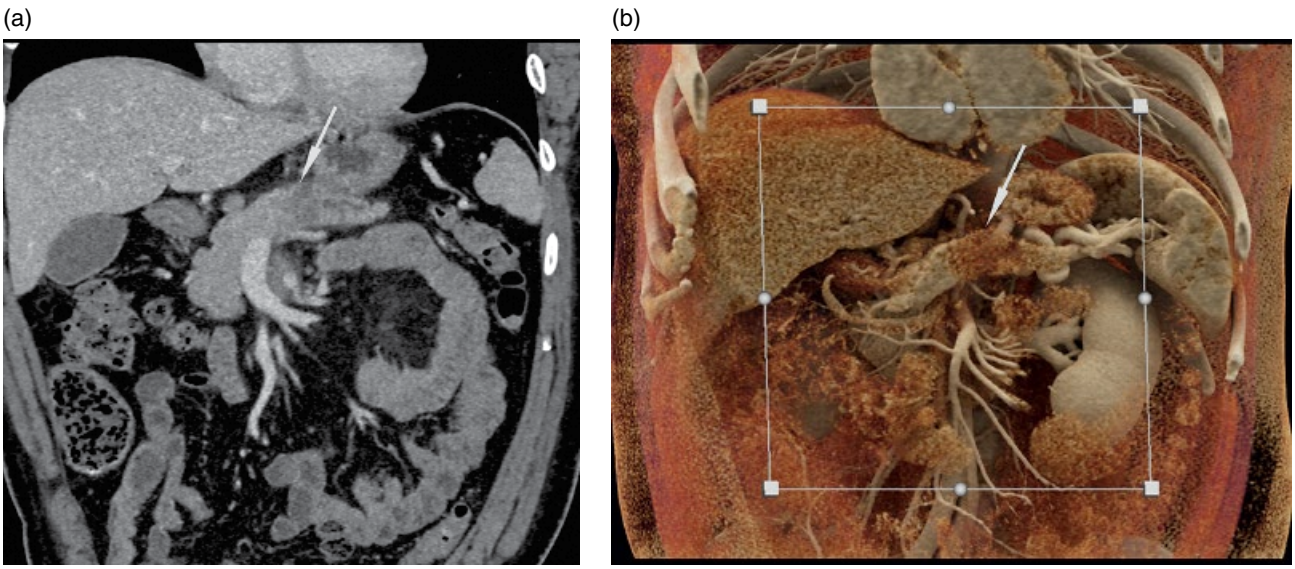


Figure 129.19 Coronal contrast-enhanced CT (a) and coronal cinematic rendered image (b) demonstrate an ill-defined pancreatic adenocarcinoma in the body of the pancreas (arrows) with upstream dilation of the main pancreatic duct. The lesion is better demonstrated on the cinematic rendered image, which highlights the textural changes associated with the tumor.

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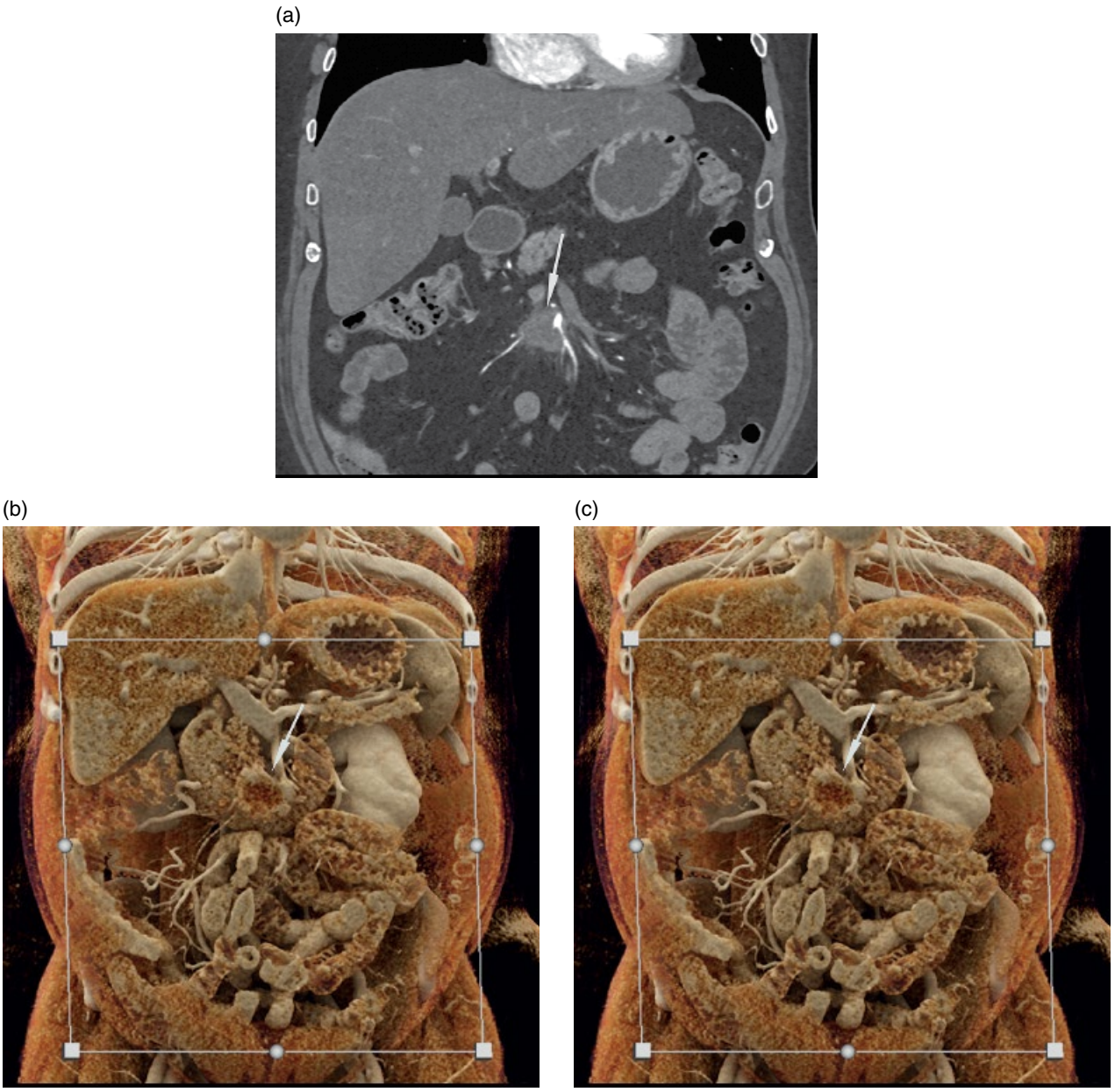


Figure 129.20 Coronal contrast-enhanced CT (a), coronal cinematic rendered image (b), and axial cinematic rendered image (c) demonstrate a mass in the head of the pancreas consistent with adenocarcinoma of the pancreas (arrows). The cinematic rendered image shows the three-dimensional relationship of the mass with the adjacent mesenteric vasculature.

a tumor's involvement of adjacent retroperitoneal vasculature and other organs), and the identification of distant metastatic (most commonly the liver and peritoneum) disease. While MRI is not currently a first-line modality in the identification and staging of pancreatic cancer, it does have a great deal of utility in terms of identifying lesions that may be occult or subtle on CT, and serving as a troubleshooting tool that might help provide more definitive answers when confronted with an indeterminate or occult liver lesion on CT. Emerging three-dimensional visual techniques such as cinematic rendering can provide improved anatomic detail and visualization of complex anatomy, which may aid in pre-surgical and treatment planning.

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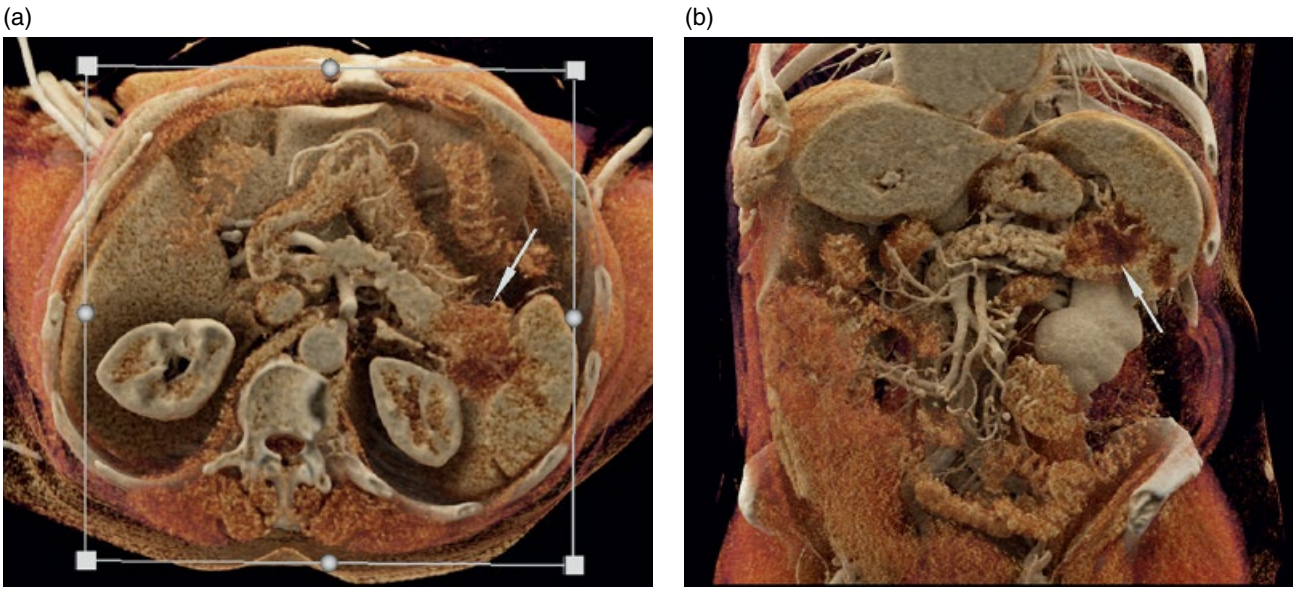


Figure 129.21 Axial cinematic rendered image (a) and coronal cinematic rendered image (b) demonstrate an infiltrative pancreatic adenocarcinoma of the tail of the pancreas (arrows). The cinematic rendered images highlight the textural differences of the tumor compared to the background pancreatic parenchyma, as well as the infiltrative nature of the lesion and its extension to involve the spleen.

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Screening of Hereditary Pancreatic Cancer

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Pancreatic Cancer Risk

Pancreatic cancer is expected to be the second leading cause of cancer-related deaths in the USA in the next decade [1]. In the USA, the average lifetime risk of developing pancreatic cancer is ~1.4%. Until recently, the long-term benefits of pancreatic screening were not well known, and for this reason screening is only offered to those individuals whose risk of pancreatic cancer is sufficiently high that the potential benefits are estimated to be greater than the potential risks of screening. Experts such as those from the Cancer of the Pancreas Screening consortium consider that pancreatic screening may be justified if the lifetime risk of developing pancreatic cancer is at least 5% which is equivalent to a ~4-fold increased relative risk) [2]. Estimating an individual's future cancer risk is an important step in deciding whether an individual should be considered for pancreatic screening.

The main tool used to quantify pancreatic cancer risk is the family history. A detailed cancer family history will determine whether or not an individual is a first-degree relative of one or more subjects with pancreatic cancer and at what age pancreatic cancer developed in the family [3]. The estimates of pancreatic cancer risk in families have been achieved by following families long term in pancreatic cancer family registries [4]. Familial pancreatic cancer has been defined as kindred having two first-degree relatives with pancreatic cancer, although pancreatic cancer often runs in families who do not meet this definition. The risk of developing pancreatic cancer in first-degree relatives increases with the number of affected relatives [5]. This risk has been estimated to be sufficiently high in individuals with at least two affected first-degree relatives on the same side of the family (lifetime risk ~8–10%), and in those with a first- and second-degree relative with pancreatic cancer on the side of the family (lifetime risk ~5%) [5]. The relative risk among those with only a first-degree relative with pancreatic cancer is not considered sufficiently high (2–3-fold elevated) to warrant long-term surveillance, unless the relative carries a susceptibility gene mutation (discussed below). The risk of pancreatic cancer is also higher in familial kindred with a young-onset pancreatic cancer (age <50 years, relative risk [RR] 9.3) in their family, compared to those without a young-onset case [3]. Individuals who have one first-degree relative with pancreatic cancer on each side of the family (bilineal risk) are not thought to have a sufficiently high risk to warrant surveillance. Other patterns of inheritance are more challenging to estimate (such as having multiple affected second-degree relatives). The increased risk of developing pancreatic cancer in pancreatic cancer families identified through prospective studies points to inherited factors, although it is suspected that in some families shared environmental factors play a role in pancreatic cancer susceptibility.

Since the risk of developing hereditary pancreatic cancer is likely to be influenced by the same factors that influence the development of sporadic forms of the disease, in principle, pancreatic cancer risk factors such as smoking, obesity, diabetes and pancreatitis history could be used to refine estimates of cancer risk. However, to date these risk factors do not confer sufficient risk on their own to be useful in clinical practice [6].

The increasing use of hereditary gene testing of patients with pancreatic and other cancers has led to more relatives being identified with susceptibility gene mutations. Indeed, in the US multiple guidelines recommend offering susceptibility gene testing not only for patients with pancreatic cancer, but also for their first-degree relatives [7,8]. This guideline recommendation is

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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based on studies that find the prevalence of deleterious mutations is about 5–10% among unselected cases with pancreatic cancer [9–11]. Indeed, most patients with pancreatic cancer who have a susceptibility gene mutation do not have a family history of the disease, and often do not have personal or family histories that point to an inherited cancer syndrome [12]. The identification of such a mutation in a pancreatic cancer family provides an opportunity for cascade testing and cancer surveillance. Gene testing to look for pancreatic cancer susceptibility genes is best performed on an affected individual with pancreatic cancer from a familial pancreatic cancer kindred, but the rapid mortality of the disease in patients often precludes such testing being done. Among patients enrolled in the CAPS program because of their familial risk, those with a germline mutation had a significantly higher risk of progression than those with a familial risk alone (and gene tested to identify known susceptibility gene mutations) [13]. Similar results were found in a Dutch cohort [14]; in this study all the pancreatic cancers were diagnosed in those with germline mutations.

The genes known to cause hereditary forms of pancreatic cancer when mutated in the germline that have implications for pancreatic surveillance include *BRCA2*, *ATM*, *PALB2*, *CDKN2A (p16)*, *BRCA1*, *STK11*, *PRSS1* genes [15–18], and the hereditary nonpolyposis colon cancer (Lynch) syndrome [19,20]. Among kindred with a significant family history of pancreatic cancer, germline mutation pancreatic cancer susceptibility genes are only identified in ~10% of individuals, indicating that much of the familial clustering of pancreatic cancer remains unexplained.

In the early years of pancreas surveillance in the CAPS program, priority was placed on enrolling subjects with the highest risk at least until the benefits of surveillance were known, and that meant limiting enrollment of germline mutation carriers in genes such as *BRCA2*, *BRCA1*, and later *ATM* to those with a family history of the disease. As the benefits of surveillance have become clearer, along with the limitations of family history in predicting an individual mutation carrier's risk, there is more interest in opening up surveillance to all *BRCA2* mutation carriers.

The average lifetime risk of developing pancreatic cancer among all *BRCA2* gene mutation carriers is thought to be >5%, likely higher in those with a family history of the disease [21,22]. Those with germline *BRCA1* mutations are estimated to have a ~2–2.5-fold elevated pancreatic cancer risk [21,22]. For this reason, the CAPS guidelines did not reach consensus on the question of whether carriers of *BRCA1* mutations should undergo pancreas surveillance, particularly in the absence of a family history of pancreatic cancer. Recent guidelines from the ASGE address the question of surveillance of *BRCA1* and *BRCA2* mutation carriers, pointing out the limitations of restricting surveillance to those with a family history of the disease [20].

One other notable difference between *BRCA1* and *BRCA2* mutation carriers is their risk of developing biliary cancer, which is higher for *BRCA1* carriers [21,22]. To date, pancreas surveillance guidelines have not addressed the potential role of early detection of biliary cancer, in large part because biliary cancer is much rarer than pancreatic cancer, but in one Japanese study the lifetime risk of biliary cancer in *BRCA1* carriers approached 10% [21]. More data are needed, but the biliary cancer risk in *BRCA1* mutation carriers may justify their inclusion in pancreatic-biliary cancer surveillance.

Germline *ATM* mutations are the second most common known cause of hereditary pancreatic cancer [15,23]. Individuals with germline *ATM* mutations are at increased risk of developing multiple types of cancer. The protein product of *ATM* functions in DNA repair pathways and undergoes somatic mutation in a variety of cancers. In one study from the National Familial Pancreas Tumor Registry, the lifetime risk of pancreatic cancer among *ATM* mutation carriers was estimated to be approximately 10% [24]. Germline *CDKN2A (p16)* gene mutations cause familial atypical melanoma mole syndrome (FAMMM syndrome). The lifetime risk of developing pancreatic cancer among *CDKN2A* mutation carriers is estimated to be ~20% [25–27] and for this reason, patients are recommended to start surveillance at age 40. It may be appropriate to reduce the surveillance interval such as to every six months in these patients though more data are needed.

Germline *PALB2* (Partner and Localizer of Brca2) mutations are found in <1% of patients with familial forms of pancreatic cancer [28]. The risk of developing pancreatic cancer among *PALB2* gene mutation carriers is thought to be similar or somewhat lower than that of *BRCA2* [29,30]. Hereditary nonpolyposis colorectal cancer (Lynch syndrome) kindred which arises from germline mutations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) gene mutations have an estimated lifetime risk of pancreatic cancer of 3.7% [19,31].

The pathologic features of pancreatic cancers with mismatch repair defects can be characteristic [32], and should be suspected when tumor sequencing shows high somatic mutation burdens, although most of these cases arise somatically, not via germline mutation. Less than 1% of pancreatic cancers have mismatch repair defects but are important to identify as these patients are more likely to respond to immunotherapy with checkpoint inhibitors [33]. Patients with Peutz–Jeghers syndrome (PJS) (who generally carry germline *STK11* gene mutations) have a very high risk of developing pancreatic

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cancer (cumulative lifetime risk 11–36%) (reviewed in [34]) and are also recommended to start pancreas surveillance at age 40.

It is known that long-standing chronic pancreatitis predisposes to the development of pancreatic cancer. Hereditary pancreatitis is a rare condition, and few such patients are enrolled into pancreas surveillance programs. The gene most commonly implicated in hereditary chronic pancreatitis is *PRSS1* [35], and affected individuals typically develop pancreatitis in their teens and have many decades of pancreatitis that often results in pancreatic insufficiency [36]. Pathologically, the pancreas of *PRSS1* mutation carriers undergoes progressive lipomatous atrophy with increasing age [37].

The pancreatic cancer risk associated with hereditary recurrent acute pancreatitis was initially estimated to be very high (40% lifetime [38] and even higher for smokers), but more recent estimates find the risk to be <10% [39]. While other genes such as *CPA1* that have been identified as pancreatitis susceptibility genes and are now suspected to be causes of hereditary pancreatic cancer [40,41], this has not been shown to be true for carriers of the pancreatitis modifier genes, *SPINK1* and *CFTR* [42] that increase the likelihood of developing pancreatitis [43]. Patients with long-standing chronic pancreatitis from hereditary causes would likely benefit from pancreatic surveillance, though imaging the pancreas in these cases is more challenging, and the best modality for imaging is not certain. Rare variants in the pancreatic secretory enzymes *CPA1* and *CPB1* that induce endoplasmic reticulum stress are enriched in patients with pancreatic cancer compared to controls [40,41]. Many of these patients do not have a history of pancreatitis. The relative risk of pancreatic cancer in such patients is not well defined and such patients are not currently enrolled in pancreatic surveillance.

Other low-penetrance genetic variants associated with pancreatic cancer susceptibility have been identified through genome-wide association studies (GWAS). Thus, carriers of non-O blood groups have an approximately 1.4-fold elevated risk of developing pancreatic cancer relative to O-blood group carriers. GWAS has also identified variants *CTRB2*, *PDX1*, *Tert* and at other loci as being associated with pancreatic cancer risk [44–46]. There is considerable interest in trying to utilize such low-risk variants clinically. Polygenic risk scores can refine risk estimates, but show promise in more common cancers [46]. Their value in refining the risk of less common diseases like pancreatic cancer remains to be determined. Combining polygenic risk scores with other risk factors (family history, smoking, obesity, etc.) is another approach, but it has yet to generate high enough risk scores to identify those at high risk [6]. Polygenic risk scores have been used to estimate PDAC risk in patients with new-onset diabetes [47]. The potential value of using polygenic risk scores with other clinical risk data to identify candidates for surveillance needs further investigation.

At What Age Should Pancreatic Screening Begin and End?

Pancreatic surveillance protocols are designed to screen individuals starting a few years earlier than their peak incidence of pancreatic cancer. The average age at diagnosis for those with familial/inherited forms of pancreatic cancer is 68 [3], similar to sporadic pancreatic cancer, although pancreatic cancer diagnosis averages a few years younger in those with germline mutations. For this reason, the CAPS screening program (clinicaltrials.gov NCT02000089) has recommended pancreatic screening to begin at age 55 for those with familial risk, or 10 years less than the youngest pancreatic cancer in the family, and age 50 for those with germline mutations in *BRCA2/ATM/PALB2/*mismatch repair genes and age 40 for those with *CDKN2A* and *STK11* mutations. Many screening programs use age 50 for familial risk and age 45 for mutation carriers. One reason for beginning pancreatic cancer screening a decade or more before the average age of pancreatic cancer diagnosis was to provide an opportunity to identify and manage the precancerous lesions in affected individuals [48].

Not all pancreatic screening guidelines have the same recommendations regarding the age at which to commence surveillance [49]. Consensus guidelines do not agree on when pancreatic screening should be discontinued in pancreatic cancer families [50]. Pancreatic screening often continues beyond age 75 in subjects who have pancreatic cysts but it is probably appropriate to discontinue pancreatic screening by age 75 or 80 in high-risk individuals without any evidence of pancreatic precancerous lesions on prior screening.

Pancreatic Screening Tests

Currently, pancreatic screening utilizes pancreatic imaging tests. In a head-to-head blinded comparison of pancreatic endoscopic ultrasound (EUS), MRI/MRCP and pancreatic protocol CT performed as part of the CAPS3 study of high-risk individuals, EUS had the highest rate of detection of pancreatic cysts, followed closely by MRI/MRCP [48]. MRCP provides the best visualization of cyst communication with the main pancreatic duct to determine the nature of the pancreatic cyst [51]. EUS has the advantage that it can probably identify subcentimeter solid lesions better than MRI, but it is more operator

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dependent [52]. One Dutch study that performed a blinded analysis of diagnostic yield of MRI and EUS in patients undergoing pancreatic surveillance found two solid lesions identified by EUS, but not by MRI, one of which was a small PDAC [53]. Such studies are valuable, though more evidence is needed, as diagnostic yield depends on operator performance and changes with evolving technology such as MRI magnet strength.

Pancreatic-protocol CT is currently less sensitive at detecting subcentimeter cysts [48] and also had the disadvantage of giving a low dose of radiation, although the technology continues to improve. Pancreatic-protocol CT is also an excellent test to evaluate selected patients undergoing screening and surveillance when lesions of uncertain significance are identified. The diagnostic potential of pancreatic imaging may improve as artificial intelligence-based methods are applied to detect subtle changes in the gland, such as changes in volume or shape or texture [54].

Lesions Identified by Pancreatic Imaging

Pancreatic cysts are commonly identified in pancreatic screening cohorts. In the CAPS3 study, the average age of the study population was 56 and over one-third of the study population had at least one pancreatic cyst, with the prevalence increasing with increasing patient age [48]. Multiple other pancreatic screening studies of high-risk groups have reported a high prevalence of pancreatic cysts [48]. With improved pancreatic imaging in recent years, it is clear that pancreatic cysts are very prevalent in the general population, particularly among subjects in their 70s and older [55]. The high prevalence of pancreatic cysts in the general population and the recognition that most of these individuals are not going to develop pancreatic cancer has also raised questions as to the significance of pancreatic cysts in high-risk individuals. Although most pancreatic cysts identified in the screening population are branch-duct intraductal papillary mucinous neoplasms (IPMNs), the vast majority are subcentimeter in diameter and will not progress to invasive cancer [56]. To date, the number of pancreatic cancers detected by pancreatic screening in the literature is quite low (~1–5% of subjects under surveillance) [57] which is consistent with the expected age-specific incidence of pancreatic cancer of those undergoing screening.

Some patients who undergo pancreatic screening will have suspicious pancreatic cysts or solid lesions detected that are found at pancreatic resection to be nonneoplastic or of minimal malignant potential (such as serous cystadenomas, pancreatic neuroendocrine tumor or lobulocentric parenchymal atrophy associated with PanIN) [58,59].

Pancreatic Pathology Not Detected by Current Screening Tests

Pancreatic cysts can be detected by pancreatic imaging even when they are quite small (~2 mm). But in the resected pancreata of patients who undergo resection for pancreatic cysts, the most common neoplasm detected is pancreatic intraepithelial neoplasia (PanIN) [58]. These lesions are generally too small (<5mm diameter by definition) to be identified by current imaging modalities [60]. Although EUS can detect subtle changes like microcysts and hyperechoic foci that are often associated with the presence of PanIN, these EUS changes are not specific for PanIN [58].

Low-grade PanINs are common in the population and have very low malignant potential, whereas high-grade PanINs are thought to have a significant risk of progressing to invasive cancer. Most pancreatic cancers are thought to arise from PanINs, and although pancreatic cysts (IPMNs) are common in patients with hereditary forms of the disease, it is thought that most cancers that arise in these patients arise from PanINs. Evidence for this comes from multiple sources. A blinded histologic review of hundreds of familial and sporadic pancreatic cancers found no significant differences in the histologic features of familial and sporadic cases, including no difference in the number of IPMN-associated cancers [61]. Second, the genetic profiles of pancreatic ductal adenocarcinomas are similar to PanINs [62,63]. Finally, although ~66% of IPMNs harbor *GNAS* mutations, *GNAS* mutations are not typically found in the pancreatic ductal adenocarcinomas from patients with a family history of pancreatic cancer [64].

Surveillance Intervals

Surveillance recommendations for high-risk individuals have developed initially from clinical judgment, and then initial experience with surveillance, and the experience of surveillance of subjects with sporadic pancreatic cysts [65], to evidence of outcomes of surveillance. Most patients are recommended to undergo annual surveillance. This recommendation reflects what is known about the underlying biology of pancreatic cancer as well as the limitations of current pancreatic imaging tests. One study that estimated the time to progression of pancreatic cancer through its clinical stages determined that it takes approximately one year on average to progress from stage I disease to stage IV disease [66]. It may be appropriate to have longer surveillance intervals (several years apart) when the risk of pancreatic cancer is lower (such as for subjects in their 50s), increasing it to annually

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for older subjects, but more evidence is needed. The presence of pancreatic cysts generally does not affect that recommendation as most pancreatic cysts (including those identified as IPMNs) have low malignant potential.

Early studies of pancreatic cancer diagnosis in the high-risk setting found many subjects with screen-detected pancreatic cancers had stage II disease [67]. Although this represented significant downstaging, many such patients are not cured despite earlier detection. However, more recent studies from the CAPS program found that the majority of patients diagnosed at stage I disease had maintained their recommended surveillance interval. Surveillance intervals can be shortened in those with concerning, "worrisome" lesions, though notably most of the pancreatic cancers diagnosed in the CAPS program do not arise from an IPMN, despite having pancreatic cystic IPMNs in their gland [57]. Similarly, a multicenter study examining the pancreatic abnormalities prior to a pancreatic cancer diagnosis found evidence that pancreatic cancers often do not arise from a clear precursor lesion detectable by imaging [68].

The choice of surveillance test is often influenced by practical considerations such as patient preference and insurance. Surveillance protocols often alternate EUS and MRI to provide complementary imaging and limit the burden of annual EUS [69]. Subjects who have large pancreatic cysts, pancreatic duct abnormalities or solid lesions undergo fine needle aspiration of any focal concerning lesion(s) and close surveillance.

Surgery for Lesions Identified by Pancreatic Screening

As clinicians have gained experience with pancreatic screening, the indications for pancreatic resection in the screening setting have become more selective. Pancreatic resections are usually undertaken once there is evidence that a pancreatic cyst has features concerning for invasive cancer or for a cancerous solid mass or suspicious mass. Most patients are likely to develop their cancer from PanIN that will grow into a solid mass and not a cystic lesion. The strategy of waiting for the emergence of a cancer risks missing opportunities for cure as most patients who present with resectable cancers will not be cured, but operating on subjects with IPMN without a cancer or strong suspicion of cancer often results in overtreatment (the detection of low-grade dysplasia in PanIN and IPMN). The rationale for performing pancreatic resection for high-risk patients with multiple medium-sized pancreatic cysts that do not individually meet criteria for resection is that some of these patients have high-grade PanIN in their resected pancreata [58,59].

The choice of operation for high-risk patients with lesions identified by pancreatic screening can be challenging since some patients will have concerning cysts or other lesions in both the head and tail of the pancreas. However, total pancreatectomy is only occasionally undertaken in this setting because of the potential morbidity associated with diabetes after total pancreatectomy. Instead, patients usually undergo partial pancreatectomy for screen-detected lesions and are then recommended to continue surveillance postoperatively. These cases are evaluated on a case-by-case basis preferably by an experienced multicenter team and at a high-volume center [70,71]. Surgical outcomes in the CAPS program have been excellent [72].

Evaluating Long-term Outcomes of Patients Who Undergo Pancreatic Screening

Proving the benefits of pancreatic surveillance requires large multicenter studies involving many patients followed for many years. Recently, the CAPS program updated its experience with pancreas surveillance, combining the results of the multicenter CAPS5 study with the overall Hopkins experience that extends over 20 years [57]. We find that the median survival of patients who maintained annual surveillance and were diagnosed with pancreatic cancer was 9.8 years, suggesting that most such patients are cured of their disease [57]. This survival benefit is likely to be largely driven by the detection of pancreatic cancer at stage I when cure is most likely. Indeed, a recent analysis of sporadic pancreatic cancer outcomes in patients in the NCI SEER registry found that five-year survival among cases with pancreatic ductal adenocarcinoma who underwent surgical resection and had stage I disease was 80%, decreasing to 60% at 10 years [73]. And the survival trends have been improving. This study builds upon our prior CAPS experience (74). Although the majority of patients diagnosed in the CAPS program have had stage I disease, some patients present with higher stage disease, pointing to the need for better risk assessment and diagnostic tests. The detection of high-grade dysplasia in PanIN or IPMN is also an important goal of pancreatic screening, as such patients have excellent long-term outcome and it is likely that removing high-grade dysplasia can reduce pancreatic cancer death.

In addition to the CAPS experience, long-term outcomes of patients enrolled in European centers have been published that include a large number of

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CKDN2A/p16 Leiden mutation carriers [75]. They reported downstaging from surveillance compared to historical controls with a five-year survival of 24%.

Developing Better Pancreatic Screening Tests

The recent outcomes of pancreatic surveillance of high-risk individuals highlight the benefits of pancreatic imaging tests, but there are also limitations. Some patients do not maintain surveillance, and some patients are diagnosed late despite surveillance. There has been considerable research into developing better diagnostic tests. Based on the experience using pancreatic imaging, diagnostic tests need to be able to perform well at diagnosing stage I pancreatic cancer. One strategy would be to combine pancreatic imaging with a blood test. A screening test that performs well at detecting stage II cancers would not have a major impact on survival since the median survival of patients with stage II pancreatic cancer is less than two years [73]. Serum CA19-9 is still the best available test but has not had the performance characteristics needed for early diagnosis. Among patients with resectable pancreatic cancers, it has a diagnostic sensitivity of only ~60%, lower still in patients with stage I disease, and false-positive elevations of CA19-9 that have limited its potential as a screening test [76]. One strategy to improve the diagnostic performance of CA19-9 is to combine it with a gene test that personalizes an individual's CA19-9 reference range, by determining variants in the genes responsible for CA19-9 synthesis (*FUT2* and *FUT3*) [77].

Another diagnostic testing approach is to test for ctDNA, but less than half of patients with resectable pancreatic ductal adenocarcinoma have detectable circulating tumor DNA mutations [78]. Other recent studies have utilized ctDNA in the form of changes in DNA fragmentation [79], methylated DNA [80] or hydroxymethylated DNA [81]. Other studies have evaluated protein markers in combination with CA19-9 [82]. Although these studies show promise, more evidence is needed. Most other circulating markers that have been reported as potential pancreatic cancer markers do not have the diagnostic characteristics that would make them suitable for pancreatic screening. Most of these circulating biomarkers have yet to be evaluated as clinical tests in the pancreas surveillance setting.

The inability of current pancreatic screening tests to detect high-grade dysplasia in PanIN lesions limits our ability to identify patients most likely to progress to cancer. Approaches that have been used to identify PanINs by pancreatic screening include pancreatic juice analysis and molecular imaging. Analysis of secretin-stimulated pancreatic juice collected endoscopically from the duodenum of patients enrolled in the Cancer of the Pancreas Screening trials (CAPS) revealed that these patients are more likely to have mutations in their pancreatic juice, especially *KRAS* mutations that are thought to arise from small PanIN lesions, and *KRAS* and *GNAS* mutations that arise from IPMN (close to what would be expected if one directly analyzed their IPMNs) [56,83,84]. Next-generation sequencing applied to pancreatic juice can identify other mutations, including those enriched in patients with pancreatic cancer and high-grade dysplasia *TP53* and *SMAD4* [85,86]. Collecting secretin-stimulated pancreatic juice from the duodenum is safe, but the low concentration of mutations in pancreatic juice in these patients is an obstacle to early detection [83].

Molecular imaging offers the possibility to detect small pancreatic cancers and precursor lesions. One molecular target is the integrin α(v)β(6) which has been shown to detect micrometastatic pancreatic cancer [87].

Conclusion

Long-term outcomes of pancreatic surveillance in high-risk individuals find that patients diagnosed with pancreatic cancer, especially those diagnosed with stage I disease, can achieve long-term survival. This downstaging and survival benefit is only evident for those who maintain annual surveillance. Similarly, resecting precancerous neoplasms with high-grade dysplasia (in PanIN or IPMN) is likely to be beneficial in preventing cancer in many cases. Managing concerning but indefinite pancreatic lesions identified by screening is best done by experienced multidisciplinary teams.

There are major unanswered questions about pancreatic screening. There is a need to better define pancreatic cancer risk so as to improve the targeting of individuals who most need pancreatic screening. There is also a need to develop better screening tests. Current pancreatic imaging tests do not reliably detect PanIN which are the most common precursor lesion. With the development of more accurate blood tests, it may ultimately be possible to improve the detection of small, potentially curable stage I pancreatic cancers.

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The Role of PET in Diagnosis of Pancreatic Cancer and Cancer Recurrence

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Introduction

Positron emission tomography (PET) is a noninvasive functional imaging technique that is used to observe metabolic processes in the body. The patient is given a radioactive glucose analogue carrying a positron emitter. During the radioactive decay of the so-called radiotracer, positrons are emitted. The positrons next collide with electrons, which cause the release of photon pairs. Detectors arranged in a circle around the patient can then record the latter. Thereby, PET can analyze both the localization and the intensity of the radioactive tracer in the patient's body. Compared with morphologic imaging, PET provides functional data of the investigated tissue, which can also be measured quantitatively.

Different radiotracers can be applied depending on the clinical problem. Currently, the radiotracer 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) is most commonly used. Its uptake reflects glucose metabolism in the cells which is significantly increased in malignant tumors. However, FDG is not a cancer-specific agent and its uptake has been described in a number of nonneoplastic inflammatory lesions.

Integrated PET-computed tomography (PET-CT) was introduced in 1999 [1]. These PET-CT scanners provide simultaneous acquisition of both high-resolution anatomic CT data and high-resolution metabolic PET information. However, as PET-CT is still a cost-intensive diagnostic tool with limited availability, reliable data evaluating the actual benefit of PET and PET-CT are of crucial importance. Therefore, this chapter gives an overview on currently available data of PET and PET-CT imaging in pancreatic cancer, summarizing its value and possible indications in the settings of primary diagnosis, staging, detection of tumor recurrence, and therapy monitoring. Finally, the potential value of recently introduced integrated whole-body PET-MRI is outlined.

Role of PET and PET-CT in Primary Tumor Diagnosisof Pancreatic Carcinoma

Despite excellent registration of anatomic and pathologic structures, morphologic imaging is unable to distinguish malignant from benign processes unconditionally. The sensitivity of multidetector CT (MDCT) has improved over the past few years. According to data from the literature, the sensitivity of MDCT in pancreatic carcinoma was reported to be between 75% and 100% in so-called multiphase scans with a specificity of 70–100%. However, concerning lesions smaller than 2 cm, the sensitivity reaches values of no higher than 77% [2,3], which mandates complementary histopathologic investigation of suspicious lesions. Magnetic resonance imaging (MRI) appears to be of outstanding impact in detection and assessment of tumor lesions of the pancreas, which cannot be directly depicted in CT imaging because of isoenhancing [4]. Concerning magnetic resonance cholangiopancreaticography (MRCP) in primary tumor diagnostics, Fusari et al. demonstrated sensitivity, specificity, accuracy, and positive and negative predictive values (describing the probabilities of FDG-positive lesions to be malignant and of negative lesions not to be malignant) to be 100%, 88%, 98%, 97%, and 100%, respectively [5]. For comparison purposes, the sensitivity and accuracy of endo-ultrasound for lesions smaller than 2 cm are reported to be as high as 100% and 95%, respectively [3].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Tumor detection and assessment of tumor dignity with FDG-PET encounter problems of a different nature. As FDG-PET displays areas of increased glucose metabolism within the body, those tissues with a naturally high metabolism and all hypermetabolic processes are depicted regardless of its dignity. This might lead to false-positive diagnosis in, for example, inflammation. The differentiation of pancreatic lesions is complicated whenever a local pancreatitis is present at the time of FDG-PET examination [6]. The glucose oxidation of activated leukocytes in inflammatory sites is highly increased, which causes an intense FDG uptake in this area as well. Additionally, within autoimmune pancreatitis an increased FDG uptake can be demonstrated in up to 100% of cases [7]. In contrast, in patients with chronic pancreatitis without active inflammatory components, PET shows a FDG uptake in only 13% [8]. Therefore, pancreatic carcinoma can be distinguished from chronic pancreatitis, because most pancreatic adenocarcinomas show a relatively high FDG uptake (Fig. 131.1).

However, recent studies have highlighted difficulties in differentiation between metastasis-free pancreatic carcinoma and mass-forming pancreatitis because of an overlap of the maximum standardized uptake value of both diseases [9]. Further, FDG uptake in tumor tissue and normal tissue is influenced by dietary state, as FDG is a glucose analogue. The investigator has to ensure a well-controlled serum glucose concentration in the patient to allow for adequate PET diagnostics. This is especially important in diabetic patients, because glucose concentrations above 8.4 mmol/L significantly reduce the detection rate of pancreatic carcinoma [6].

Kauhanen et al. reported a higher diagnostic accuracy of PET-CT compared to conventional MDCT and MRI in primary diagnosis of pancreatic cancer [10]. In their analysis including 38 patients, the pooled sensitivity and specificity were 85% and 94%, respectively. For comparison, sensitivity and specificity were 85% and 92% for MDCT, and 85% and 72% for MRI. In two prospective studies on primary diagnostics of pancreatic cancer, the sensitivity of PET-CT (89%) was comparable to both CT [11] and endo-ultrasound [12]. However, no homogeneous consent has been reported so far concerning any superiority of PET or PET-CT compared with MDCT and MRI. A published metaanalysis including 35 studies reports on pooled sensitivity (SN), specificity (SP), positive predictive value, and negative predictive value of 90%, 76%, 90%, and 76% for PET and 90%, 76%, 89%, and 78% for FDG-PET-CT, respectively. In contrast, sensitivity and specificity of CT and MRI are 91% and 85% versus 84% and 82%. Therefore, Rijkers and colleagues could not derive any superiority or additional benefit of both FDG-PET and FDG-PET-CT in primary diagnosis of pancreatic carcinoma [13]. These data therefore support the current guidelines of the NCCN, which do not recommend PET-CT for standard primary diagnostics in patients with pancreatic carcinoma.

Taken together, PET-CT is a useful diagnostic method *in addition* to conventional imaging procedures, especially when the results are inconclusive or show cystic and complex lesions in the pancreas [14]. Therefore, currently, the role of PET and PET-CT in diagnosis of primary pancreatic carcinoma cannot be finally determined.

Role of PET and PET-CT in Oncologic Staging of Pancreatic Carcinoma

Whereas primary diagnostics exclusively aim for the detection and proof of a pancreatic carcinoma, TNM staging focuses on gathering information on the oncologic extent of the primary tumor and its potential metastases, which is essential for individual evaluation of therapeutic options.

Regarding tumor resectability and reasonableness of surgical procedures, both local tumor infiltration of vessels and detection of distant metastases have a crucial impact on therapeutic strategy. As a result of high surgical standards and improvements in downstaging of

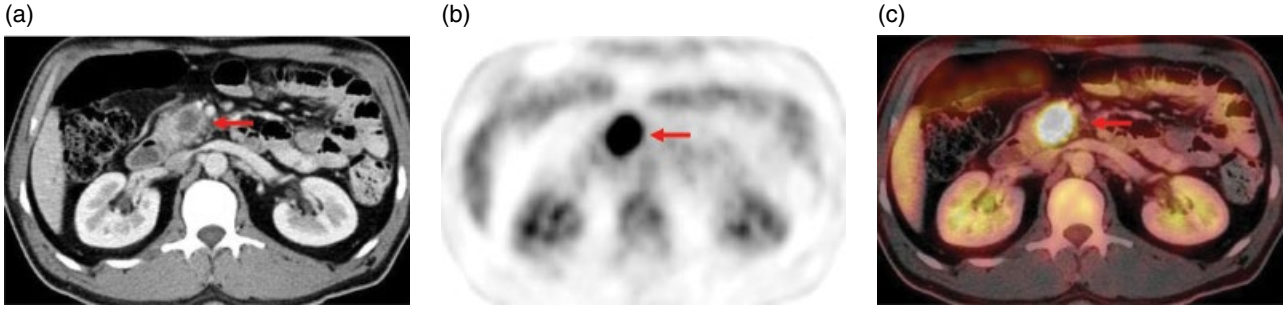


Figure 131.1 (a–c) FDG-PET-CT examination of a patient with primary diagnosis of pancreatic cancer presenting with an intense, focal FDG uptake in the pancreatic head.

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pancreatic carcinomas, the classification of *resectable*, *borderline resectable*, *locally advanced/irresectable*, and *metastasized* tumors has gained increasing attention. MDCT and MRI are the most commonly used methods in staging of pancreatic carcinomas. Here, T-staging is of special importance because unresectability of pancreatic cancer is defined morphologically as infiltration of the superior mesenteric artery and/or the celiac trunk. The preference of either method depends on both local availability and experience of the investigator. The NCCN guidelines support both contrast-enhanced pancreatic CT and MRI and the International Study Group of Pancreatic Surgery (ISGPS) recommends investigation of the pancreas by use of contrast-enhanced CT imaging. Nevertheless, assessment of local resectability remains difficult even with these tools. In ambiguous cases, the decision has to be forwarded to a pancreatic surgery reference center.

A study by Strobel et al. revealed that the use of enhanced FDG-PET-CT as a one-stop-shop imaging protocol for assessing the resectability of pancreatic cancer is feasible and accurate. In their study, enhanced PET-CT was significantly superior to PET alone and although not being significant, there was a trend for enhanced PET-CT to be superior to unenhanced PET-CT [15]. Therefore, PET-CT should always include diagnostic contrast-enhanced CT as unenhanced PET-CT has limited value in T-staging.

During recent years, combined FDG-PET-CT has made distinct progress in the staging of malignant pancreatic tumors. The advantage of this whole-body examination especially concerns the M-staging where its specificity reaches up to 100%, for example in the detection of lung and bone metastases [15]. Heinrich et al. proved that in patients with known metastatic spread, more metastases were visible by PET compared with CT scan alone [11]. In addition, the authors evaluated the oncologic impact of PET-CT on further therapeutic decision making. In 16% of the patients investigated, the detection of metastasis prompted the physicians to refrain from surgical therapy. This is concordant with the results of Bang et al. who revealed that PET scan increased the tumor stage in approximately a quarter of investigated patients because metastases had not been visible with CT imaging alone [16].

Another study demonstrated the superior sensitivity of FDG-PET (88%) compared to MDCT (38%) and MRI (38%) regarding the detection of liver metastases. This study also reported a change of therapeutic strategy in 29% of patients as the palliative situation made surgical procedures unnecessary [10]. These results could be augmented by a metaanalysis which reported an increased sensitivity of PET-CT compared to PET alone (82% vs 67%) regarding the detection of liver metastases [17].

The sensitivity of PET-CT in the detection of lymph node metastases has been reported to be as low as 21–38% [10,11]. Conversely, other studies underline the role of PET-CT in staging of locoregional and distant lymph node metastases. Here, PET-CT has been reported to be more accurate than CT or PET alone with regard to locoregional N-staging. However, the differences were rather small (85.3% vs 83.8% and 79.4%) [18]. Because of the contrary results published in the literature, the value of PET-CT for N-staging has to be questioned.

In summary, PET seems to be more sensitive in detection of distant metastases but has not achieved significance in routine staging and has not given proof of cost-effectiveness yet [19] (Fig. 131.2).

Therapy Control and Diagnostics of Malignant Pancreatic Tumor Recurrence by PET and PET-CT

The impact of FDG-PET and PET-CT in terms of response prediction after neoadjuvant chemotherapy in patients with pancreatic adenocarcinoma is promising. They are particularly expected to allow for decision

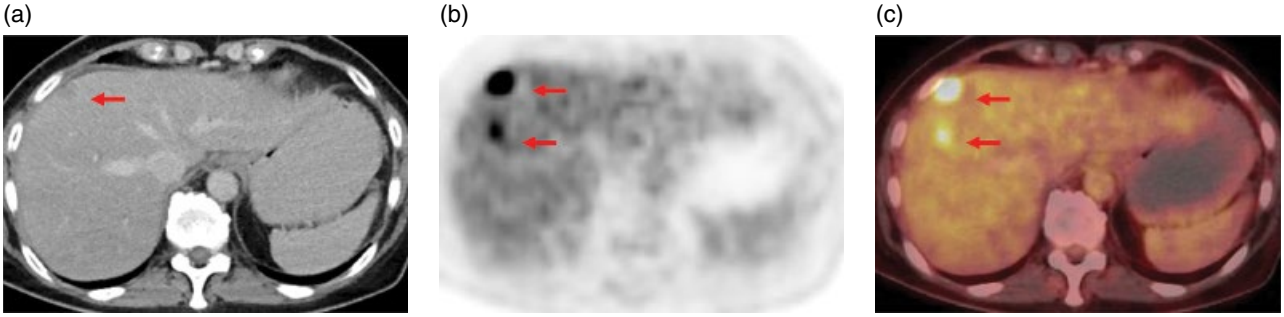


Figure 131.2 FDG-PET-CT of a patient presenting with two liver metastases of pancreatic cancer with high, focal FDG uptake (b,c). However, note that only one of them was visible with diagnostic CT (a).

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making in tumors that were initially described as borderline. Both the depiction of metabolic processes and the morphologic evaluation of lesions are highly difficult because of neoadjuvant chemotherapy-induced regional alterations around the tumor. Katz and coworkers demonstrated that the resectability of a tumor could be predicted on the basis of imaging procedures in only 0.8% of investigated patients after intended downstaging. However, tumors actually turned out to be resectable in 66% of the patients during surgical exploration [20]. The ISGPS therefore recommends explorative laparotomy in all patients without proof of metastatic spread or other indicators of tumor progress after neoadjuvant therapy.

FDG-PET and PET-CT show a significant advantage compared with CT and MRI in the detection of local recurrence after initial surgical resection of pancreatic carcinoma. Tumor recurrence could be confirmed in 96% of patients by use of FDG-PET but in only 39% when CT or MRI imaging were performed [21]. In another study, proof of tumor recurrence by FDG-PET was successful in 96.8%, whereas CT scan was accurate in only 55.6% [22]. Therefore, PET gains some significance in monitoring of surgical patients after resection of pancreatic cancer.

However, pancreatic tumors are often unresectable when diagnosed. FDG-PET served as therapy control of pancreatic carcinoma in several investigations. Advantages of PET-CT compared with CT scan could be demonstrated in terms of decreasing standardized uptake values in case of a tumor response in both follow-up monitoring after radiotherapy [23] and after chemotherapy [24]. These findings allow for some prognostic assessment concerning the survival of every single patient. Nevertheless, the correlations between metabolic response and prognosis remain under debate because of very heterogeneous results. However, new therapeutic agents can be tested and validated by use of FDG-PET-CT within studies.

Value of PET-MRI in Patients with Pancreatic Cancer

With the introduction of integrated whole-body PET-MRI into clinical practice, a novel metabolic anatomic imaging technique is available with the opportunity to perform multiparametric oncologic imaging that reflects different aspects of tumor biology (tumor diffusion, perfusion, and glucose metabolism). It also combines the strengths of PET (metabolic imaging) with the advances of MR (soft tissue contrast, functional imaging, e.g., using diffusion-weighted imaging and dynamic contrast-enhanced imaging) (Fig. 131.3). This multiparametric approach allows for noninvasive phenotyping of tumor biology which, by combining different functional and molecular imaging methods, might lead to higher

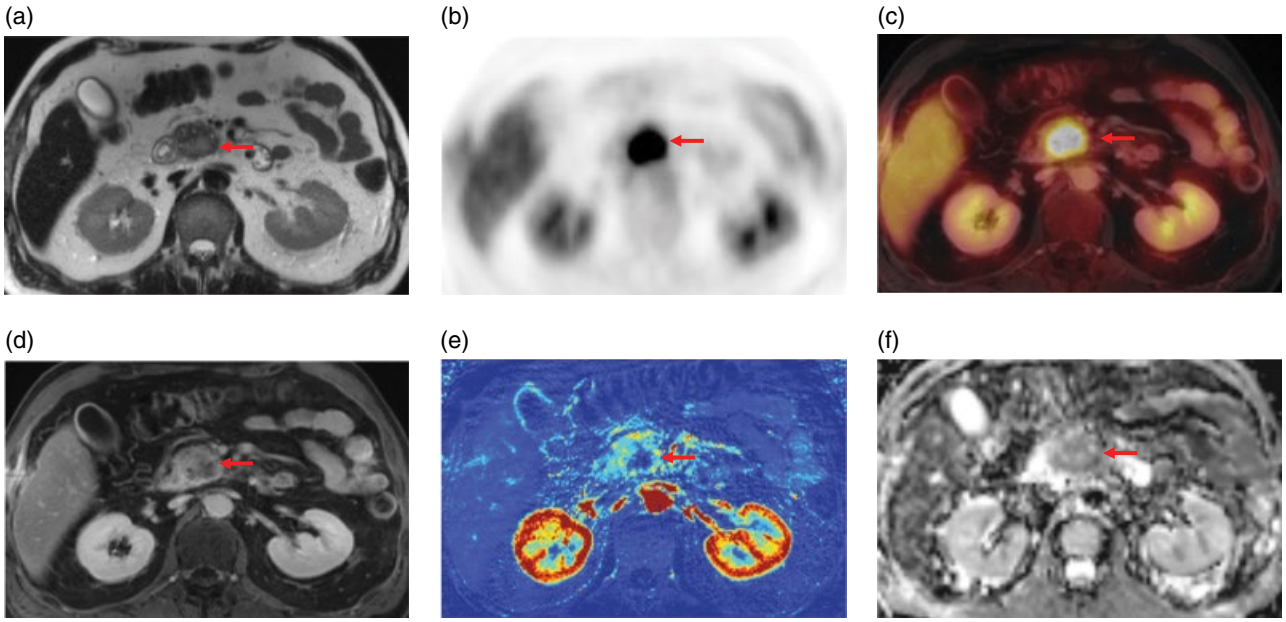


Figure 131.3 Multiparametric FDG-PET-MRI of a patient with primary diagnosis of pancreatic cancer. The MR image shows an inhomogeneous, hypointense tumor in the pancreatic head (a) with a high, focal FDG uptake (b,c). Dynamic contrast-enhanced (DCE) MRI shows peripheral hypervascularity (d) and the parametric map of iAUC60 (initial area under the DCE-MRI contrast agent concentration-time curve after 60 s) confirmed a high wash-in rate (e). Corresponding diffusion-weighted imaging presents low ADC values within the tumor indicating low cellularity (f).

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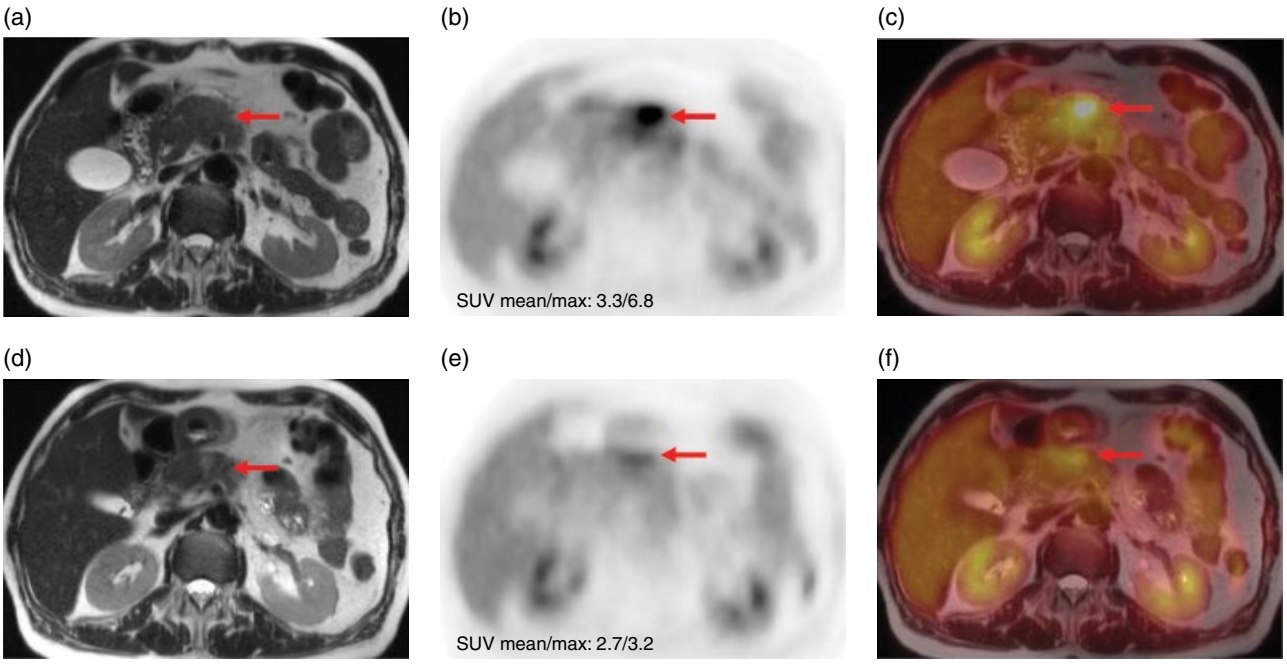


Figure 131.4 FDG-PET-MRI of a patient with pancreatic cancer before (a–c) and six weeks after beginning chemotherapy (d–f). Note the decrease of SUV values (b,e) after chemotherapy indicating a tumor response (decrease of SUVmean/max 18% and 53%).

accuracy for tumor detection and differentiation as well as response (Fig. 131.4).

In a study by Joo et al., a similar diagnostic performance in the preoperative staging and resectability assessment of pancreatic neoplasms was obtained comparing PET-CT plus contrast-enhanced CT with FDG-PET-MR imaging [25]. Further, in a preliminary study by Gao et al., multiparametric and textural features of primary tumors in FDG-PET-MR images were reliable biomarkers for predicting synchronous metastatic disease in pretreatment PDAC, which might be helpful for the selection of optimal therapeutic methods [26]. In detail, metastatic PDAC patients showed significantly larger tumor sizes, more frequent body/tail locations and higher SUVpeak, MTV, and TLG values in the primary tumor than those in nonmetastatic patients (P <0.05 for all). Further, significant differences between M0 and M1 PDAC for two first-level features (histogram skewness and kurtosis from ADC map) and 15 third-level features (four from PET and 11 from ADC map) were found. Additionally, Chen et al. showed that multiparametric PET-MR imaging biomarkers of pancreatic cancer patients were associated with overall survival [27].

Few data on sequential FDG-PET-MRI for response prediction in PDAC have been reported in the literature so far. In a preliminary analysis by Harder et al., FDG-PET-MRI was performed before and two weeks after therapy initiation indicating that early changes in FDG-PET-MRI-derived biomarkers MTV, TLG, and ADC enable differentiation between responders and nonresponders [28]. In a similar study, Wang et al. evaluated FDG-PET-MRI before and four weeks after treatment initiation in advanced PDAC [29]. Here again, FDG-PET-MRI-derived parameters MTV, TLG, and ADC enabled early discrimination between responders and nonresponders, further underlining the potential role of early PET-MRI after treatment initiation.

Conclusion

The final appraisal of the patient-relevant benefit of PET and PET-CT with regard to primary diagnostics, diagnostics of tumor recurrence, or staging cannot be based on a comparison with standard methods only. In fact, the major matter of interest is the question of the impact of an improved diagnostic tool on therapy and therefore patient morbidity, mortality, and quality of life. Randomized studies are needed to investigate the impact of findings from PET and PET-CT in all those cases where they indicate different results or tumor stages compared with standard methods. At the moment, there are no studies that allow for any statement concerning PET and PET-CT in this respect. However, many studies validate the quality of PET and PET-CT by scrutinizing the improvement in primary diagnostics, diagnostics of tumor recurrence, and tumor staging of pancreatic carcinoma compared with standard methods without PET.

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The current literature does not obligatorily recommend the use of PET-CT within primary diagnostics of pancreatic carcinoma, but it is considered to be a useful modality. However, PET-CT plays a promising role in the assessment of borderline resectable tumors and locally advanced tumors. Furthermore, the additional use of PET scanners demonstrated auspicious results in the staging of locally resectable lesions with synchronous CT and MRI morphologically occult metastases. Nevertheless, the sensitivity of detection of lymph node metastases is rather low. The impact on therapeutic consequences in tumor therapy will play a relevant role in future socioeconomic concerns, however, while sparing patients unnecessary surgical procedures. Finally, PET-CT already plays an important role in detection of tumor recurrence after surgical resection and therapeutic monitoring in unresectable pancreatic cancer.

PET-MR is a new and increasingly used multimodal imaging technique, which is expected to improve diagnostic performance especially in oncologic patients. The combination of PET and MR in hybrid whole-body PET-MR systems has the potential to combine excellent morphologic, functional, and biologic information in one imaging session with precise image coregistration. In contrast to PET-CT, the MR part of PET-MR provides superior soft tissue contrast and imposes no ionizing radiation.

The application of PET-MR has just started, and more research is needed to determine its potential value. Radiomics in nuclear medicine is developing fast and might improve the clinical value of multiparametric PET-CT and PET-MR in predicting disease phenotypes and personalizing diagnosis and treatment.

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Tumor Markers in Pancreatic Malignancies

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Conventional Tumor Markers for Pancreatic Cancer

Carbohydrate Antigen 19-9

Carbohydrate antigen (CA) 19-9 is a sialyl-Lewis A antigen, which is recognized by a mouse monoclonal antibody NS 19-9 established by Koprowski et al. [1]. This monoclonal antibody was established by immunizing mice with human tumor cell lines and binds to glycosphingolipid. Elevation of CA 19-9 was confirmed in the pooled serum samples from patients with advanced adenocarcinoma of the upper gastrointestinal tract, pancreas and biliary tract, compared to healthy donors [2].

In the normal pancreas, CA 19-9 expression is limited to the apical surface of pancreatic duct epithelium, while its expression increases in the pancreatic cancer cells [3]. Synthesis of CA 19-9 sialyl-Lewis A antigen requires α-1,4-fucosylation of sialyl-Lewis C precursor, which is regulated by the *Le* gene encoding fucosyl transferase [4]. Patients lacking the *Le* gene are unable to synthesize CA 19-9, and thereby represent low serum CA 19-9.

CA 19-9 is a standard marker of pancreatic ductal adenocarcinoma (PDAC). For PDAC diagnosis, the sensitivity of CA 19-9 was 79% and the specificity was 82% [5]. However, CA 19-9 is not a suitable marker for "early" detection of pancreatic cancer in the general population. Another study assessed the diagnostic ability of CA 19-9 according to the stage of PDAC, and the diagnostic sensitivity of CA 19-9 was only 55.6% in stage I [6]. Currently, the clinical usefulness of CA 19-9 is mainly for follow-up after surgery, assessment of chemotherapy effect, and prognosis. Patients with a low postoperative CA 19-9 value have a better prognosis [7]. Similarly, patients with low CA 19-9 before surgery or adjuvant chemotherapy also have a better prognosis [7]. Another study reported that decrease of CA 19-9 during gemcitabine-based chemotherapy could predict better median survival, suggesting the possibility as a determinant factor of chemotherapy continuation [8]. Based on this line of evidence, measurement of CA 19-9 before and after surgery or during chemotherapy is strongly recommended.

Measurement of CA 19-9 is also useful for detection of recurrence. Patients who received resection of pancreatic cancer with continuously elevated CA 19-9, referred as denormalization, frequently developed early recurrence [9]. Multivariate analyses revealed that CA 19-9 denormalization was an independent risk factor for early recurrence, together with no postoperative adjuvant chemotherapy and serosal invasion. In another study, patients who developed postoperative recurrence revealed elevation of CA 19-9 prior to the detection of recurrence by imaging studies [10]. The sensitivity and specificity of 2.45 times elevated CA 19-9 were 90% and 83.33%, respectively, with an area under the curve of 95%.

Elevation of CA 19-9 could be a feature of malignant intraductal papillary mucinous neoplasm (IPMN) [11]. CA 19-9 elevation was a preoperative predictor of malignant IPMN. A subsequent study also confirmed that CA 19-9 could be a noninvasive diagnostic tool for differentiating invasive IPMN [12]. The diagnostic sensitivity and specificity of CA 19-9 were 0.74 and 0.859, respectively. Preoperative CA 19-9 elevation is also a risk factor of postoperative recurrence of IPMN [13], similar to pancreatic cancer. A metaanalysis confirmed that raised CA 19-9 is most specific for the prediction of malignant IPMN [14], which will be beneficial for follow-up.

Several noncancer conditions also lead to the elevation of CA 19-9 besides pancreatobiliary cancers. Obstructive jaundice is a cause of CA 19-9 elevation [15]. Biliary drainage reduces serum CA 19-9 in these patients,

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suggesting that basal CA 19-9 level needs to be measured after biliary drainage. Elevation of CA 19-9 is also seen in patients with liver disease. Patients with acute hepatitis, liver cirrhosis, and hepatocellular carcinoma showed CA 19-9 elevation [16]. Lymphoepithelial cyst is a rare benign cystic tumor of the pancreas, and is accompanied by CA 19-9 elevation. In this report, half of the cases revealed CA 19-9 elevation [17]. Some polycystic liver disease and polycystic kidney disease patients also had elevated serum CA 19-9 [18,19]. Furthermore, a wide variety of diseases such as bronchiectasis, interstitial lung disease, endometriosis, and even diabetes mellitus could present with CA 19-9 elevation [20]. In cases of CA 19-9 elevation without evidence of pancreatobiliary malignancy, these possibilities should be considered.

DU-PAN-2

DU-PAN-2 is a sialyl-Lewis C antigen, which is a precursor of CA 19-9. Mouse monoclonal antibody against DU-PAN-2 was established by immunizing mice with the HPAF human pancreatic cancer cell line [21]. Since Lewis-negative individuals can synthesize this antigen [4], DU-PAN-2 becomes an alternative marker of pancreatic cancer in these patients. DU-PAN-2 elevation is also reported in patients with biliary obstruction, similar to CA 19-9 [15]. Elevation of DU-PAN-2 in pancreatic cancer patients who received surgical resection also predicts worse disease-specific survival, suggesting similar utility to CA 19-9 [22].

SPan-1

SPan-1 is recognized by a monoclonal antibody raised against mucins purified from the SW1990 pancreatic cancer cell line [23], which therefore recognizes both sialyl-Lewis A and C antigens [24]. Pre- and postoperative SPan-1 elevation also has prognostic impact in patients with resectable pancreatic cancer [25]. Figure 132.1 shows an algorithm for measuring CA 19-9 or DU-PAN-2/SPan-1 during pancreatic cancer diagnosis.

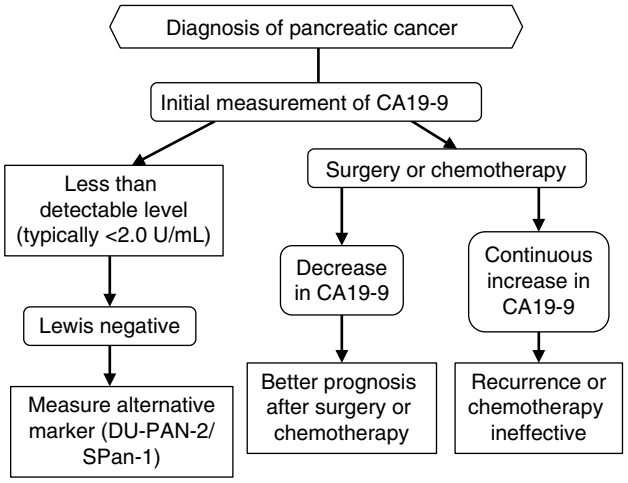


Figure 132.1 Clinical flowchart for CA 19-9 measurement in patients with pancreatic cancer.

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is a cell surface glycosylphosphatidylinositol (GPI) anchor glycoprotein, frequently used as a tumor marker for colorectal cancer [26]. Elevated serum CEA has been reported in patients with pancreatic cancer [27].

A recent systematic review summarizing 19 studies analysed the diagnostic ability of serum CEA in pancreatic cancer [28]. The pooled diagnostic sensitivity and specificity of CEA for pancreatic cancer diagnosis were 0.43 and 0.82, respectively. The pooled diagnostic sensitivity and specificity of CA 19-9 were 0.78 and 0.73, respectively, in the same study. Regarding prognostic significance, higher CEA level was associated with worse overall survival (OS) (hazard ratio 1.43) [28]. Similarly, measurement of CEA after surgical resection of pancreatic cancer had prognostic significance [29]. In this study, patients with elevated postoperative CEA had shorter recurrence-free survival and OS.

Elevated CEA in IPMN is also useful in distinguishing invasive IPMN [12]. The diagnostic sensitivity and specificity of CEA were 0.40 and 0.924, respectively.

These studies suggest that CEA measurement at the time of diagnosis or surgery would be useful for pancreatic cancer or IPMN.

Tumor Markers for Other Pancreatic Malignancies

α-Fetoprotein (AFP)

Acinar cell carcinoma is a rare type of pancreatic cancer. Elevation of AFP has been reported in cases of acinar cell carcinoma [30], and a decrease in serum AFP levels after therapeutic intervention has also been described [31]. Measurement of AFP in patients with pancreatic tumor suggestive of acinar cell carcinoma by imaging studies or pathologic diagnosis will be beneficial for follow-up after surgery and during and after chemotherapy.

Neuron-specific Enolase (NSE)

Neuron-specific enolase is a neuron-specific glycolytic enzyme and is also expressed in peripheral neuroendocrine cells [32]. Serum NSE is a marker of

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gastroenteropancreatic neuroendocrine tumor (GEP-NET). Serum NSE level reflects tumor burden and was correlated with OS of stage IV GEP-NET [33]. Another study reported increased serum NSE level according to the increase of tumor grade of pancreatic NET [34].

Chromogranin A (CgA)

Chromogranin A belongs to the granin family of acidic glycoproteins, regulating secretory granule biogenesis [35]. Since CgA is a major component of secretory granules, its serum level correlates with amount of endocrine cells. CgA is another marker of pancreatic NET. Similar to NSE, increase of serum CgA level was observed according to tumor grade of pancreatic NET [34]. Elevated CgA level was an independent risk factor for recurrence and OS by multivariate analysis.

Novel Marker Candidates

MicroRNAs

MicroRNA is a noncoding, single-stranded RNA of 21–24 nucleotides length [36]. MicroRNAs contribute to regulation of a wide variety of cellular functions, in both normal cells and cancer cells. MicroRNAs are released from cells in a small extracellular vesicle called an exosome, encapsulated by a lipid bilayer [36]. Exosomes are found in biological fluids such as urine, saliva, serum, and so on.

Many studies have tried to detect pancreatic cancer by microRNA detection in samples obtained via noninvasive methods. Detection of oncogenic microRNA, such as miR-21, miR-196, and miR-1246, in serum or urine samples had some diagnostic capability comparable to conventional tumor markers [37]. Some of these microRNAs were detectable in early-stage pancreatic cancer, suggesting the possibility of early diagnosis. However, further validation and confirmation of superiority over conventional biomarkers are necessary for clinical application.

Circulating Tumor Cells

Circulating tumor cells (CTCs) in peripheral blood are detectable in many solid tumors, including pancreatic cancer. Among patients with pancreatic cancer who received surgical resection, epithelial cell adhesion molecule (EpCAM)-positive CTCs were detected in 68.8% [38]. Patients with detectable CTCs in peripheral blood had a shorter OS after surgery, indicating predictive value. For CTC collection, surface marker-based and size-based filtration methods have been developed, which affect the quality of collected CTCs [39]. Optimization of sampling methods and timing of detection would be the next steps for clinical application.

Cell-free DNA

Peripheral blood also contains cell-free DNA (cfDNA). Several studies have reported an altered status of cfDNA in pancreatic cancer patients, affecting prognosis. The cfDNA contains circulating tumor DNA (ctDNA), which represents tumor-derived gene mutations [40]. This systematic review identified a negative impact of detectable ctDNA for the prognosis of patients with pancreatic cancer [40]. Another study reported that ctDNA samples from pancreatic cancer patients could be subjected to next-generation sequencing (NGS), as a screening method for panels of gene mutations [41].

Recent advances in NGS have enabled detection of gene mutations in each case, and detection of druggable mutations changes therapeutic strategy. For example, use of platinum-based therapy or poly-ADP ribose polymerase inhibitors is recommended for *BRCA*-mutant pancreatic cancer patients [42]. Even though the prevalence of the *NTRK* fusion gene is rare, targeted therapy for this fusion gene is now available, such as entrectinib and larotrectinib [43].

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The Role of Laparoscopy and Peritoneal Cytology in the Management of Pancreatic Cancer

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death for both males and females, with five-year survival rates of 39%, 13%, and 3% for localized, regional, and distant PC, respectively, in the United States [1]. One of the main reasons for the dismal prognosis is the delayed diagnosis at later stages. More than 80% of patients are estimated to have unresectable disease at the time of initial diagnosis due to local invasion and/or distant metastases involving the liver and peritoneum [2]. Despite advances in imaging, peritoneal metastases and small liver metastases on the liver surface are frequently missed during preoperative evaluation. Such a condition is called radiologically "occult metastases." A metaanalysis including 16 studies with a total of 1146 participants demonstrated that 41% of patients with potentially resectable pancreatic and periampullary cancers on contrast-enhanced computed tomography (CE-CT) actually presented with unresectable diseases at laparotomy [3]. Since inaccurate evaluation of resectability may result in unnecessary "open-and-close laparotomy," accurate evaluation before laparotomy is crucial for the better management of pancreatic cancer.

Staging laparoscopy (SL) is a minimally invasive approach to detect such occult metastases. The standard procedure of SL is exploration of the peritoneal cavity including the Douglas pouch and the liver surface. With more extensive SL procedures, surgeons can explore the lesser sac, perform lavage cytology, and sample possible metastatic tissues for histologic evaluation. Furthermore, intraoperative ultrasound (IOUS) can be utilized in searching for potential liver metastases and assessing the extent of local invasion.

Detection of radiologically occult metastases during SL can preclude unnecessary laparotomy and facilitate appropriate treatments based on accurate staging. In a metaanalysis including 2827 patients with potentially resectable pancreatic/peripancreatic cancers, the pooled sensitivity in detecting unresectable diseases by SL with IOUS was 64% (95% confidence interval [CI] 61–66%) [4]. In particular, the sensitivities in detecting liver and peritoneal metastases were 88% (83–92%) and 92% (84–96%), respectively. Unnecessary laparotomy was avoided in 25% of patients, and the resection rate improved from 61% to 80% using SL with IOUS.

In this chapter, we describe the indications and procedure of SL and the significance of peritoneal cytology for PC with special reference to current topics in the era of highly sensitive imaging modalities and minimally invasive approaches to pancreatic resections.

Indication for Staging Laparoscopy

The National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2021 (https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf) recommend considering SL in high-risk patients for potential metastases, including those with borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes. The optimal cutoff value of CA 19-9 varies among studies, but 150 U/mL has been most commonly adopted [5–8]. The cutoff value of primary tumor size considered as an indication of SL would be 30 mm [5,7,9]. Body and tail tumors are at higher risk of peritoneal dissemination than head tumors [10,11], because the former directly face the free space of the lesser sac compared to the latter which is

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covered by the gastrocolic ligament and transverse mesocolon. Therefore, the threshold for SL should be lowered for body and tail tumors. Even for locally advanced unresectable tumors, the presence or absence of occult peritoneal or liver metastases would still affect prognosis, and SL should be considered in this setting [12,13].

Procedure

Typically, three or four ports are placed. Both sides of the infraphrenic space are explored along with the liver surface (Fig. 133.1a). In the Trendelenburg position, the small intestine is gently moved upward and the Douglas pouch becomes accessible. The sample for lavage cytology is usually taken from the Douglas pouch by washing with 100 mL of normal saline (Fig. 133.1b). The posterior liver surface, paraduodenal retroperitoneum, proximal jejunal mesentery, and lesser sac are possible sites of metastasis, which might be missed during standard SL [14]. By dividing the midportion of the gastrocolic ligament, the lesser sac can be easily entered (Fig. 133.1c). Primary tumors may be visualized and the presence or absence of direct invasion into surrounding organs can be evaluated.

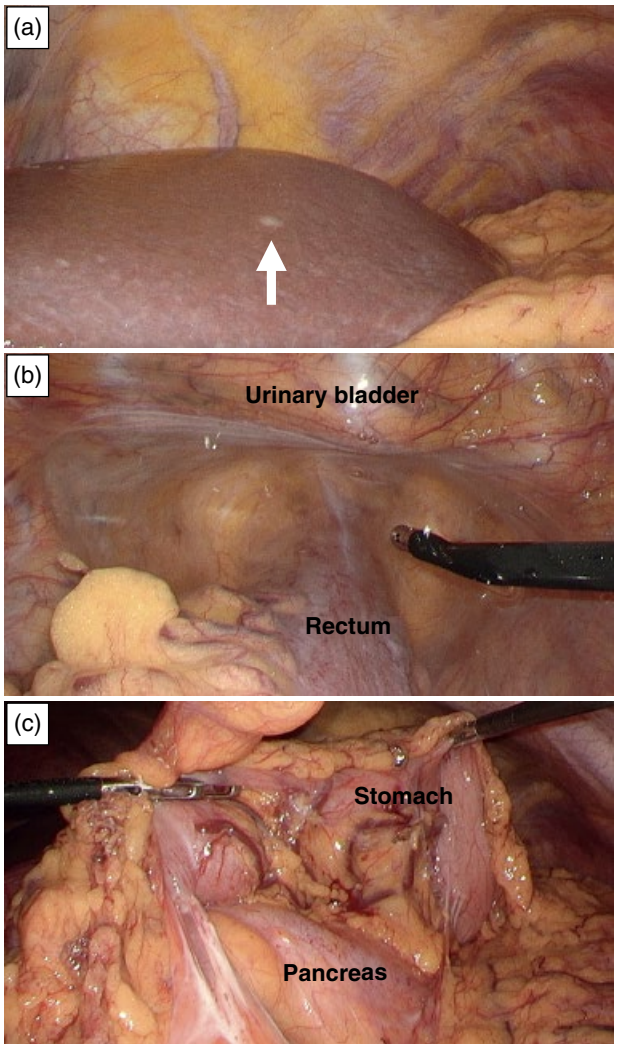


Figure 133.1 (a) An occult liver metastasis was found on the liver surface during SL, which was not detected on CE-CT, EOB-MRI, or FDG-PET. (b) By moving the small intestine upward, the Douglas pouch becomes accessible. Lavage cytology is collected at the Douglas pouch. (c) By dividing the gastrocolic ligament widely, the lesser sac can be fully explored.

Intraoperative US is useful for detection of liver metastases and assessment of local invasion of the major vessels. Contrast-enhanced IOUS facilitates the detection and characterization of liver masses (Fig. 133.2). The procedure is relatively safe with reported morbidity and mortality rates of <0.5% and <0.05%, respectively [4].

Significance of Peritoneal Cytology

Positive peritoneal cytology is considered as the precursor of peritoneal dissemination. The American Joint Committee on Cancer staging system defines CY+ as M1 [15]. However, the prognostic significance of CY+ and whether resection should be precluded only by CY+ have been controversial. A recent Japanese nation-wide cancer registry-based study including 1970 patients who underwent pancreatectomy for PC between 2008 and 2012 showed that the prognosis was significantly worse for patients with CY+ than those with CY- (the median survival times were 17.5 and 29.4 months respectively, and the five-year survival rates 13.7% and 31.1%, respectively) due to higher risk of peritoneal recurrence [10]. Meanwhile, a single-institution retrospective study including 523 patients demonstrated that although the overall survival of patients with resected CY+ tumors was worse than that of patients with resected CY- tumors, it was significantly better than the survival of unresected patients regardless of CY status [16].

These findings suggest that CY+ otherwise resectable is not always a contraindication for pancreatectomy, but upfront surgery may not be recommended in the era of neoadjuvant therapy. In order to reduce the risk of peritoneal recurrence, strong chemotherapy and other modalities are needed in the neoadjuvant setting for patients with CY+ otherwise resectable PC. In such cases, repeated SL after neoadjuvant therapy might be useful for restaging and determining the indication for subsequent pancreatic resections.

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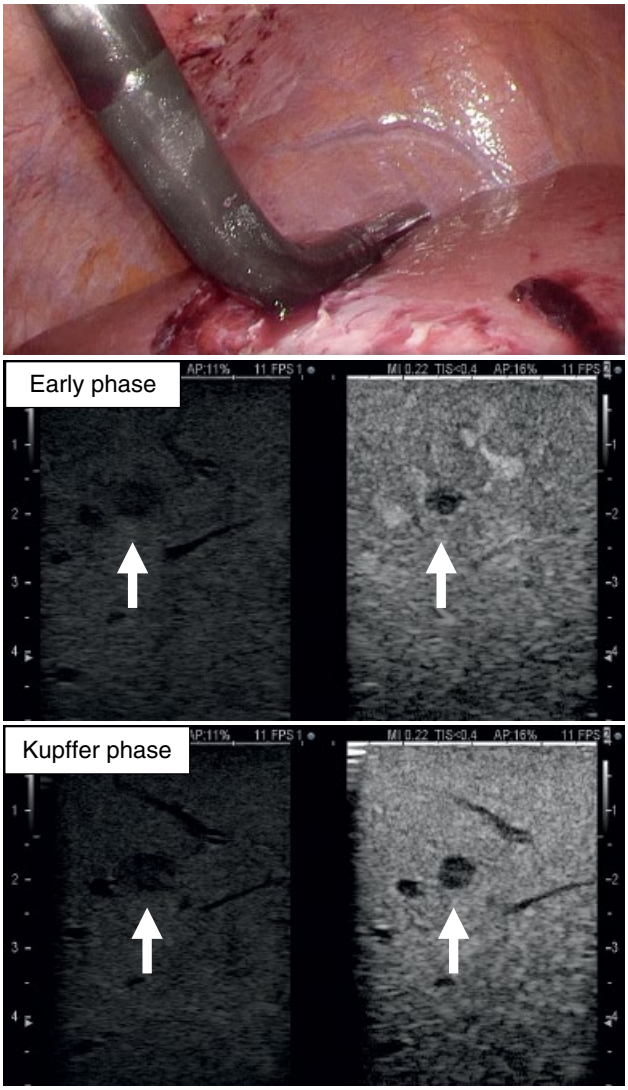


Figure 133.2 Contrast-enhanced IOUS using Sonazoid® facilitates detection and characterization of liver masses. A 5 mm nodule exhibited rim enhancement on early phase (middle panel) and clear defect on Kupffer phase (lower panel), which was considered to be a liver metastasis. The left-hand images are B-mode and the right-hand images are their simultaneous Sonazoid® mode.

Recent Topics in Staging Laparoscopy

Superiority of SL to Imaging Modalities in the Modern Era

Several metaanalyses have demonstrated the usefulness of SL in detecting occult metastases of the liver and peritoneum compared to conventional CE-CT [3,4,17]. However, there has been a limited number of studies examining the superiority of SL to gadoxetic acid disodium-enhanced magnetic resonance imaging (EOB-MRI) or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) combined with conventional CE-CT. EOB-MRI has been recognized as the most reliable imaging modality in detecting liver metastases. In a retrospective series of patients with potentially resectable PC diagnosed with CE-CT, the sensitivity and specificity of EOB-MRI for liver metastases, which CE-CT had failed to detect, were 77.5% and 94.7%, respectively [18]. FDG-PET is useful in detecting metastatic deposits, including those in the liver and lymph nodes, and sometimes in the peritoneum as well. In a metaanalysis, the pooled sensitivity and specificity of FDG-PET were 64% and 81% for N staging, and 67% and 96% for liver metastases, respectively [19]. These findings suggest that SL is still useful for avoiding unnecessary laparotomy after negative EOB-MRI and FDG-PET studies for unresectable diseases, but positive EOB-MRI or FDG-PET study could preclude SL. Further accumulation of evidence would be needed to define the additional diagnostic value of SL to these imaging modalities in the modern era.

Staging Laparoscopy with Intent for Minimally Invasive Pancreatectomy

Recently, minimally invasive (laparoscopic or robot-assisted) distal pancreatectomy has become common and minimally invasive pancreatoduodenectomy is also undertaken in specialized high-volume centers. By means of these minimally invasive approaches, "unnecessary laparotomy" can be avoided even if unresectable disease is detected intraoperatively. Complete abdominal exploration should be undertaken to rule out unresectable disease before the point of no return. Even in cases of minimally invasive pancreatectomy, SL should be done beforehand for high-risk patients to save costs and resource use.

Conclusion

Staging laparoscopy is a useful, minimally invasive technique for detecting occult metastases and avoiding unnecessary "open-and-close laparotomy" in patients with potentially resectable PC. Although CY+ is not always a contraindication for pancreatectomy, neoadjuvant therapy should be considered for patients with CY+ otherwise resectable PC. SL still plays a significant role in the era of highly sensitive imaging modalities and minimally invasive pancreatectomy and may contribute to best practice for patients with a high risk for recurrence.

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Clinical Assessment and Staging of Advanced Pancreatic Cancer

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a global problem with 495 773 new cases and 466 003 new deaths attributed to this lethal disease worldwide in 2020 [1]. In the United States, PDAC is the fourth leading cause of cancer deaths [2]. However, with an increased incidence and limited improvements in survival outcomes, it is projected to be the second leading cause of death by 2030 [3]. With vague symptoms at presentation, PDAC is often diagnosed at an advanced stage and treatment is limited to palliative interventions to manage symptoms and prolong survival.

This chapter focuses on the clinical assessment, diagnosis, and staging of patients diagnosed with advanced pancreatic cancer.

Clinical Presentation

Pancreatic ductal adenocarcinoma is a deadly disease with five-year overall survival of only 10% [2]. This has changed marginally over the past 40 years, in part because most newly diagnosed patients present with advanced disease. Of the estimated 60 430 newly diagnosed cases of PDAC in the US in 2021, only 15–20% will be candidates for surgical resection. The remainder will harbor metastatic disease (40–50%) or locally advanced tumors (30–40%) that are radiographically confined to the pancreas and peripancreatic tissues, but unresectable due to regional vascular involvement [2,4].

Symptoms of pancreatic cancer are often vague, resulting in a delay in diagnosis and advanced stage at presentation. Common clinical features for newly diagnosed patients include abdominal pain, back pain, abnormal liver function tests, nausea or vomiting, change in bowel habits, fatigue, and weight loss [5]. Tumor location plays an important role in the type and timing of symptoms at diagnosis. For lesions in the head and uncinate process, biliary obstruction often leads to an earlier presentation due to associated jaundice, pruritus, acholic stool, and choleuria. Tumors in the neck and body of the pancreas are marked by local extension to the celiac nerve plexus and present with epigastric and back pain that is often a hallmark of locally advanced disease. Those in the tail of the gland are frequently diagnosed at an advanced stage as tumor growth in this location is less likely to impact the function of regional structures and produce symptoms [6]. Regardless of tumor location, chronic obstruction of the pancreatic duct with resultant gland atrophy can promote both endocrine and exocrine insufficiency leading to new-onset diabetes, diarrhea, malabsorption of fat-soluble vitamins, and steatorrhea [7].

Examination can confirm signs of biliary obstruction with scleral icterus and jaundice. For obstructing right-sided tumors, a distended and palpable gallbladder may be appreciated. The presence of ascites, confirmed with a distended abdomen and fluid wave, raises suspicion for peritoneal disease. Involved supraclavicular (Virchow's node) or umbilical (Sister Mary Joseph node) nodes or peritoneal implants found in the pelvic cul de sac on rectal exam (Blummer's shelf lesions) are consistent with metastatic disease.

Evaluation for Pancreatic Cancer

Serologic and Genetic Evaluation

Serologic workup may include a comprehensive metabolic panel inclusive of liver function tests, complete blood count, amylase, lipase, coagulation studies, and albumin. Patients

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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with obstructive jaundice will present with a conjugated hyperbilirubinemia and elevated alkaline phosphatase level. Elevations in transaminases may be absent or mild. For those who are newly diabetic, hemoglobin A1C (HgbA1C) may be grossly elevated or demonstrate a rapid rate of rise, similar to those with type 1 diabetes [8].

CA 19-9 is the only FDA-approved serologic tumor marker for PDAC. Initially described in colon cancer, the test is based on a sialyated Lewis (a) antigen (Le^a) produced by epithelial cells on the surface of erythrocytes and in the mucin produced by pancreatic cancer cells [9]. With a sensitivity of 79–81% and specificity of 82–90% in symptomatic patients, it is an important assay for diagnosis, treatment response, and prognosis. False-positive values are seen in patients with biliary obstruction and pancreatitis, and a baseline value should be obtained only after adequate biliary drainage is achieved. False-negative values are seen in the 5–10% with a Lewis-a-negative genotype who are unable to secrete CA 19-9 [10].

Pretreatment CA 19-9 levels have been shown to correlate with disease stage and resectability, making it a useful tool for treatment planning [11,12]. In patients with resectable disease, a postoperative reduction in CA 19-9 levels and an absolute level less than 180–200 U/mL have been shown to be strong predictors of survival [13,14]. For those with localized disease treated with preoperative therapy, normalization of pretreatment CA 19-9 predicts survival, while failure to normalize after neoadjuvant therapy and resection is associated with a greater than four-fold increased risk of death [15]. CA 19-9 has also shown prognostic value in patients with advanced disease treated with chemotherapy where higher baseline levels and increasing levels during treatment were associated with worse survival [16]. Additionally, CA 19-9 levels exceeding 305 U/mL combined with CEA levels greater than 7 ng/mL were reported as having a 91.4% positive predictive value in diagnosing advanced pancreatic cancer [17].

Current guidelines recommend measuring serum CA 19-9 levels prior to initiating treatment, after completing neoadjuvant therapy, before surgery, prior to initiating adjuvant therapy, and for surveillance [18]. In Lewis antigen nonsecretors, additional carbohydrate antigens have been evaluated as diagnostic biomarkers, including CA 242, CA 50, CA 195, CA 72-4, CEA, and CA 125. However, due to inferior sensitivity relative to CA 19-9, all are of limited clinical utility [19,20].

Pancreatic ductal adenocarcinoma biomarker development has been an area of active research over the last decade, with over 300 novel biomarkers reported in the literature [21]. This effort has been driven by the need for innovative tools to aid in early tumor detection, understanding individual tumor biology and behavior, predicting response to therapy, and prognosis [22].

Among the most promising are newly described techniques of serum liquid biopsy. Liquid biopsy describes the identification of biomarkers such as circulating tumor cells (CTCs), circulating tumor DNA, and tumor-derived exosomes to diagnose and characterize tumor behavior from circulating fluids as an alternative to standard tissue biopsies [23]. In a recent metaanalysis, Zhu et al. reported on the diagnostic utility of CTCs in PDAC with a pooled sensitivity of 74% and pooled specificity of 83% [24]. MicroRNA expression panels obtained from whole blood samples combined with CA 19-9 levels have been used to distinguish patients with pancreatic cancer from healthy controls with greater accuracy than CA 19-9 levels alone [25]. As a predictive tool, the identification of the exosomal miRNA, miR-17-5, in serum samples of pancreatic cancer patients is associated with advanced stage at diagnosis [26]. Additionally, the presence of CTCs has been shown to be of prognostic value, with CTC-positive PDAC patients having worse overall and progression-free survival [27].

Liquid biopsy is an appealing diagnostic modality for patients with locally advanced PDAC where tissue samples for diagnostics are less likely to be obtained through surgical resection. Collectively, these and other emerging biomarkers in development show promise for the future but await further large-scale validation studies prior to adoption in clinical practice.

Current guidelines recommend genetic testing for all patients with newly diagnosed pancreatic cancer [28]. Approximately 1 in 10 PDACs is associated with a hereditary component, which can be divided into three general categories: hereditary pancreatitis (e.g., related to mutations in *PRSS1*, *SPINK1*, *CTRC*, and *CFTR*), hereditary cancer predisposition syndromes (e.g., familial atypical mole malignant melanoma syndrome, Peutz–Jeghers syndrome, von Hippel–Lindau disease, Li–Fraumeni, breast and ovarian cancer syndrome, adenomatous polyposis coli and Lynch syndromes, among others), and familial pancreatic cancer syndrome [29]. Presently, the results of germline testing are of greatest utility to patients with advanced PDAC harboring *BRCA1/2* and *PALB2* mutations, for whom treatment with platinum-based chemotherapy and the PARP inhibitor olaparib is preferred [30,31]. This and other precision medicine approaches to treatment are an area of active research for patients with advanced PDAC and offer the promise of improved outcomes through tailored treatment strategies [32].

Radiologic Evaluation

Imaging studies are of vital importance in the initial diagnosis and staging of PDAC. With a sensitivity exceeding 90%, dual-phase multidetector CT angiography of the pancreas with thin axial cuts is the

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recommended initial imaging assessment [33,34]. A pancreas protocol study is performed with intravenous contrast and a neutral enteral contrast agent. Late arterial phase images are obtained 25–35 seconds after IV contrast administration during peak contrast enhancement of the pancreas. This phase is optimal for pancreatic tumor detection as most tumors appear hypodense relative to normal pancreatic tissue. Additionally, the late arterial phase allows for assessment of the relationship of the tumor to the regional arterial vasculature and identification of aberrant arterial anatomy. The portal veinous phase images are obtained 60–70 seconds after IV contrast administration and are most useful in assessing the relationship of the tumor to regional venous structures, identifying unique regional venous anatomy, and identifying liver, lymph node, and peritoneal metastases.

Computed tomography is the preferred initial diagnostic imaging study as it is widely available, fast, familiar to providers, and has excellent spatial resolution (Fig. 134.1). An initial pancreas protocol CT is ideally obtained prior to any biliary interventions or attempts at tissue diagnosis, and prior to initiating treatment as these factors may prompt peripancreatic inflammation that obscures the tumor–vascular interface, thereby limiting the sensitivity of the study in determining resectability [34–38].

Contrast-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) is an alternative to CT for patients unable to receive intravenous iodinated contrast. MRI provides superior soft tissue contrast and can be a useful adjunct in the identification and characterization of subtle liver findings or iso-attenuating pancreatic tumors not visualized on CT. Additionally, MRCP offers a more detailed look at the biliary tree and pancreatic duct [38]. A CT chest is obtained to complete the assessment for metastatic disease and radiographic staging. Positron emission tomography (PET) CT with 18F-fluorodeoxyglucose (FDG) is not routinely obtained during imaging assessment but is useful for identifying metastatic disease in patients with high-risk features including large tumors, enlarged regional lymph nodes, and markedly elevated CA 19-9 levels [39].

Endoscopic Evaluation and Treatment of Advanced Pancreatic Cancer

Endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and other advanced endoscopic techniques are critical in the diagnosis and treatment of patients with pancreatic cancer. EUS is a useful adjunct to CT in the detection of small, radiographically occult tumors. In a recent metaanalysis, EUS successfully identified a mass in 70% of patients with clinical suspicion of a PDAC but indeterminant CT findings with a mean tumor size of 21 mm [40]. With a sensitivity of 85–91% and specificity of 96–98%, EUS with fine needle aspiration (FNA) has also supplanted ERCP, with duct brushings as the preferred mode of tissue acquisition for diagnosis [41].

Recently, dedicated EUS fine needle biopsy (FNB) devices have been developed, allowing endoscopists to collect both cytologic and histologic tissue specimens. FNB offers the advantage of gross visual inspection for specimen adequacy and requires fewer passes to obtain a

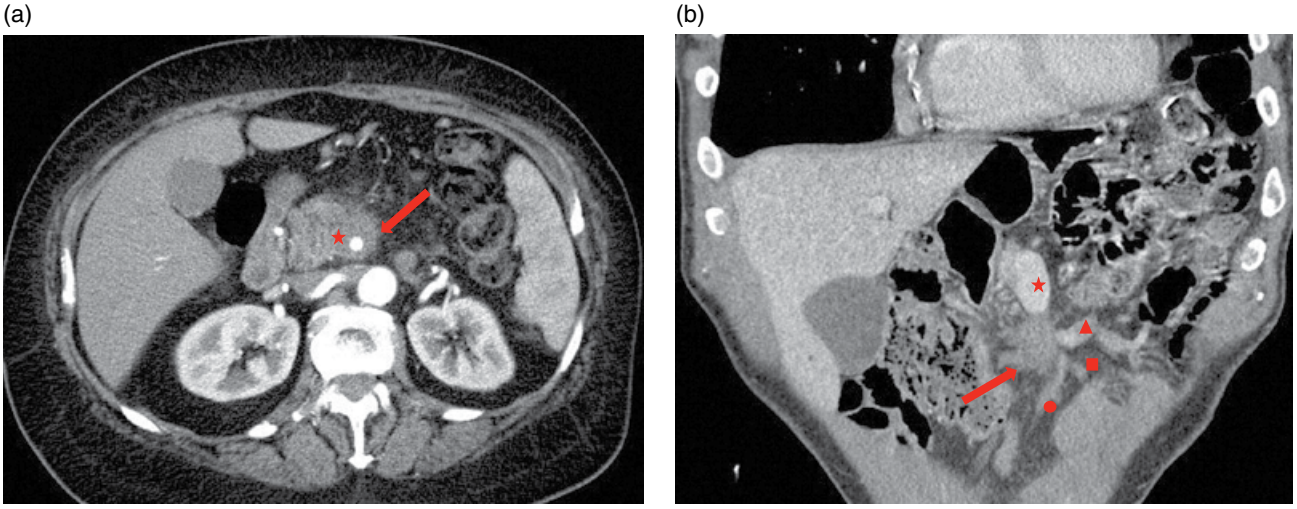


Figure 134.1 (a) CT pancreas protocol, late arterial phase, axial view showing a locally advanced tumor (arrow) with encasement of the SMA (star). (b) CT pancreatic protocol, portal venous phase, coronal view showing a locally advanced tumor of the uncinate process (arrow) producing occlusion of the SMV (star) at the confluence of first jejunal vein (triangle), second jejunal vein (square), and ileocolic vein (circle).

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diagnostic sample [42]. Additionally, the larger sample sizes and preserved tissue architecture of FNB samples permit immunohistochemical, biomolecular, and genomic profiling of PDAC tumor tissue without the need for a surgical specimen or core needle biopsy [43,44].

Presently, current guidelines recommend genomic assessment of PDAC tumor specimens to identify actionable somatic fusion proteins (*ALK*, *NRG1*, *NTRK*, *ROS1*), mutations (*BRAF*, *BRCA 1/2*, *HER2*, *KRAS*, *PALB2*), and mismatch repair deficiency [18]. EUS/FNB will likely play an important future role in tailoring the treatment approach for patients with advanced PDAC as novel therapies are developed to target tumor-specific somatic changes.

Endoscopic transpapillary biliary drainage via ERCP and stent placement is the preferred approach to managing PDAC patients with malignant biliary obstruction (MBO). Compared to surgical bypass, endoscopic biliary drainage (EBD) is equally effective and associated with lower morbidity, lower cost, and improved quality of life [45–49]. Similarly, EBD has been shown to be more effective with faster resolution of hyperbilirubinemia than percutaneous transhepatic biliary drainage [50].

When rapid cytologic assessment confirms a PDAC diagnosis, placement of self-expanding metal stents (SEMS) is preferred over plastic stents as they have greater long-term patency. Uncovered metal stents are standard, but can be associated with tumor ingrowth, leading to occlusion [51]. Covered metal stents may offer more durable patency for patients with advanced disease who are not candidates for surgical resection. Additionally, covered metal stents are potentially removable if a PDAC diagnosis is uncertain, but are associated with higher cost and higher risk of both cholecystitis and pancreatitis [52].

EUS-guided biliary drainage is an important alternative when endoscopic transpapillary drainage is not achievable. Using this technique, the biliary tree is accessed endoscopically under US guidance via a transgastric approach to the left biliary tree or transduodenal access to the common hepatic duct. Following guidewire placement, a self-expanding metal stent is positioned to create a hepaticogastrostomy or choledochoduodenostomy. Alternatively, in a rendezvous procedure, the guidewire may be advanced distally across the ampulla to facilitate transpapillary drainage. These techniques are particularly important in patients with simultaneous malignant bowel and biliary obstruction, as advanced tumors in the head of the pancreas that cause obstruction in the second portion of the duodenum will also prevent endoscopic access to the major papilla [53].

Gastric outlet obstruction (GOO) is observed in up to 25% of patients presenting with advanced PDAC [54]. Options for management include surgical gastrojejunostomy, enteral stent placement, and EUS-guided gastroenterostomy (EUS-GE). Laparoscopic gastrojejunostomy is safe, effective, and associated with a lower rate of reinterventions compared to enteral stenting. This approach is favored for patients with advanced PDAC who have preserved functional status, are candidates for cancer-directed therapy, and have a life expectancy exceeding six months [55]. Alternatively, endoscopic placement of self-expanding enteral stents is considered for patients with advanced disease, poor performance status, limited life expectancy, and those who wish to avoid the potential morbidity of a surgical procedure [56]. Compared to gastrojejunostomy, stent placement is associated with more rapid symptom resolution, but higher rates of symptom recurrence.

Occlusion due to tissue ingrowth is frequently seen in patients with stents in place longer than 2–3 months [52,57]. To combat this issue, EUS-guided gastroenterostomy has been advanced as a novel approach to relieve GOO that combines the durability of surgical bypass with the more limited morbidity of an endoscopic approach. In this procedure, a bypass is created between the stomach and small bowel using EUS and fluoroscopic guidance to place lumen-apposing metal stents [58]. Ge et al. recently reported a lower rate of stent failure, greater initial success, a similar rate of adverse events, and greater stent durability for malignant GOO patients treated with EUS-GE compared to enteral stent placement [59]. EUS-GE is an attractive alternative to enteral stent placement at centers with expertise in advanced endoscopy; however, it should be employed with caution in patients where resection may be considered as its impact on subsequent pancreatoduodenectomy is unreported.

Surgical Evaluation in Advanced Pancreatic Cancer

Surgery for the initial diagnosis and management of advanced PDAC has largely been supplanted by endoscopic procedures and imaging studies in the modern era. However, staging laparoscopy remains a useful adjunct in the search for radiographically occult metastatic disease.

There is no consensus regarding the routine use of staging laparoscopy in PDAC patients with localized disease on imaging. However, multiple studies suggest high-risk features for occult metastases including large tumors (>3 cm), enlarged regional lymph nodes, CA 19-9 values above 150 U/mL, and significant abdominal pain at diagnosis. Under these circumstances, the diagnostic yield of staging laparoscopy is as high as 20–30% [60–62]. During laparoscopy, all visible peritoneal surfaces should be examined for evidence of gross tumor implants with special

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attention paid to the liver, omentum, and peritoneal surfaces overlying the diaphragm and anterior abdominal wall. Tissue samples of suspicious lesions can be obtained via core needle biopsy of the liver, partial omentectomy, and local peritonectomies. Intraoperative ultrasound may be considered for further evaluation of the liver and the tumor–vascular interface. Peritoneal washings with isotonic fluid should be collected as positive peritoneal cytology, even in the absence of gross peritoneal tumor deposits, is considered metastatic disease [63].

In the unfortunate scenario where metastatic or unresectable local disease is noted during attempted resection, the value of palliative surgical procedures to maximize patient quality of life should be weighed against the potential morbidity of those procedures and resultant delay in initiating alternative cancer-directed therapies. Consideration should be given to gastrojejunal bypass in patients with GOO, while surgical biliary bypass should be reserved for individuals without endoscopic means of palliating MBO. Additionally, celiac plexus neurolysis (CPN) performed in this setting is an effective means to palliate cancer-related pain, improve quality of life, and survival [64].

Staging for Advanced Pancreatic Cancer

Patients with advanced PDAC are staged per the American Joint Cancer Committee (AJCC) TNM Staging System, 8th edition [65]. Validation studies have demonstrated a correlation between TNM stage and survival (Table 134.1) [66,67]. Although useful as a prognostic tool, the TNM stage has limited utility in guiding treatment decisions at diagnosis.

Table 134.1 Summary of AJCC Staging, 8th edition with correlation to five-year survival.

TNM staging	Five-year survival (%)
Stage IA T1N0M0	39.2
Stage IB T2N0M0	33.9
Stage IIA T3N0M0	27.6
Stage IIB T1-3N1M0	21.0
Stage III T1-3N2M0 T4N0-2M0	10.8
Stage IV T1-4N0-2M1	3.0

Amended from [65–67].

For patients with locoregional disease, surgical resection in combination with systemic therapy is the only treatment associated with long-term survival, and status as a surgical candidate is the most important factor in treatment planning [68]. Determinants of resectability include patient factors (performance status, goals of care, perioperative support), tumor biology (CA 19-9 level, response to preoperative therapy), and the anatomic relationship of the tumor to regional vascular structures.

Originally described by MD Anderson and later refined by the International Association of Pancreatology, PDAC tumors are defined as resectable, borderline resectable (BR), locally advanced (LA), and metastatic based on their appearance on pancreas protocol CT (Table 134.2) [69,70]. LA tumors demonstrate any/all of the following criteria without evidence of metastatic disease: narrowing or occlusion of the portal vein/superior mesenteric vein (SMV) without options for vascular reconstruction, ≥180° abutment or encasement of the superior mesenteric artery (SMA), and abutment of the celiac artery or proper hepatic artery. While nearly 70% of patients with BR tumors undergo surgical resection after neoadjuvant therapy, most with LA tumors are not candidates for pancreatectomy and are treated with palliative intent similar to those with metastatic disease [71]. Ineligibility for surgical resection due to local anatomic factors or metastatic disease defines advanced PDAC.

For patients with advanced PDAC, palliative chemotherapy is standard first-line treatment to address symptoms and prolong survival. FOLFIRINOX is the preferred regimen for those with good performance status (ECOG 0–1) as it has been shown to prolong survival compared to gemcitabine alone in patients with metastatic disease (median OS 11.1 months vs 6.8 months; P <0.001) [72]. In a recent systematic review, patients with LA disease treated with FOLFIRINOX had a pooled median survival of 24.2 months [73]. In a separate observational study, 29% of LA patients treated with FOLFIRINOX had a 30% reduction in CT tumor volume and half of those underwent surgical resection [74]. Even without a significant radiographic treatment response, there is growing enthusiasm for the aggressive treatment of local disease in patients who remain free of metastases after 4–6 months of induction chemotherapy. In the era of modern chemotherapy, multiple centers have reported favorable surgical and oncologic outcomes for patients with LA disease treated with neoadjuvant therapy followed by pancreatectomy employing vascular resections or periarterial divestment (Table 134.3) [75–80].

These reports highlight the emerging challenge of restaging LA patients after neoadjuvant therapy to determine who may benefit from surgical resection. Ferrone et al. demonstrated that posttreatment CT was

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Table 134.2 Classification of borderline resectable and locally advanced PDAC.

	Borderline Resectable		Locally Advanced		Locally Advanced Modification	
Vascular Structure	**MDACC**	**IAP**	**MDACC**	**IAP**	**Type A**	**Type B**
Superior Mesenteric Artery	Tumor abutment ≤ 180°	Tumor contact ≤ 180° without deformity or stenosis	Encased (>180° involvement)	Tumor contact or invasion of >180°	>180° encasement but ≤270°	>270° encasement
Celiac Artery (CA) or Hepatic Artery (HA)	Short-segment encasement/ abutment of HA	Tumor contact with common HA without contact of the proper HA or CA	Encased and no technical reconstruction option	Tumor contact or invasion of the proper hepatic artery	>180° CA involvement, no extention to aorta	>180° CA involvement and abutment of aorta
					>180° encasement of HA with extension to CA but options for reconstruction	>180° HA encasement with extension beyond bifurcation of proper HA
Superior Mesenteric Vein or Portal Vein	Short-segment occlusion with suitable vessel above and below	Tumor contact ≥180° or bilateral narrowing or occlusion, not exceeding inferior border of duodenum	Occluded and no technical reconstructive option	Bilateral narrowing or occlusion exceeding inferior border of duodenum	Occlusion without option for reconstruction	Occlusion without option for reconstruction

Amended from [69,70,79].

Table 134.3 Recent studies reporting outcomes following surgery for locally advanced PDAC.

Author	Year	Procedures (%)	Cases	R0 (%)	Major Morbidity (%)	Mortality (%)	Median OS (months)	1-year survivial (%)	3-year survival (%)	5-year survival (%)
Tee et al. (78)	2018	AR (100)	87	NA	54	13	NAT+ 53.6 NAT- 16.6	NAT+ 81 NAT- 72	NA	NA
Chatzizacharias, et al. (79)	2018	AR (32), VR (17.5), AR+VR (2.5)	40	80	15	0	38.9	NA	NA	NA
Del Chiaro et al. (77)	2019	AR (32), AR+VR (68)	34	NA	12	2.9	NA	63.7	23.4	23.4
Loos et al. (80)	2020	PAD (49.5), AR (50)	385	28	NA	8.8	20.1	NA	NA	12.5
Truty et al. (76)	2021	AR (33), AR+VR (25.8)	194	94	36	6.7	58.8	96	62	NA

AR: Arterial resection; VR: Vein resection; PAD: Periarterial divestment; OS: Overall survival; NAT: Neoadjuvant therapy; NA: Not available

ineffective in determining resectability in LA patients as 92% meeting LA imaging criteria underwent an R0 resection after neoadjuvant FOLFIRINOX [81]. Combined with findings from Gemzenetzis et al. that showed a 77% treatment response rate in LA PDAC specimens after neoadjuvant therapy, these data suggest that posttreatment CT imaging is unable to differentiate between treatment-induced peritumoral fibrosis and viable tumor tissue and may be of limited utility to determine resectability [82].

Chatzizacharias et al. recently proposed and validated a dichotomized refinement to the LA classification based on pretreatment CT imaging findings at diagnosis into LA type A tumors with anatomic features suggesting surgery may be possible after neoadjuvant therapy (≤270° SMA encasement, >180° celiac encasement but without extension to the aorta, >180° encasement of the hepatic artery with option for reconstruction), and LA type B tumors for whom resection is unlikely (see Table 134.2). In their study set, 62% of LA type A patients underwent

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resection with an 80% R0 resection rate compared to only 24% of LA type B patients; they reported a median overall survival for resected patients of 38.2 months [79].

Beyond imaging findings, CA 19-9 response to neoadjuvant therapy has been shown to be a powerful predictor of outcome for LA patients treated with resection. Truty et al. recently showed that LA patients with an elevated or normal CA 19-9 level at diagnosis that normalized or remained normal at <37 U/mL after neoadjuvant therapy had a significantly longer median survival after resection (27.3 vs 10.5 months, P <0.001) [76]. At present, defining resection criteria for LA patients after neoadjuvant therapy remains an ongoing area of active research as traditional anatomic criteria are reassessed in the context of emerging biomarkers of treatment response.

Given the limited data available to guide patient selection, surgery for LA PDAC should be approached with caution and is best performed at high-volume centers with extensive experience in vascular resection and reconstruction. Additionally, the oncologic benefit of surgical resection for LA patients remains to be defined in larger, multiinstitutional prospective studies. Without these data, it is difficult to justify the procedure-associated risks attributable to these highly complex operations, including a 90-day mortality of 6.7% that is nearly double the expected value for high-volume hospitals after standard pancreatoduodenectomy [76,83].

In addition to surgery, alternative local ablative therapies have been proposed for the treatment of LA disease without metastases after induction chemotherapy. These include chemoradiation or stereotactic body radiation therapy (SBRT), irreversible electroporation (IRE), and radiofrequency ablation (RFA). However, none has demonstrated a survival benefit relative to chemotherapy alone for patients with LA PDAC and, at present, they should be reserved for patients with isolated local progression or for symptom management [18].

In addition to defining treatment options and prognosis, accurate staging for patients with advanced PDAC can help facilitate early palliative care consultation. The American Society of Clinical Oncology recommends a goals of care and advanced directive discussion, a full symptom evaluation, and a psychosocial status and social support assessment at diagnosis [84]. In patients with advanced PDAC, palliative care consultation is associated with a reduction in chemotherapy use near death, ED visits, ICU admissions, and hospitalizations [85].

Conclusion

Despite an extensive research effort, PDAC remains a devastating disease, in part due to the high percentage of patients who present with advanced tumors at diagnosis. Management of these patients requires a comprehensive clinical, radiologic, and endoscopic approach to define the tumor and stage. Treatment involves a multidisciplinary approach, and many times, the tools employed for clinical workup, as summarized here, can also be extrapolated for palliation of symptoms in the advanced setting. While emerging diagnostics have the potential to identify patients at an earlier stage, and incremental improvements in survival have been seen with the initiation of modern chemotherapeutics, much work remains to be done to improve outcomes for patients with advanced PDAC.

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Pancreatic Cancer: Indications for Resection

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Introduction

Pancreatic cancer has the worst survival outcomes among all gastrointestinal neoplasms. In the United States, an estimated 48 220 patients died of pancreatic cancer in 2021 [1]. This disease is now the fourth most common cause of death among all malignant neoplasms in the United States and Japan. Despite recent developments in surgical techniques and the clinical spread of effective chemotherapy, the prognosis of pancreatic cancer remains poor. However, surgical resection offers the only possibility of a cure. Although the morbidity and mortality of pancreatoduodenectomy (PD) were extremely high around 30–40 years ago, the morbidity and especially mortality of PD have since greatly decreased, and the operative mortality rate has fallen to 2.8% in Japan [2].

Clinical Criteria for Surgical Resection

Age and Concomitant Diseases

The peak incidence of pancreatic cancer occurs in the seventh and eighth decades of life. In our experience and that of high-volume centers, the morbidity and especially mortality of pancreatic resection have been greatly reduced, and no statistically significant difference in the mortality rate between patients aged >70 and <70 years has been reported [2]. In recent years, patients' age, comorbidities, performance status, and frailty have all been topics for discussion during multidisciplinary reviews. One of the few medical contraindications for PD is liver cirrhosis with ascites and portal hypertension.

Diagnosis and Staging

The diagnosis of pancreatic cancer is discussed at length in Chapter XX. For preoperative disease staging, multidetector-row computed tomography (MDCT) is an extremely useful diagnostic tool. Endoscopic ultrasound (EUS) is also useful for both diagnosis and staging of pancreatic cancer. Laparoscopy is another potentially valuable diagnostic tool for cancer staging, especially in patients with distant metastasis such as liver metastasis or peritoneal dissemination.

Biopsy

Confirmation of malignancy by biopsy is considered necessary before proceeding with surgical resection. Histologic diagnosis of pancreatic adenocarcinoma is often performed using fine-needle aspiration biopsy with either CT or EUS guidance. Pancreatic ductal blushing or biopsies can also be obtained at the time of endoscopic retrograde cholangiopancreatography. However, histologic or cytologic diagnosis of the malignancy is not always essential before surgical resection, such as in patients with a high clinical suspicion of pancreatic cancer.

Tumor-associated Antigens

The clinical usefulness of tumor-associated antigens, such as carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, DU-PAN-2, and SPan-1, has been advocated in connection with pancreatic cancer. In particular, a CA 19-9 concentration of >1000 U/mL might be correlated with the presence of distant metastasis or unresectable tumors in patients with pancreatic cancer [3].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Surgical Criteria for Resection

Preoperative Staging for Extent of Disease

There are no universally accepted criteria for resection of pancreatic cancer. However, it is clear that patients with liver, peritoneal, and pleural metastases derive no benefit from pancreatic resection. Therefore, preoperative staging to assess the extent of disease is indispensable.

The initial staging procedure involves the use of MDCT with contrast imaging, which reportedly predicts resectability well. Factors contraindicating surgical resection are extrapancreatic disease, obstruction of the portal or superior mesenteric vein, and direct tumor extension to the celiac axis and superior mesenteric artery (SMA), which are assessed by MDCT. Since 2006, the use of criteria to define the resectability status (resectable, borderline resectable, or locally advanced) according to the National Comprehensive Cancer Network (NCCN) guidelines (Table 135.1) has been widespread in the clinical setting [4]. This resectability classification accurately reflects survival outcomes [5,6]; thus, the fourth edition of the Japan Pancreas Society classification of pancreatic carcinoma proposed a similar scheme based on the probability of achieving R0 resection [7] (Table 135.2). As other diagnostic tool, EUS is complementary to CT, providing additional information for patients in whom CT shows no lesions in the pancreas or who have questionable involvement of major vessels or lymph nodes. Laparoscopy can reveal peritoneal deposits or liver metastasis that might be missed even with the use of MDCT.

Surgery for Pancreatic Cancer

The ideal surgical procedure for pancreatic cancer is isolated pancreatectomy. "Isolated" refers to *en bloc* resection using a nontouch isolation technique. Isolated distal pancreatectomy for cancer in the pancreatic body or tail is easier to perform than isolated PD, which is technically difficult because of the complex vascular anatomy in the pancreatic head region. However, isolated PD is also technically possible using a mesenteric approach [8] along with catheter bypass for the portal system [9] if necessary.

The indication for total pancreatectomy or PD in patients with pancreatic head cancer is an important clinical question in pancreatic cancer surgery. In this regard, previous studies using histopathologic and immunohistochemical analyses of total pancreatectomy specimens have clarified that cancer development from the head to the body or tail of the pancreas is continuous [10,11]. Thus, rapid intraoperative histopathologic diagnosis using frozen sections is indispensable to detect the development of intrapancreatic cancer during PD for pancreatic head cancer as well as during distal pancreatectomy for pancreatic body or tail cancer [12].

Historically, pylorus-preserving PD was performed in an effort to improve delayed gastric emptying and provide nutritional benefits [13]; however; no consistent data have suggested that pylorus preservation leads to better quality of life or improved nutritional status [14]. The superiority of recent laparoscopic or robotic surgery compared with open surgery for pancreatic cancer has not yet been clarified either surgically or oncologically.

Invasion

Local Invasion

Invasion into the distal bile duct, duodenum, stomach, or mesocolon can often be treated by *en bloc* resection. The retroperitoneal margin is often involved in pancreatic cancer. This margin includes connective tissues composed of extrapancreatic nerve plexuses behind the pancreas and adjacent to the SMA. Achieving a negative margin is considered an important prognostic factor [15], and the mesenteric approach is an ideal procedure to obtain negative surgical margins [8,16].

Extrapancreatic Nerve Plexus Invasion

Pancreatic carcinoma often invades the extrapancreatic nerve plexus [17–19]. There is no clear explanation for invasion of the extrapancreatic nerve plexus in the Union for International Cancer Control classification [20]; however, the precise anatomy of the extrapancreatic nerve plexus is explained in the third English edition of the Japan Pancreas Society classification [21] (Fig. 135.1).

The grade of intrapancreatic neural invasion correlates with extrapancreatic nerve plexus invasion, and the manner of neural invasion has no relationship with lymph node metastasis [19]. In patients with pancreatic head cancer, complete dissection of the extrapancreatic nerve plexus, especially the second portion of the pancreatic head nerve plexus, is necessary to obtain a cancer-free surgical margin (Figs 135.2 and 135.3). However, complete or right-half dissection of the nerve plexus around the SMA can cause refractory diarrhea after surgery [22], and the prognosis of pancreatic cancer invading the extrapancreatic nerve plexus is poor [15]. The main cause of cancer-positive surgical margins is extrapancreatic nerve plexus invasion [15,17,19]. Although the term "mesopancreas" is sometimes used [23], it is better to use the term "second portion of the pancreatic head nerve plexus."

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Table 135.1 Criteria defining resectability status.

Resectability status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline resectable	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumor contact with the SMA of ≤180° • Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of ≥180° without involvement of the aorta and intact and uninvolved gastroduodenal artery (some members prefer this criteria to be in the unresectable category).	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable	• Distant metastasis (including nonregional lymph node metastasis). *Head/uncinate process*: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch. *Body and tail*: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement.	*Head/uncinate process*: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV. *Body and tail*: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).

Vascular Invasion

Cancer invasion into the superior mesenteric and portal veins is common in patients with pancreatic head cancer. During the past 40 years, the operative mortality rate of PD combined with portal vein resection has decreased, and portal vein resection in pancreatic cancer surgery has become a safe procedure [24].

In our institution, 344 patients with pancreatic cancer underwent tumor surgery during the past 10 years, and portal vein resection was performed in 149 (43.3%) of these patients. Arterial resection was undertaken in 10 patients. The survival outcomes in these patients are shown in Fig. 135.4. Higher operative morbidity, more advanced stages of cancer, and a higher incidence of positive cancer invasion on the dissected peripancreatic margin were observed in the combined portal and arterial resection group.

Basically, upfront surgery is not recommended in patients with cancer invasion to the SMA, celiac artery, and common hepatic artery. One exception is pancreatic body cancer that invades the celiac axis. This type of cancer can be resected by distal pancreatectomy with celiac axis resection; however, introduction of neoadjuvant therapy should be considered as well. Thus, vascular resection is

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Table 135.2 Japan Pancreatic Society resectability classification.

Resectable: R
No tumor contact with SMV or PV or less than 180 degrees contact or invasion without occlusion. Clear fat Planes around SMA, CA, and CHA, showing no contact or invasion.

Borderline resectable: BR
Subclassified according to SMV/PV invasion alone or arterial invasion.

BR-PV (SMV/PV invasion alone)
No findings of contact and invasion of SMA, CA, and CHA. Tumor contact or invasion of the SMV/PV of 180 or more degrees or occlusion of the SMV/PV, not exceeding the inferior border of the duodenum.

BR-A (Arterial invasion)
Tumor contact or invasion of SMA and/or CA of less than 180 degrees without showing stenosis or deformity. Tumor contact or invasion of CHA without showing tumor contact or invasion of PHA and/or CA.

Unresectable: UR
Subclassified according to the status of distant metastasis.

UR-LA (Locally advanced)
Tumor contact or invasion of SMV/PV of 180 or more degrees or occlusion of SMV/PV, exceeding the inferior border of the duodenum. Tumor contact or invasion of SMA and/or CA of 180 or more degrees. Tumor contact or invasion of CHA showing tumor contact or invasion of the PHA and/or CA. Tumor contact or invasion of the aorta.

UR-M (Tumor with distant metastasis)
Distant metastasis including non-regional lymph node metastasis.

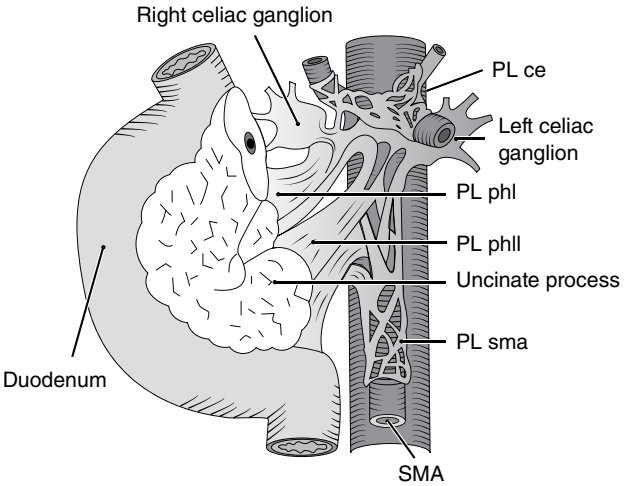


Figure 135.1 Extrapancreatic nerve plexus. PLce, celiac plexus; PLphI, first portion of pancreatic head nerve plexus; PLphII, second portion of pancreatic head nerve plexus; PLsma, nerve plexus around the superior mesenteric artery; SMA, superior mesenteric artery. Source: Japan Pancreas Society, Classification of Pancreatic Carcinoma, 3rd English edition, 2011.

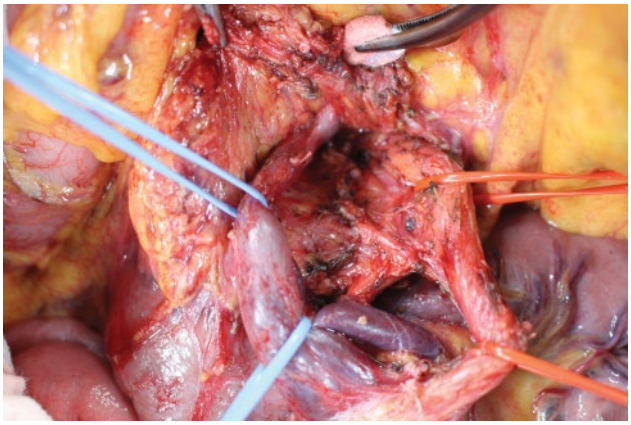


Figure 135.2 Exposure of the mesopancreas (second portion of the pancreatic head nerve plexus) using the mesenteric approach. The nerve plexus around the superior mesenteric artery is completely preserved in this case.

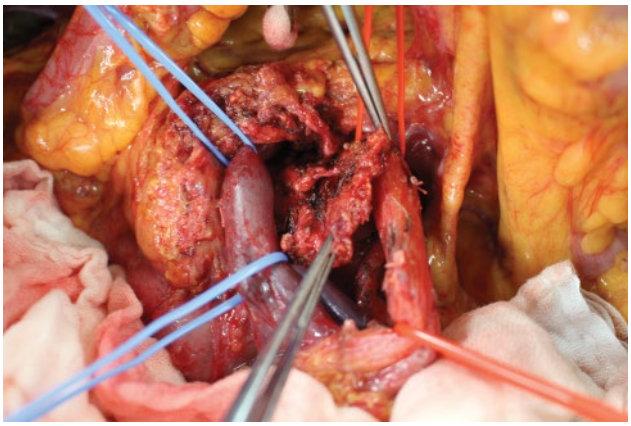


Figure 135.3 Total mesopancreas excision along the superior mesenteric artery.

indicated when cancer-free surgical margins are necessary. Conversely, there is no indication for extended resection in patients in whom surgical margins could become cancer positive, although such operations are conducted.

Metastases

Lymph Node Metastases

Optimum lymph node dissection is an important component of pancreatic cancer surgery. The high cancer incidence of 56–77% [25–28] in resected lymph node specimens is the reason for extensive dissection of lymph

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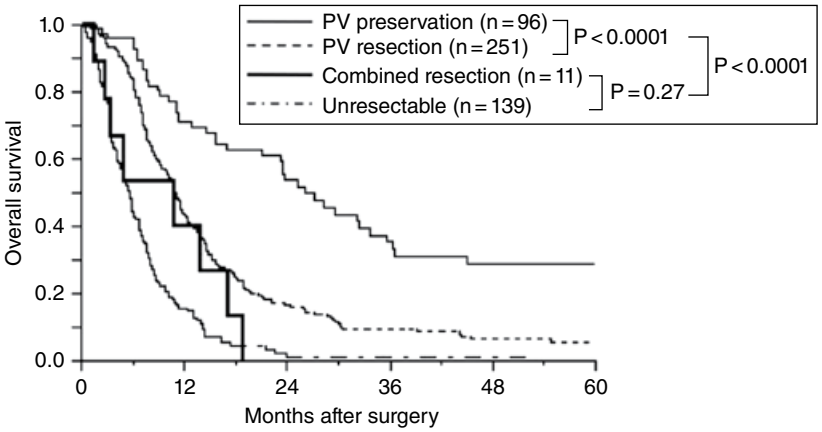


Figure 135.4 Cumulative survival rates of the portal vein (PV) preservation, PV resection, and arterial resection groups.

nodes in pancreatic cancer surgery. Notably, there are few reports concerning para-aortic lymph node metastasis: its reported incidence in pancreatic head cancer is 16% [26] and 26% [27,29], while that in pancreatic body and tail cancer is 13% [30] and 17% [31]. Although the efficacy of extended lymph node dissection in pancreatic cancer was historically suggested, it was not verified in some prospective controlled studies [32–36]. Therefore, extended dissection of lymph nodes, including the para-aortic lymph nodes, should not be considered a routine part of PD. However, although it does not have survival benefit, it might allow accurate staging.

Peritoneal Metastases

Peritoneal dissemination frequently occurs in pancreatic cancer and is one of the contraindications for surgical resection. Peritoneal deposits are too small to diagnose by preoperative CT or ultrasound images in patients with no ascites. Therefore, the diagnosis of peritoneal dissemination is confirmed by direct visualization using laparoscopy or at the time of surgical exploration. Using conventional staining, the incidence of cancer cells ranges from 0% to 17% [37–39]. However, high incidences of 58% [40], 39% [41], and 22% [39] have been obtained by immunocytochemical staining using monoclonal antibodies to tumor-associated antigens and cytokeratins.

Positive washing cytology is certainly a significant prognostic factor in pancreatic cancer; however, the clinical implications for surgical exploration in this situation have been discussed [42,43]. In the era of neoadjuvant chemotherapy in pancreatic cancer, it is weakly recommended that surgical resection with a surgery-first approach should not be performed in patients who have resectable pancreatic cancer with positive washing cytology.

Liver Metastases

Liver metastases are also common in patients with pancreatic cancer, and the expected survival period is so short that resection of the primary tumor is contraindicated [44]. Metastases are usually multiple in number, and there are no data showing longer survival by pancreatectomy either with or without resection of liver metastases.

Other Distant Metastases

Distant metastases to the lungs, bone, and supraclavicular lymph nodes are also contraindications for resection of a primary tumor.

Treatment Options for Recurrent Disease

In the management of pancreatic cancer, the high recurrence rate, even when curative resection is accomplished, is a major problem. There are various initial recurrence patterns, such as local or lymph node recurrence as well as peritoneal, liver, lung, and bone metastasis. Chemotherapy or radiotherapy should be a treatment option in these situations to prolong the patient's life. Among the various recurrence patterns, solely recurrent pancreatic cancer in the remnant pancreatic cancer might be an indication for surgery. This treatment option could offer a favorable outcome and a chance for cure in selected patients [45].

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Conversion Surgery for Initially Unresectable Disease

In our clinics, most patients (70–80%) diagnosed with pancreatic cancer have initially unresectable disease based on the NCCN criteria [4]. However, recent advances in multimodal treatment have provided better clinical responses; thus, conversion surgery for this initially unresectable disease has become widespread in our practice of pancreatic surgery. Even in patients with peritoneal metastasis, conversion surgery has been aggressively pursued after effective chemotherapy [46]. The indication for surgery is considered to be a clinical response or decreased concentrations of tumor markers (CA19-9, DU-PAN-2, etc.) after multimodal treatment [47]. Notably, early recurrence after surgery has been reported despite improved survival [48]. In this regard, a further prospective study is necessary to clarify the optimum indication for conversion surgery.

Effect of Clinical Volume

Several studies have revealed the effect of institutional volume on patients' clinical outcomes. In 1995, Lieberman et al. assessed 1972 pancreatectomies, including total pancreatectomy, performed in 184 institutions in the state of New York and showed that high-volume centers with >40 cases per year had significantly lower mortality than low-volume centers (4.0% vs 12.3%, respectively) [49]. Several other studies have also shown decreased mortality rates, shorter lengths of hospitalization, and lower overall costs in high-volume than low-volume centers [50]. Furthermore, negative margin status and five-year survival rates are reportedly higher in high-volume centers [51]. The definitions of high- and low-volume centers vary among all these studies, but the NCCN Panel recommends that pancreatic resections should be conducted at institutions that perform at least 15–20 pancreatic resections annually [4].

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Pancreatoduodenectomy for Pancreatic Cancer: Short- and Long-term Outcome after Kausch-Whipple and Pylorus-preserving Pancreatoduodenectomy

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Introduction

Dr William Stewart Halsted performed the first successful resection of a periampullary tumor in 1898. The first successful regional resection of the head of the pancreas was performed by Kausch and reported in 1912. The operative procedure of pancreatoduodenectomy was then popularized by Whipple, when he presented three patients to the American Surgical Association in 1935. During that era, and extending into the 1970s, pancreatoduodenectomy was performed only infrequently because of a hospital mortality in the range of 25%. Since the 1980s, pancreatoduodenectomy has become a safe procedure, performed in virtually any age group in high-volume centers, with an in-hospital mortality rate reaching less than 1% [1].

Pancreatic ductal adenocarcinoma (PDAC) is a common cause of cancer death and difficult to treat because of late presentation, a high propensity to metastasize, and treatment resistance. Long-term overall survival remains poor with a five-year survival rate of 12%. Nevertheless, for PDAC in the head of the pancreas, pancreatoduodenectomy is the only treatment modality that offers a chance for cure. With the development of multiagent neoadjuvant chemotherapy, more patients with PDAC will benefit from pancreatoduodenectomy [2].

Accurate diagnosis of PDAC relies on high resolution computed tomography (CT), preferred with a pancreas-specific protocol. Tissue diagnosis is necessary if neoadjuvant chemotherapy is part of the treatment plan. This can be achieved by endoscopic ultrasound-guided fine needle aspiration. PDAC without visible distant metastasis is currently classified into resectable, borderline resectable (BRPC), or locally advanced (LAPC) based on tumor–vein–artery relationships indicated by CT imaging at the time of diagnosis [3]. However, the utility of this resectability staging is increasingly being challenged as outcomes in PDAC are observed to be superiorly predicted by individual tumor biology than by anatomic criteria [4].

In this chapter, we will discuss the established short- and long-term outcomes after pancreatoduodenectomy for pancreatic cancer. In addition, we summarize the recent literature covering innovative developments to advance vascular and robotic resections.

Perioperative and Oncologic Outcomes

Approximately 10–20% of patients with PDAC present with resectable disease. Surgery with curative intent should achieve an R0 resection. The five-year overall survival rate after a successful resection is approximately 20% and close to 40% for those with negative nodes and margins [6,7].

Regardless of the disease stage in patients undergoing pancreatoduodenectomy (resectable vs BRPC vs LAPC), factors affecting the short-term surgical outcome include patient age, vessel resection and reconstruction, extension of lymph node dissection, and techniques of intestinal reconstruction. In patients aged 80 or above, pancreatoduodenectomy is associated with higher morbidity (55% vs 44%) and in-hospital mortality (4% vs 1%) [1]. Younger patients (below 45) have fewer complications after curative resections and better survival compared to older patients (over 70) [8].

In patients with resected BRPC/LAPC, Ferrone et al. reported no postoperative pancreatic fistula (POPF) in 40 patients after preoperative FOLFIRINOX and a lower postoperative morbidity rate (36% vs 63%) compared to 87 patients after upfront surgery [9]. In contrast, in a multicenter cohort of 171 and 375 patients with and

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without preoperative chemotherapy in Japan, Motoi et al. published similar postoperative morbidity rates (60% vs 52%) and POPF grade B/C frequencies (both 12%) after PDAC resection [10]. Extended lymphadenectomy is not universally indicated as randomized trials and systematic reviews have shown no benefit and more postoperative complications [11].

For reconstruction of the pancreatic duct, pancreaticojejunostomy is preferred at our hospital. POPF can be significantly reduced by a meticulous anastomosis with optimization of blood supply at the pancreaticojejunostomy. While similar with regard to POPF rate, pancreaticogastrostomy has a slightly increased incidence of postpancreatectomy hemorrhage compared to pancreaticojejunostomy (14% vs 9%) [12].

In an initiative to determine benchmark outcomes (benchmark defined as the 75th percentile of median values from participating centers), an international multicenter retrospective study analyzed almost 2400 patients with low-risk comorbidities after pancreatoduodenectomy. For in-hospital mortality, severe complications (Clavien–Dindo grade ≥IIIa) or overall complications, frequencies of ≤1.6%, ≤30.0%, and ≤73.0% were determined benchmarks (Table 136.1) [13].

Table 136.1 Published pancreatoduodenectomy (PD) benchmark values in patients with low-risk comorbidities. Benchmarks represent the 75th percentile of median values of the 23 participating international high-volume centers for each of the variables.

	PD	PD with mesoportal venous resection
Multicenter benchmark cohort	N = 2375 patients	N = 840 patients
In-hospital mortality	≤1.6%	≤4.0%
Duration of PD	≤7.5 hours	≤8.0 hours
Intraoperative blood transfusion rate	≤23.0%	≤27.0%
Length of hospital stay	≤15.0 days	≤14.0 days
90-day complications, any CD	≤73.0%	≤83.0%
90-day complications, severe (CD grade ≥IIIa)	≤30.0%	≤34.0%
90-day complications, CCI	≤20.9	≤23.0
Until discharge, POPF grade B/C	≤19.0%	≤14.0%
Until discharge, severe PPH (grade ≥III)	≤7.0%	≤7.0%

CCI, Comprehensive Complication Index; CD, Clavien–Dindo; POPF, postoperative pancreatic fistula (ISGPS); PPH, postpancreatectomy hemorrhage (ISGPS).
Source: Table compiled from published data by Sánchez-Velázquez et al. [13] and Raptis et al. [28].

In our institution's series of open pancreatoduodenectomy for 1687 patients with PDAC, the overall complication rate was 41%, with the most common complications including delayed gastric emptying (DGE, 16%), wound complications (11%), and POPF (6%) [6]. DGE and wound complications are often triggered by POPF. Patients with DGE might benefit from prokinetics such as metoclopramide and erythromycin. The antecolic location for the gastrojejunostomy has been shown to reduce the incidence of DGE in several publications. In a series of 160 pancreatoduodenectomies, Nakamura et al. analyzed that a side-to-side anastomosis for gastrojejunostomy on the greater curvature significantly reduced the incidence of DGE (2.5% vs 21% from end-to-side anastomosis) [14]. Our standard practice is therefore an antecolic side-to-side gastrojejunostomy. However, the influence of an antecolic vs retrocolic reconstruction on DGE has recently been questioned in a Japanese multicenter randomized controlled study (DGE in 12.6% vs 15.6%, $P = 0.06$) [15].

Oncologic outcomes after pancreatoduodenectomy for patients with PDAC are not optimistic. Although the 30-day mortality has been low at 1% since the 1990s, the median survival for PDAC remained at 19 months in our analysis of PDAC patients from 1981 to 2011 [6]. In this large series, resection margin status and lymph node positivity were associated with overall survival. For patients with negative resection margin and negative lymph node metastasis, the overall survival was 42 months compared to 18 months for patients with either positive margin or nodal metastasis. The commonly proven prognostic factors of five-year survival include tumor size, lymph node status, margin status, tumor differentiation, lymphovascular and perineural invasion, and adjuvant chemotherapy. Completion of the full course of adjuvant chemotherapy was an independent prognostic factor for survival, but time to treatment initiation after surgery was not [16]. Notably, these parameters are time dependent and their prognostic value is restricted to the first five years following pancreatoduodenectomy.

More recently, we characterized patterns and timing of recurrence in detail for patients after pancreatoduodenectomy for both upfront surgery and preoperative chemotherapy with subsequent resection. In the Baltimore upfront surgery cohort of 692 patients with complete follow-up data (96% pancreatoduodenectomy), 77% of patients developed recurrence with a median recurrence-free survival of 11.7 months. At the time of the initial recurrence diagnosis, of all patients who developed recurrence, 58% were at distant-only (most commonly hepatic), 24% at local-only, and 19% at local and distant locations [17]. In 581 patients who underwent preoperative chemotherapy (70% pancreatoduodenectomy), the median recurrence-free survival was 16.6 months (from start of systemic treatment)

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with detected recurrence in 70% of patients. Of all patients who developed recurrence, the initial location at onset was 40% at distant-only (mostly hepatic), 36% at local-only, and 24% at local and distant locations [18]. Here, 5-fluorouracil (5-FU)-based chemotherapy (mostly FOLFIRINOX) was predictive for improved overall but not recurrence-free survival when compared to gemcitabine-based treatment.

Whether patients benefit from upfront chemotherapy is intensively investigated. During the last decade, neoadjuvant chemotherapy and/or chemoradiation therapy have been increasingly utilized, especially for patients with BRPC and LAPC [9]. A metaanalysis of more than 4000 patients with PDAC showed that 32% of those with locally advanced disease underwent conversion surgery after neoadjuvant chemoradiation therapy, with a survival rate similar to patients with resectable disease [19]. The most commonly used regimen for neoadjuvant chemotherapy is FOLFIRINOX (5-FU, oxaliplatin, irinotecan, and leucovorin) if the patient has a good performance status. The rationale for using FOLFIRINOX is based on data extrapolated from the metastatic and adjuvant settings where FOLFIRINOX showed better improvements in median overall survival (11.1 months and 54.4 months, respectively) compared to gemcitabine [20,21]. An alternative established regimen for neoadjuvant chemotherapy is gemcitabine with nab-paclitaxel. This is also based on data from metastatic and adjuvant settings where the combination of both drugs improved overall survival (8.7 and 40.5 months) [2,22]. An alternative gemcitabine-based regimen is gemcitabine with oral capecitabine which demonstrated a median overall survival of 28.0 months as an adjuvant regimen (ESPAC-IV trial) [23].

A completed randomized controlled trial that tested preoperative gemcitabine-based chemoradiotherapy for resectable and BRPC patients is PREOPANC-1 conducted in the Netherlands. Although the initial results after a median follow-up 27 months demonstrated similar overall survival, a survival improvement was observed after an extended median follow-up of 54 months in the BRPC subgroup that underwent preoperative chemotherapy [24,25].

Several national trials are enrolling patients with resectable PDAC (SWOG S1505), BRPC (Alliance A201501), or LAPC (RTOG 1201) to determine the benefit of neoadjuvant chemotherapy and/or radiation. We are expecting level I evidence in the next few years regarding the benefit of neoadjuvant chemotherapy and/or radiation therapy. Prospective data are also being collected for patients with limited liver metastasis (oligometastatic, often defined as less than three lesions) and response to a full course of neoadjuvant chemotherapy (12 cycles or six months).

Outcomes of Vascular Pancreatic Surgery and Periadventitial Dissection

Approximately 70% of patients with PDAC and undetectable distant metastasis have tumor contact to a major surrounding vessel (mesoportal venous axis, common hepatic artery, and/or superior mesenteric artery) [5]. Therefore, surgeons face additional complexity in achieving a margin-free resection and safe operation [26]. In the late 1990s, early experience with resection and reconstruction of the mesoportal venous axis during pancreatoduodenectomy showed no 90-day postoperative mortality [27]. These encouraging results were reproduced at other institutions. In 2020, an international multicenter study that included almost 1500 patients with pancreatoduodenectomy and portomesenteric vein resection calculated an in-hospital mortality rate benchmark of below, further demonstrating the feasibility and safety of vein resections (see Table 136.1) [28].

For arterial resections, initial experiences were gained and safety achieved from distal pancreatectomies with celiac axis resections which often do not require reconstruction of hepatic arterial inflow due to retrograde blood supply through the intact arterial superior mesenteric-gastroduodenal arcade [29]. For hepatic artery and superior mesenteric artery reconstructions, an increased perioperative morbidity and mortality (5–14%) has been recognized across centers, although it is consistently decreasing with advancement on the learning curve at three high-volume centers (Heidelberg, Strasbourg, and Rochester). To prevent fatal events and achieve safety, applied strategies included optimization of vascular conduit characteristics (e.g., utilization of autologous veins) and relatively liberal conversion from pancreatoduodenectomy to total pancreatectomy (rules out POPF to protect the vascular anastomoses and conduit) [30–32].

Collectively, acknowledging the impact of surgical complexity on perioperative outcomes, Mihaljevic et al. directly compared 90-day mortalities of different types of pancreatoduodenectomies within their single-center cohort of 4000 cases accumulated during the last two decades. When differentiating for four types of pancreatoduodenectomy, perioperative mortalities were 2.9% (standard pancreatoduodenectomy), 4.2% (with mesoportal vein resection), 6.3% (with additional organ resection), and 10.3% (with arterial resection) [33].

An intriguing finding from pancreatoduodenectomy specimens after vein or arterial resections was that major vein or artery contact translated to a spectrum of invasion depths at the microscopic level. In a case series of 41 specimens that met these criteria, true invasion into the mesoportal vessel wall was confirmed in 41% of patients [34]. This feature, as well as the capability of invasion into small veins as apparent in 65% of pancreatic cancers, may reflect

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a selective advantage of the tumor to metastasize hematologically (following venous flow into the liver) [35]. As observed in veins, however, tumor contact with the common hepatic or superior mesenteric artery also does not universally mean true wall invasion. In contrast to the thin tunica media of veins, this layer is prominent in arteries through abundant elastic fibers and smooth muscle cells. Although dynamically exposed to the systemic pulse wave, this relatively rigid texture is exploitable surgically.

Pioneered in 2017 by Miao et al. in patients after induction chemotherapy, entering and dissecting off the adventitial plane on top of the tunica media allowed for margin-free resection while ensuring arterial continuity. This technical refinement and substep during pancreatic surgery has been termed (peri)arterial divestment or periadventitial/subadventitial dissection [36]. A radiologic "halo sign" was described to be potentially predictive for the feasibility of this technique, whereas a "string sign" may be indicative of tunica media invasion with a consecutive mass effect [36]. While this novel development of an arterial resection-sparing technique is still being investigated, case series suggest a perioperative mortality of 4.7–8.0% and superiority over arterial resection (adjusted odds ratio 3.31, $P = 0.01$) [31,37].

In addition to safety, oncologic efficacy of the proposed implications from the histologic tumor–vessel relationship on surgical techniques needs to be determined. Patients with arterial involvement frequently undergo preoperative chemotherapy according to guidelines for LAPC. Loos et al. found equal long-term outcomes between the cohorts of 190 patients with periadventitial dissection and 195 patients with arterial resection (combined postoperative median overall survival 20.1 months) [31]. In contrast, upfront surgery is performed in the majority of patients with isolated venous involvement. In almost 1200 patients with pancreatoduodenectomy and mesoportal venous resection from 23 centers, retrospective survival analyses revealed higher R0 rates (57% vs 47%) and superior oncologic outcomes (five-year overall survival 29% vs 18%) in the 26% of patients who underwent neoadjuvant treatment [38]. However, inferences need to be carefully reevaluated with the acquisition of prospectively randomized controlled trial data.

Outcomes of Minimally Invasive Pancreatoduodenectomy

After surgeons succeeded in advancing open pancreatoduodenectomy toward a safe operation, efforts emerged to perform resection in a minimally invasive fashion. A total laparoscopic pancreatoduodenectomy was first described in 1994 by Gagner et al. in a patient with chronic pancreatitis.

Recently, a large multicenter randomized controlled trial conducted in China that enrolled 656 patients investigated safety and postoperative complications of laparoscopic vs open pancreatoduodenectomy. The results demonstrated similarity in postoperative 90-day mortality rates (both 2%), severe complication rates (Clavien–Dindo grade ≥IIIa, 29% vs 23%, $P = 0.13$) and overall morbidity assessed by the Comprehensive Complication Index (median 8.7 vs 0, $P = 0.06$). Postoperative length of stay was one day shorter after laparoscopic resection (median 15 vs 16 days, $P = 0.02$). Importantly, both procedures were exclusively performed by surgeons with high laparoscopic pancreatoduodenectomy experience (at least 104 prior cases) [39]. In potentially less experienced hands, even after completion of a specifically designed training curriculum, securing safety remains controversial as presented in the multicenter randomized controlled Dutch LEOPARD-2 trial (terminated prematurely after 50 laparoscopic procedures due to postoperative mortality in five patients) [40].

Besides the utilization of rigid laparoscopic instruments for pancreatoduodenectomy, robotically assisted techniques have emerged which substantially increase dexterity for the operating surgeon. Pioneered in 2001, Giulianotti et al. applied the DaVinci® Surgical System for a hybrid pancreatoduodenectomy (resection laparoscopically, gastrointestinal reconstructions robotically) and eventually the total robotic approach. Starting in 2008, Zeh et al. established a program in Pittsburgh implementing structured training with evolving anatomic criteria for patient selection. While experience accumulated, a well-recognized finding was the acknowledgment of learning curves for optimized performance of the individual surgeon (approximately 20 cases to reach the benchmark conversion-to-open rate and 80 cases for operative time) [41]. Their retrospectively reported short-term survival of 500 consecutive robotic pancreatoduodenectomies demonstrated 30- and 90-day mortality rates of 1.4% and 3.1% [42]. Comparable 90-day mortality rates were achieved in international high-volume centers in Shanghai (2.7%, 450 patients), Pisa (3.6%, 112 patients), and Baltimore (2.1%, 96 patients) [43–45].

When compared to open pancreatoduodenectomy, two analyses of propensity score-matched cohorts coherently suggested no differences in perioperative mortality, anastomotic insufficiencies (any site), and POPF rate. In contrast, the robotic approach resulted in decreased wound infections, intraoperative blood loss, and postoperative hospital length of stay [43,45]. Notably, most of the available data reported robotic pancreatoduodenectomies without venous end-to-end or short segmental reconstructions. Nevertheless, a few centers started to

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explore techniques to achieve segmental mesoportal venous resection and arterial resection with reconstruction robotically [46,47]. Overall, data from randomized controlled trials comparing robotic vs open pancreatoduodenectomy are unavailable but under way and will be essential to confirm the proposed inferences (EUROPA trial).

Furthermore, oncologic efficacy is yet to be determined. To meet this aspiration, critical state-of-the-art surgical techniques of the open approach for radical tumor margins, such as retropancreatic nerve plexus and TRIANGLE resections (retropancreatic nerve plexus resection within triangular-shaped space between the mesoportal vein, common hepatic artery and superior mesenteric artery with periadventitial dissection of arteries), were recently demonstrated to be feasible (Fig. 136.1) [48]. Therefore, they should be transferred to the robotic procedure to deliver noninferior oncologic outcomes.

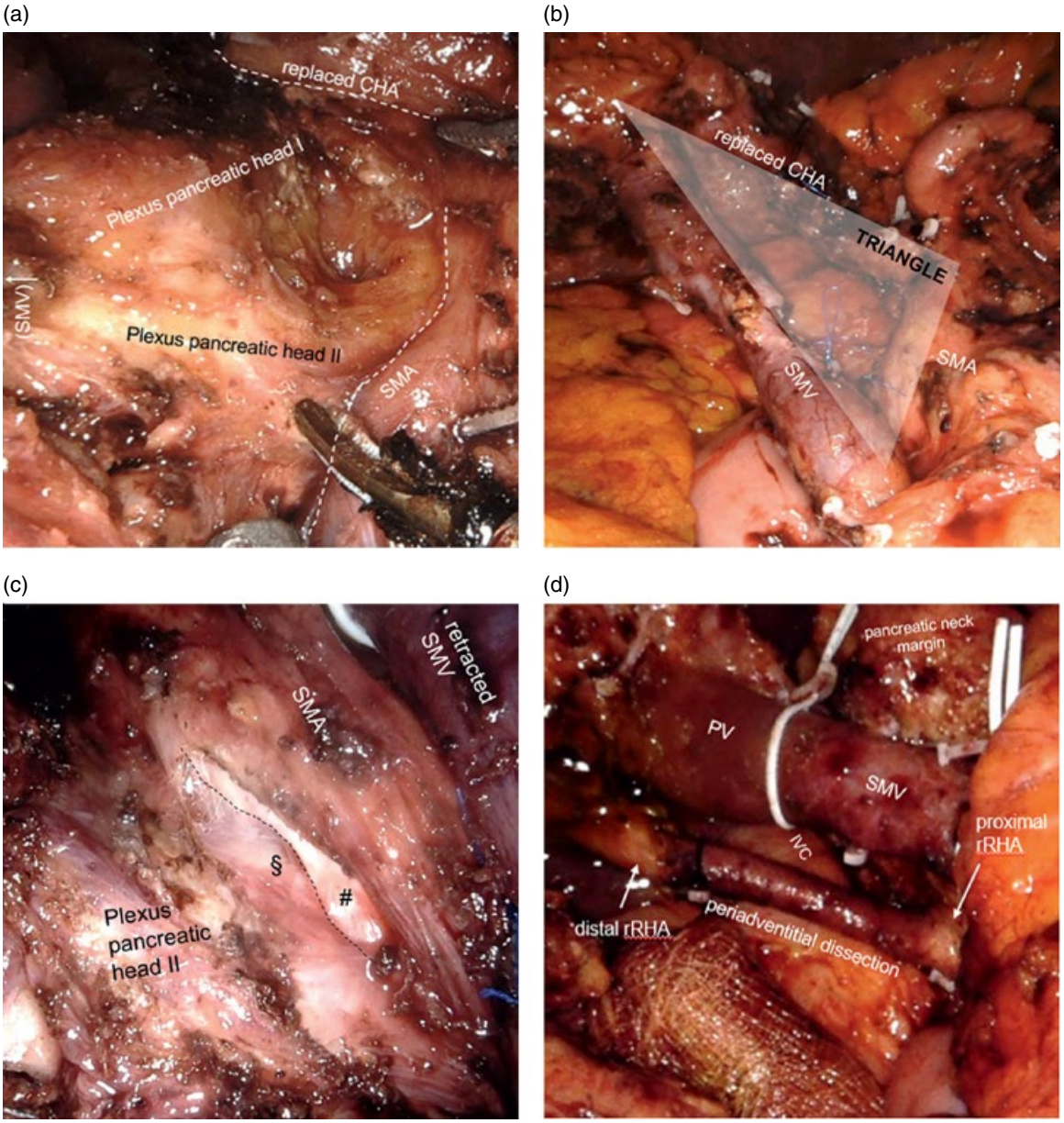


Figure 136.1 Achieving a radical dorsal resection margin during robotic pancreatoduodenectomy. Illustration of the retropancreatic nerve plexuses before resection (a) and after resection (b) within the TRIANGLE area. Periadventitial dissection of arteries such as the superior mesenteric artery (c; # marks the tunica media and § the dissected internal surface of the tunica adventitia) and replaced right hepatic artery (d) is feasible and should be considered. CHA, common hepatic artery; IVC, inferior vena cava; PV, portal vein; rRHA, replaced right hepatic artery; SMA, superior mesenteric artery; SMV, superior mesenteric vein. *Source:* [48], Kinny-Köster et al. (2021). Adapted with permission from Springer Nature.

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Besides surgical performance in regard to specimen margin, lymphadenectomy, and *en bloc* resection, survival is strongly determined by tolerability, timing, and response to systemic chemotherapy [7]. The often underlying micrometastatic disease burden of PDAC at the time of diagnosis is recognized due to the high probability to demonstrate distant recurrences (33–59% of patients after upfront surgery, discussed above) [17,49]. More specifically, retrospective analyses of recurrences in the Baltimore cohort after 692 upfront pancreatoduodenectomies revealed a recurrence-free survival of 18 vs 10.5 months ($P = 0.008$) in patients who underwent adjuvant vs no adjuvant chemotherapy [17]. Further dissecting the reasons for failing administration of adjuvant chemotherapy, Wu et al. found that severe postoperative complications (Clavien–Dindo grade >IIIa) after pancreatoduodenectomy (vast majority underwent an open approach) were associated with no receipt of adjuvant chemotherapy and that any complication independent of severity was associated with a delay in systemic treatment [50]. In contrast, when quantifying the cumulative dose of adjuvant chemotherapy, prospectively randomized data from the ESPAC-3 trial illustrated that completion of systemic treatment (six cycles of either gemcitabine or fluorouracil/folinic acid) was strongly associated with improved survival compared to less than six cycles of chemotherapy in a cohort of 985 patients (median survival 28.4 vs 19.3 months, $P < 0.001$) [16].

Taken together, robotic pancreatoduodenectomies, if technically feasible and performed safely, may be oncologically valuable through a favorable tolerability of adjuvant chemotherapy due to decreased complications, systemic inflammation, and length of hospital stay as surrogates for subsequently enhanced recovery.

Future Perspectives

Promisingly, our expanding understanding of the genetic PDAC features is driving the concept of tumor biology which may translate into clinical decision making. This paradigm is opposing the current practice of predominantly relying on anatomic-morphologic criteria. Furthermore, focus on tumor biology is reflected by contemporary research efforts to identify patients who benefit from preoperative treatment and who have predicted sensitivity to distinct chemotherapeutic regimens. A modern surgical posture to offer curative-intent care has resulted in the emergence of vascular pancreatic surgery as a discipline and implies a versatile skillset of the operating team.

Future technologic innovations and results from rigorously conducted randomized controlled trials will determine the ability of the robotic approach to produce optimized clinical outcomes. Surgery together with early detection and improved efficacy of systemic treatments, potentially immunotherapy as an alternative to chemotherapy, will lead to better outcomes in patients with PDAC in the future.

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Left Pancreatectomy for Body and Tail Cancer

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Introduction

Approximately 25% of patients with pancreatic ductal adenocarcinoma (PDAC) present with a tumor in the pancreatic body or tail [1]. Patients with these tumors typically present more often with larger tumors and metastatic disease compared to patients with PDAC in the pancreatic head (metastatic disease: head 42%, body 69%, tail 84%; P <0.001; tumor size >4 cm: head 21%, body 40%, tail 51%; P <0.001) [1]. In fact, less than 15% of PDAC of the body and tail tumors is resectable at initial presentation [2,3].

Pancreatic cancer is defined in this chapter as pancreatic ductal adenocarcinoma (PDAC). In the literature, different definitions are used which often results in different interpretations of oncology outcomes, including survival. According to the 2019 World Health Organization classification of tumors of the digestive system, PDAC may also include, albeit rarely, adenosquamous carcinoma, colloid carcinoma (mucinous noncystic carcinoma), hepatoid carcinoma, medullary carcinoma, signet ring cell carcinoma, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells [4]. Precursor lesions, including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms and mucinous cystic and other types of lesions (e.g., acinar cell), are considered a different entity and not classified as PDAC.

Diagnosis of Pancreatic Body and Tail Cancer

Diagnosis and treatment modalities are optimally decided by a multidisciplinary team. The preferred imaging in case of suspicion of pancreatic body or tail cancer is abdominal computed tomography (CT) (pancreas protocol) so vascular involvement can be assessed. If the CT images are inconclusive, endoscopic ultrasound (with or without fine needle aspiration [FNA] or biopsy [FNB]) can provide additional information. Magnetic resonance imaging (MRI) and positron emission tomography (PET)-CT scan are not generally used as diagnostic modalities but can be of important value in specific cases. In addition, tumor markers (carbohydrate antigen [CA] 19-9 and carcinoembryonic antigen [CEA]) should be measured. However, these tumor markers are not sensitive enough to differentiate between a benign and malignant tumor [5–8]. Pathology proof is not mandatory before performing surgical resection, unless in the setting of neoadjuvant treatment.

Staging and Resectability

Pancreatic tumors are staged according to the 2016 Union for International Cancer Control (UICC) 8th edition TNM classification for pancreatic carcinoma [9]. In this classification, T-stage is based on tumor size and vascular involvement. Different criteria for resectability of pancreatic body and tail cancer are available. Tumor involvement of the celiac axis is generally regarded as a criterion for unresectable [10–13] or borderline resectable disease [14–17] (Table 137.1). In case of borderline or unresectable tumors, neoadjuvant or palliative/induction treatment should be considered. With the introduction of FOLFIRINOX chemotherapy, in case of unresectable tumors, restaging after 4–6 cycles of chemo(radio)therapy could be performed and in case of tumor regression to borderline tumor, diagnostic laparoscopy or laparotomy could be considered [18].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Table 137.1 NCCN 2.201 resectability criteria for pancreatic body and tail cancer.

Vascular structure	Resectable	Borderline resectable	Locally advanced
Arteries	No tumor contact with: celiac axis (CA) common hepatic artery superior mesenteric artery (SMA)	≤180^0 contact with CA >180^0 contact with CA **without** involvement of the aorta and gastroduodenal artery	>180^0 contact with SMA Contact with the CA **and** aortic involvement
Veins	No tumor contact with: portal vein (PV) superior mesenteric vein (SMV) ≤180^0 contact without contour irregularity	>180^0 contact with the PV/SMV ≤180^0 contact with the PV and SMV **with** contour irregularity/thrombosis and suitable for complete resection and reconstruction tumor contact with the inferior vena cava	Unreconstructible PV/SMV (can be due to tumor or bland thrombus)

Source: Adapted from NCCN guideline (version 2.2021).

Surgical Technique

In case of resectable disease, surgical resection in combination with systemic treatment is the treatment of choice and provides the highest chance of cure. Resection of the pancreatic body and tail is usually referred to as distal pancreatectomy. Surgery for patients with a proven or suspected malignancy in the pancreatic body or tail is specifically referred to as radical antegrade modular pancreatosplenectomy (RAMPS), proposed by Strasberg et al. [19,20] for open surgery, and laparoscopic radical "no-touch" left pancreatosplenectomy (LRP) for minimally invasive left pancreatectomy, proposed by Abu Hilal et al. [21]. Both techniques allow safe and complete oncologic resection of the pancreatic body and tail. It is advised that if an open resection is performed, a diagnostic laparoscopy is carried out first to check for peritoneal or liver metastasis [22].

The goal of surgery is to perform a radical (R0) resection and an adequate regional lymph node dissection. Extended resections (beyond pancreas and spleen) should be classified according to the International Study Group on Pancreatic Surgery extended resection guideline [23].

Whichever procedure is performed and whichever technique is followed, the bottom line is that splenectomy and resection of Gerota's fascia are advised in left pancreatectomy for PDAC or high suspicion of PDAC. For lymphadenectomy, the ISGPS criteria for lymph node resection should be followed [24]. These include resection of lymph node stations 10, 11, and 18 for tumors of the pancreatic body and tail (Fig. 137.1). Additional resection of stations 8 and 9 will be performed when tumors affect the body of the pancreas. In specific cases, an extended lymphadenectomy could be considered.

Minimally Invasive vs Open Resection

Laparoscopic distal pancreatectomy was first described by Gagner in 1996 [25]. In 2019, the first multicenter randomized trial was published: the LEOPARD trial, comparing minimally invasive distal pancreatectomy (laparoscopic and robot) with open distal pancreatectomy in 14 Dutch hospitals. This trial showed a two-day reduction in time to functional recovery, less blood loss, and less delayed gastric emptying seen after the minimally invasive approach. Other complications (including postoperative pancreatic fistula) were comparable. Quality of life in the first 30 days after surgery was improved and overall costs were less after minimally invasive distal pancreatectomy [26]. Quality of life and costs were comparable between groups after one year [27]. In 2020, a second (monocenter) randomized trial was published: the LAPOP trial. This showed shorter hospital stay (one day less), faster time to recovery, and less blood loss after laparoscopic distal pancreatectomy. Postoperative complications were comparable between groups [28].

However, both the LEOPARD and LAPOP trials included only a minority of patients with PDAC and are therefore insufficient to draw solid conclusions on the oncologic efficacy of MIDP. Therefore, the oncologic safety of MIDP remains a subject of debate which hampers its further implementation [29,30]. A European survey on minimally invasive pancreatic surgery performed in 2016 demonstrated that 31% of participating surgeons expected MIDP to be inferior to open distal pancreatectomy (ODP) concerning oncologic outcomes [31].

Based on these results, the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS) initiated an international propensity score-matched study including 1377 patients after distal pancreatectomy (minimally invasive or open) for PDAC [32]. This study showed

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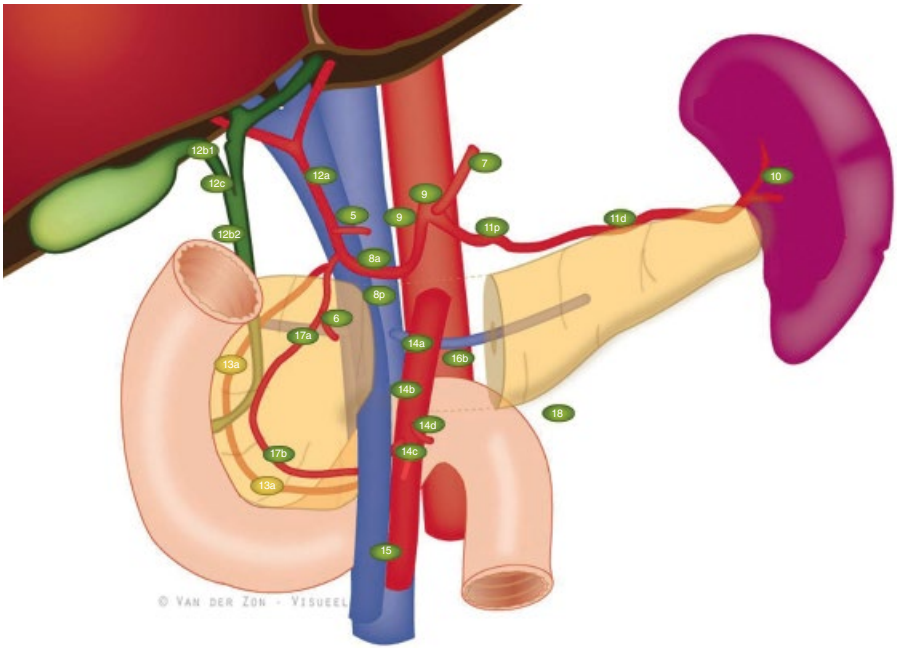


Figure 137.1 Anatomy and lymph node stations for pancreatic surgery. *Source:* Gastroenterology Research and Practice. Illustration by Van Der Zon Visueel.

higher R0 resection rates for MIDP, but lower median number of harvested lymph nodes with similar survival months for MIDP and ODP [32]. However, MIDP was associated with lower rates of lymphovascular tumor invasion, perineural tumor invasion, and lower lymph node stage, suggesting that, despite matching, treatment allocation bias could still have influenced these results. Therefore, in 2019 the DIPLOMA trial was initiated. This European multicenter, patient- and pathologist-blinded, noninferiority randomized trial completed recruitment of all 244 patients in 2021. Primary outcome of this trial is radical (R0) resection. The short-term outcomes are expected in 2023 [22].

Radical Antegrade Modular Pancreatosplenectomy (RAMPS)

In 2003, Strasberg et al. described a technique for safe oncologic resection of malignant tumors of the pancreatic body and tail [19]. The RAMPS technique relies on early control of major blood vessels, improved visualization of the posterior resection margin, and extensive lymph node dissection [19,20].

The dissection takes place in an antegrade fashion (from right to left). The parenchyma is dissected first at the pancreatic neck using a stapler and the underlying vascular structures are exposed. The splenic vessels are ligated first, followed by extended dissection of celiac and superior mesenteric artery nodes. The final resection plane is decided based on tumor extension. The anterior renal fascia (i.e., Gerota) is always excised; if the pancreatic lesion invades the ipsilateral adrenal gland or further, the resection plane extends towards the anterior surface of the kidney, behind the perinephric fat (posterior RAMPS).

Improved five-year survival has been reported in patients with PDAC of the left pancreas who underwent RAMPS but the available evidence is limited [20,34]. Modifications of the RAMPS procedure can also be found in the literature [34,35]. Randomized trials comparing standard distal pancreatectomy and RAMPS will be needed to support the improved oncologic outcome of these techniques.

Laparoscopic Radical "No-Touch" Left Pancreatosplenectomy

This technique was proposed by Abu Hilal et al. in 2016 [21,36]. In that time, laparoscopic left pancreatectomy became more and more popular. The technique was developed to facilitate an oncologic laparoscopic resection introducing specific laparoscopic tips and tricks. The most important steps are mobilization of the pancreas (including Gerota's fascia) proximal and distal from the tumor, permitting a pancreas "hanging" on to slings and therefore avoiding tumor touching and manipulation. The dissection of the inferior margin and the development of the posterior plane are continued

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clockwise towards the splenic/superior mesenteric vein junction. Subsequently, the dissection is continued in a medial–lateral direction. The pancreas is transected at the neck, keeping a clear margin from the lesion. A full nodal clearance, including station 8, and splenectomy is performed.

Distal Pancreatectomy with *En Bloc* Celiac Artery Resection

Distal pancreatectomy with celiac artery resection (DP-CAR) is performed for PDAC of the pancreatic body or tail with involvement of the celiac artery [37]. After resection of the celiac axis, compensatory retrograde flow from the superior mesenteric artery via the inferior pancreatoduodenal arcades feeds the pancreatic head and the liver (Fig. 137.2). In the current era, the use of neoadjuvant FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) may lead to higher downstaging rates for pancreatic cancer which may increase the application of this type of surgery [18,38]. In 2017, Klompmaker et al. [39] collected data on DP-CAR in 20 centers from 12 countries. Data on 68 patients were collected and in 62 patients, the pathology report showed PDAC. Outcomes showed high major morbidity (25%) and 16% 90-day mortality. Median overall survival was 18 months and 82% received neoadjuvant or adjuvant chemotherapy.

These outcomes show the importance of strict patient selection for performing DP-CAR. A flowchart guiding this patient selection was also proposed by Klompmaker et al. (Fig. 137.3).

Standardized Pathology Reporting

Currently, consensus regarding macroscopic assessment of distal pancreatectomy specimens is lacking. Since the most recent (8th edition) of the TNM classification is mostly based on tumor size, standardized measuring and reporting are necessary. As part of the previously mentioned DIPLOMA trial [33], a standardized pathology assessment is proposed [40]. This approach includes standardized measurement of the resected part of the pancreas and inking of relevant surgical margins and anatomic surfaces. Then, measurement of tumor size (for T-stage) is performed and assessment of splenic vessel involvement (and other organs if present) (Fig. 137.4). All margins are assessed and relevant blocks are selected to confirm these parameters microscopically. This standardized assessment will hopefully improve uniform reporting of outcomes (most importantly R0 resection) in the future.

Postoperative Pancreatic Fistula

Morbidity rates after distal pancreatectomy are high (up to 50%), even in high-volume centers [41]. Postoperative pancreatic fistula (POPF) is the most common major

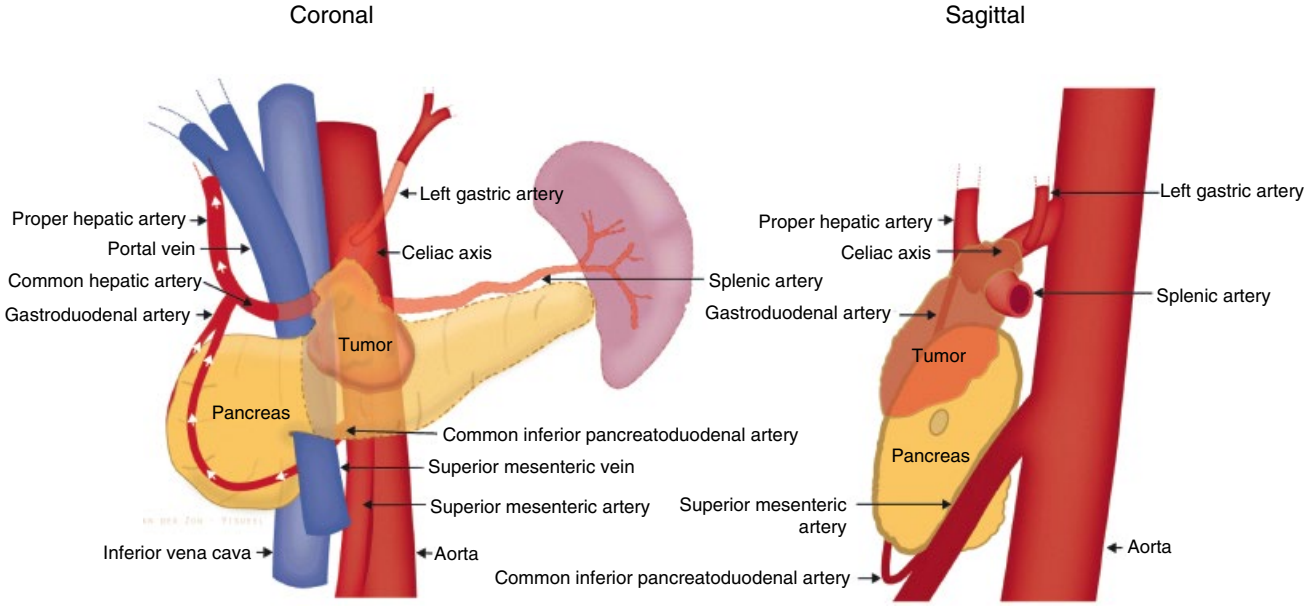


Figure 137.2 Anatomy of DP-CAR resection. *Source:* Journal of Gastrointestinal Surgery. Illustration by Van Der Zon Visueel.

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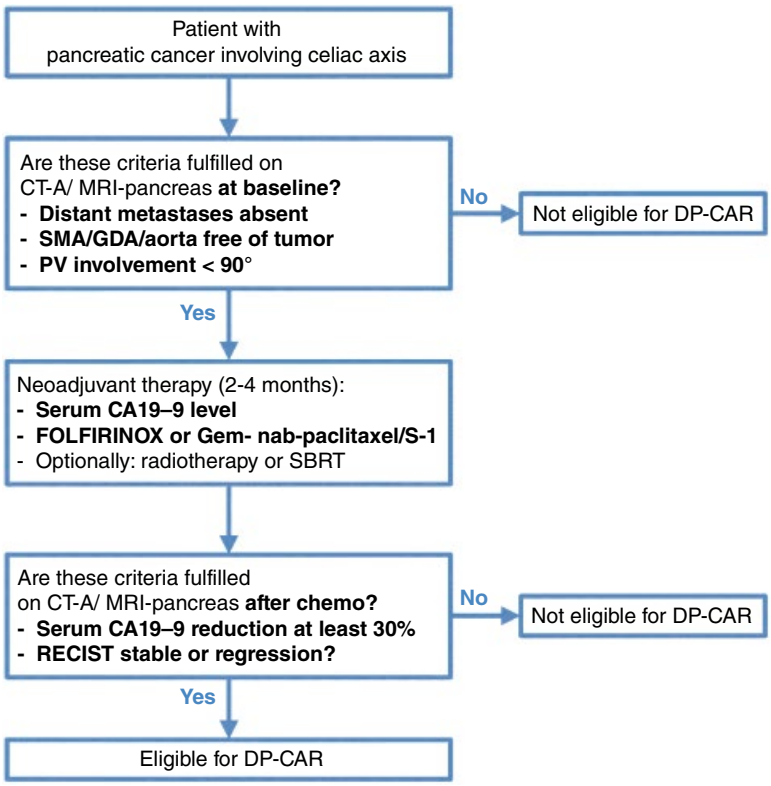


Figure 137.3 Flowchart for patient selection for DP-CAR. *Source:* Journal of Gastrointestinal Surgery.

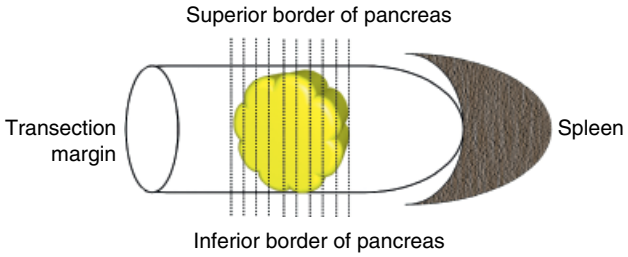


Figure 137.4 Standardized block taking for pathology specimens after distal pancreatectomy.

complication of this procedure, with reported rates up to 20–30% [42–44]. POPF is classified according to the 2016 ISGPS guideline [43]. Risk factors for the development of POPF after distal pancreatectomy identified in the literature are younger age, smoking, obesity, hypoalbuminemia, neuroendocrine or nonmalignant pathology, pancreas thickness, concomitant splenectomy, extensive lymphadenectomy, and vascular resection [45–48].

Numerous studies investigating ways to minimize POPF after distal pancreatectomy have been published [49–53]. Multiple closure techniques have been proposed over the years; suturing, (reinforced) stapling, stepwise compression stapling, direct ligation of the main pancreatic duct, and fibrin sealant patches [49–55]. So far, no high-quality evidence has been presented in favor of one of these approaches; this was also stated in the 2020 expert consensus guidelines by the ISGPS [56].

Routine Surgical Drain Placement

The benefit of routine placement of postoperative drain(s) on the surgical bed after distal pancreatectomy remains unclear. The goal of this prophylactic drain placement is to recognize a pancreatic leak early and allow controlled drainage of the pancreatic fluid when a leak is present. However, it is also suggested that routine drain placement could facilitate the development of POPF or introduce bacteria in the initially sterile peripancreatic fluid [57,58]. Alternatively, a selected drain strategy based on preoperative risk factors is proposed. But evidence showed that the prediction of POPF after distal pancreatectomy remains difficult [46].

Evidence on routine prophylactic versus no drain placement is limited. One multicenter randomized trial found no difference in complications and POPF rates in the drain vs the no-drain group [59]. A recent systematic review by Lyu et al. confirmed that clear evidence on prophylactic drainage after DP is lacking [60]. Therefore the PANDORINA trial was developed. This binational

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Table 137.2 Postoperative complications.

Postoperative complication	Percentage
New-onset diabetes mellitus	7–28%
Exocrine insufficiency	12%
Clavien–Dindo score 3 or higher	17–22%
Postoperative pancreatic fistula grade B/C	20%
Delayed gastric emptying grade B/C	2–7%
90-day mortality	2–4%
90-day readmission	14%

(The Netherlands and Italy), multicenter, randomized controlled trial will randomize 280 patients into drain vs no-drain groups and will compare postoperative morbidity and POPF rates [61]. Results are expected in 2023.

Postoperative Metabolic Complications

Pancreatic surgery is associated with several metabolic complications such as new onset or worsening of preexistent diabetes mellitus (Table 137.2). High-quality prospective studies focusing on this complication are lacking. A systematic review showed a cumulative incidence of new-onset diabetes varying from 7% to 28% [62]. Among these patients with new-onset diabetes, 36–100% were reported to have insulin-dependent diabetes. New-onset diabetes is less often seen after left pancreatectomy for cancer compared to chronic pancreatitis. Risk factors associated with the development of new-onset diabetes are age, higher BMI, higher preoperative Hba1c, fasting plasma glucose, and lower remnant pancreatic volume [63].

Data regarding a switch from insulin-independent to insulin-dependent diabetes is lacking although one study did report that an increase in diabetic medication claims was seen in patients who preoperatively already received diabetic medication [64]. Even less information is available on exocrine insufficiency after distal pancreatectomy; a median prevalence of 12% was mentioned but this was based on subjective diagnosis without additional testing [65].

Conclusion

Patients diagnosed with PDAC of the pancreatic body and tail more often present with locally advanced or metastatic disease. In those cases where the tumor is resectable on preoperative imaging, oncologic surgery with negative margins combined with neo- or adjuvant chemotherapy provides the best survival rates. Postoperative morbidity rates remain relatively high. Data of future trials will give more insight into the oncologic safety of MIDP.

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Total Pancreatectomy: Indications and Limitations

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Introduction

Total pancreatectomy (TP) was first described by Rockey in 1943 [1], and its popularity increased during the 1960s [2]. The rationale for TP was to avoid pancreatic anastomosis-related complications and to optimize oncologic surgical radicality in pancreatic cancer patients. After the first enthusiasm for TP, results of large series of TP for pancreatic cancer were published in the late 1980s and 1990s [3–8]. They showed that TP could not improve the rates of R0 resections for pancreatic cancer, had perioperative mortality rates similar to or higher than partial pancreatic resections (13–27%), and no survival advantage was found [3–8]. Furthermore, TP was complicated by permanent pancreatic endocrine and exocrine deficiencies [9]. These results led to surgeons largely abandoning TP and no longer considering it as a viable option for pancreatic disease.

However, recently, surgical techniques, perioperative management, and the development of high-volume surgical centers have advanced, and TP can be performed with lower mortality rates than in the past [10–14]. Furthermore, with improved long-acting insulin and high-quality enzyme replacement formulations, brittle diabetes mellitus and malabsorption from exocrine insufficiency can be controlled more effectively after TP [10–15].

In this chapter, recent indications and limitations of TP are considered, based on short- and long-term outcomes after TP reported in the literature.

Elective Total Pancreatectomy and Salvage Completion Pancreatectomy

Total pancreatectomy is classified mainly into elective TP and salvage completion pancreatectomy for complications after partial pancreatectomy [12,16,17].

An elective TP includes primary TP and two-stage TP after previous partial pancreatic resection. Primary elective TP is performed in cases with central tumor location in the pancreas or multifocal tumors with preoperatively planned TP, the intraoperative finding of a more extended tumor than preoperative imaging suggested, or tumor-positive intraoperative frozen pancreatic transection margin with the need for extension of the pancreas. Two-stage elective TP is performed in cases of tumor recurrence or new tumors developing in the remnant pancreas after partial pancreatic resection.

Indications for salvage completion pancreatectomy arise when the clinical options for the patient with a severe complication after pancreatic resection, such as pancreatic fistula or abdominal hemorrhage, and conservative treatment strategies have been exhausted [12,17].

Perioperative Outcomes After Total Pancreatectomy

Elective TP

High perioperative mortality and morbidity rates after TP have long been reported [3–8] but a dramatic decrease has been achieved in recent years by improvement of surgical techniques and postoperative management [10–13,16,17]. Recent single-institution series have reported perioperative mortality rates ranging from 3% to 12.5%, and perioperative morbidity rates ranging from 25% to 54% (Table 138.1) [10,12,16–21]. Advanced age (>70 years), the presence of comorbid conditions, long operative time (>420 minutes), high blood loss (>2000 mL), and/or arterial resections were reported as independent risk factors for mortality after TP [21,22].

Surgical complications after TP include delayed gastric emptying, intraabdominal abscess, abdominal hemorrhage,

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Table 138.1 Perioperative mortality and morbidity rates after an elective total pancreatectomy reported in main literature.

Author	Period of time	Total number	Disease PDAC	IPMN	Others	Mortality rate (%)	Morbidity rates (%)
Billings et al. [10]	1985–2002	99	33	26	40	5%	32%
Müller et al. [12]	2001–2006	124	67	18	39	4.8%	24% (surgical) 14.5 (nonsurgical)
Stauffer et al. [18]	2002–2008	47	10	31	6	2%	37%
Casadei et al. [19]	2006–2009	20	7	8	5	5%	25%
Crippa et al. [16]	1996–2008	65	19	31	15	0%	38.5%
Barbier et al. [20]	1993–2010	56	4	39	13	3.6%	45%
Hartwig et al. [21]	2001–2012	434	289	75	70	7.8%	37.3% (surgical) 37.6% (nonsurgical)
Almond et al. [17]	1987–2013	98	45	12	41	12.5%	46%
Latenstein et al. [14]	2014–2018	1,579	836	229	514	5.4%	26.8%(≥ Clavien Dindo grade 3)

IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma.

anastomotic leak, and wound infection. Several reports described that the rate of delayed gastric emptying was the most common perioperative complication after TP [12,20,21], and the relationship between delayed gastric emptying and surgical technique, whether preserving the pylorus or not during TP, was not clear [12,21].

Although mortality rates after TP have decreased, perioperative morbidity rates remain substantial. Therefore, careful patient selection, surgical procedure, and postoperative management are essential for decreasing morbidity rates after TP.

Salvage Completion Pancreatectomy

High mortality rates after emergent complete pancreatectomy have been reported, ranging from 39% to 48%, and reported morbidity rates were also high, ranging from 79% to 91% [12,17]. Furthermore, postoperative outcomes after salvage completion pancreatectomy, including complications, hospital stay, and survival, were significantly worse than those after elective TP [12,17]. The poor outcomes after salvage completion are associated with severe abdominal sepsis or hemorrhage after partial pancreatectomies.

As the techniques of interventional radiology, including drainage of pancreatic fistula or intraabdominal abscess, and arterial embolization for abdominal hemorrhage have advanced, salvage TP should be avoidable for complications after partial pancreatectomies, if possible, according to the reported poor outcomes [23,24].

Minimally Invasive TP

There have been a few reports about outcomes after minimally invasive TP, including laparoscopic and robotic TP, compared to those after open TP [25–28]. According to these reports, although operative time was significantly longer in minimally invasive TP than in open TP, there were no significant differences in other factors, such as intraoperative blood loss, morbidity rate, and mortality rate, between minimally invasive and open TP [25–28]. Furthermore, a European group reported that the incidence of major morbidity, defined as Clavien–Dindo ≥3a complications, after minimally invasive TP was significantly lower than that after open TP [25]. Therefore, minimally invasive TP may be feasible and safe in selected patients, although further large-scale studies and/or prospective studies are necessary to confirm this.

Long-term Outcomes After Total Pancreatectomy

With the increased number of long-term survivors after TP [21,29,30], management of late complications and evaluation of quality of life (QOL) after TP are important, although there have been few reports about long-term outcomes [10,12,16,19–21,31,32]. Late complications after TP include anastomotic ulcer at gastrojejunostomy and hepatic steatosis as well as diabetes mellitus and malabsorption caused by endocrine and exocrine insufficiency. Furthermore, long-term QOL

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may be associated with postoperative symptoms, such as diarrhea, appetite loss, and weight loss [10,12,21,32].

Diabetes Mellitus After Total Pancreatectomy

Diabetes mellitus after TP is caused by a complete lack of endogenous insulin and glucagon, leading to frequent and deep states of hypoglycemia with hyperglycemic episodes that can be difficult to control (brittle diabetes) [9]. Recently, advanced management of the diabetic state using well-established long-acting insulin formulations [10] and continuous subcutaneous insulin infusion systems [33] has dramatically improved diabetic outcomes after TP [20,24]. Several reports have shown that hemoglobin A1c (HbA1c), as a long-term marker of blood glucose concentrations, could be kept within a tolerable range (median HbA1c, ranging from 6.5% to 8.0%) (Table 138.2) after TP [10,12,16,19–21]. However, the potential morbidity associated with endocrine deficiency must not be underestimated, because there are several reports of deaths owing to hypoglycemia and hyperglycemia after TP [10,20]. Therefore, preoperative endocrinology referral and determination of postoperative management using insulin formulations and postoperative education by specialists are essential for the treatment of diabetes mellitus in patients undergoing TP.

Exocrine Insufficiency After Total Pancreatectomy

Exocrine insufficiency is also an important late complication after TP [9]. Exocrine insufficiency may cause diarrhea, steatorrhea, weight loss, osteopathy and osteoporosis, and hepatic steatosis (see Table 138.2). Diarrhea and/or steatorrhea after TP contributes to the loss of fat-soluble vitamins, especially vitamin D, magnesium, and trace elements, leading to osteoporosis and hepatic steatosis [34]. Increasing attention has been devoted to the development of hepatic steatosis after pancreatectomy, because it may potentially progress and lead to life-threatening hepatic decompensation [35–37]. However, the etiology and pathogenesis remain largely unknown. Malnutrition from lack of pancreatic enzyme formulations can be hypothesized [36,37], and female sex and early postoperative nutritional status were reported to be independent risk factors for hepatic steatosis after TP [35].

Pancreatic exocrine enzymes process ingested food into micronutrients for absorption [34,38]. Disruption of this process leads to severe diarrhea and steatorrhea with subsequent nutritional deficiencies [34]. Therefore, nutritional interventions, such as low-fat diets and pancreatic enzyme replacement therapy, are used to improve clinical symptoms. Pancreatic enzyme replacement, including ingestion of more than 40 000–50 000 units of lipase per day, is a standard therapy for pancreatic exocrine insufficiency after TP, because it significantly improves absorption of fat and nitrogen as well as clinical symptoms [35,39,40]. Therefore, specific attention should be paid to patient educations with regard to exocrine insufficiency and pancreatic enzyme treatment after TP.

Anastomotic Ulcer After Total Pancreatectomy

An anastomotic ulcer at gastrojejunostomy can occur both in the early postoperative course and in the long term after TP [20,41]. This complication can be severe,

Table 138.2 Long-term outcomes after total pancreatectomy reported in main literature.

Author	Total number	HbA1c % of patients	Diabetes symptoms	Weight loss	Digestive
Billings et al. [10]	27	7.4% (5.0–11.3%)	Three deaths owing to hypoglycemia	70%	–
Müller et al. [12]	67	Malignant: 7.5% Benign: 6.7%	No death related to diabetes, 8.3% readmission for diabetes control	41%	Diarrhea 41% Abdominal pain 15%
Casadei et al. [19]	13	8% (5.2–10.3%)	No death related to diabetes, 23% readmission for glycemic control	85%	–
Crippa et al. [16]	45	7–9% in 56% of patients, >9% in 11% of patients	No death related to diabetes	45%	Abdominal pain 22% Diarrhea 13% Steatorrhea 27%
Barbier et al. [20]	25	7.8% (6.3–10.3%)	One death owing to hypoglycemia, one death owing to ketoacidosis	60%	28% with night stools

HbA1c, hemoglobin A1c.

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resulting in reoperation or even death. An anastomotic ulcer could be observed after TP with or without pylorus preservation, indicating that this complication could not be prevented technically [20]. However, it was reported that routine administration of a proton pump inhibitor could prevent anastomotic ulcer after TP [20].

Long-term QOL After Total Pancreatectomy

There have been a few reports evaluating long-term QOL after TP [10,12,21,32]. According to these reports, overall QOL after TP was acceptable, although most impaired items after TP were symptom scales, with a decrease of QOL focusing mainly on fatigue and diarrhea, and the score of healthcare satisfaction was also slightly poor [10,12,21,32]. Therefore, information delivery before and after TP may be necessary to increase QOL for patients who underwent TP.

Indications for Total Pancreatectomy

Total pancreatectomy is a reasonable procedure in some diffuse pancreatic disease, as perioperative mortality is low and long-term consequences are now better managed, with an acceptable morbidity and QOL [10–13,16,17, 19–21]. Therefore, TP should no longer be generally avoided for patients in whom the complete removal of the pancreas is required for oncologic prophylactic reasons. Furthermore, with extension of resection criteria in pancreatic malignant or premalignant disease, and more advanced knowledge of specific disease entities of the pancreas, which often affect the whole pancreas and require TP, the number of cases requiring TP has been increasing. Diseases which might require TP include extensive pancreatic head or body cancers, recurrence or new tumors developing in the remnant pancreas after previous partial pancreatic resection, diffuse or multifocal intraductal papillary mucinous neoplasms (IPMNs), renal cell metastases, multifocal neuroendocrine tumors and inherited neoplastic disease, including multiple endocrine neoplasia 1 (MEN1) syndrome, history of familial pancreatic cancer, and hereditary chronic pancreatitis. Furthermore, TP may also be performed in cases with avoidance of pancreatic-enteric anastomotic-related complications or salvage complete pancreatectomy for severe complications after partial pancreatectomies [12,21], although these indications are controversial.

Pancreatic Ductal Adenocarcinoma

The frequency of TP in patients with pancreatic ductal adenocarcinoma (PDAC) varies from 3% to 9%, according to previous reports [17,30,42,43]. Less than one year of median overall survival time was reported in the past [6,43,44] but recent reports described better overall survival after TP, ranging from 12 months to 18 months [21,29,30,42] because of improved surgical techniques and postoperative management, and advanced adjuvant therapies.

Hartwig et al. reported that poor tumor grade, high American Joint Commission on Cancer tumor stage, age 70 years or more, and an R1 resection were independent risk factors of poor survival for patients who underwent TP [21]. Satoi et al. reported that the rate of completion of adjuvant therapy was lower and the frequency of postoperative liver metastasis was higher in PDAC patients undergoing TP, compared to those with pancreatoduodenectomy; however, overall survival was similar between the TP and pancreatoduodenectomy matched-pairs groups [42]. Schmidt et al. reported that among PDAC patients with positive transected margin at permanent pathological findings in the absence of other margin positivity, patients undergoing subsequent TP to achieve a R0 resection were compared with the R1 patients undergoing pancreatoduodenectomy, and they showed that mortality and morbidity rates were similar between the two groups; however, conversion of pancreatoduodenectomy to TP was associated with survival benefits [30]. However, it was unclear whether oncologic surgical radicality, including extended lymphadenectomy and increased soft tissue clearance around the pancreatic gland by TP, could improve survival or not, compared to partial pancreatectomies [21,31,30,42].

Based on these results, TP seems to be a powerful strategy for patients with positive margin of transected pancreas after pancreatoduodenectomy to achieve a R0 resection, and completion of adjuvant therapies after TP is necessary to improve survival, as with other pancreatectomies. Then, adequate control of endocrine and exocrine pancreatic insufficiency after TP is essential to improve survival for PDAC patients undergoing TP.

Intraductal Papillary Mucinous Neoplasm

According to international consensus guidelines for the management of IPMN [45], main duct IPMN is an indication for surgical resection, because of the risk of malignancy. Diffuse main duct IPMNs or multifocal branch duct or mixed IPMNs sometimes require TP, and long-term outcomes for these cases are favorable [21,23,46,47]. Therefore, these IPMNs are a good indication for TP, although careful preoperative diagnosis of malignancy [17,48] and patient selection are necessary to obtain survival benefits.

Inherited Diseases

Patients with a family history of hereditary pancreatic cancer and those suffering from hereditary chronic pancreatitis have a considerable risk of developing

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pancreatic cancer during their lifetime [23,49]. Therefore, TP is a prophylactic measure for patients with high risk of pancreatic cancer, used to eliminate the risk of cancer development, although the timing and extent of surgery are still controversial.

Tumor Recurrence or New Tumor Developing in the Remnant Pancreas After Previous Partial Pancreatic Resection

Tumor recurrence or new tumor, such as PDAC or IPMN, developing in the remnant pancreas without distant metastasis is sometimes found, and several reports showed survival benefits by a two-stage completion pancreatectomy with low rate of mortality and morbidity [12,16,21,50–53]. Therefore, tumor developing in the pancreas remnant is an indication for two-stage complete pancreatectomy.

Conversion from Partial Pancreatectomy to Total Pancreatectomy to Avoid Pancreatic-Enteric Anastomosis-related Complications

Pancreatic-enteric anastomotic leakage, called pancreatic fistula, after partial pancreatectomy could cause life-threatening complications, and conversion to TP from pancreatoduodenectomy is sometimes performed intraoperatively. Hartwig et al. reported that in 20% of all TP cases, intraoperative conversion to TP was performed because of the morphology of the remaining pancreas, including extremely soft or lipomatous pancreas that would have a high risk of postoperative pancreatic fistula, and combined arterial reconstruction during pancreatectomy, which could cause life-threatening complications by pancreatic fistula [21]. However, this indication for conversion to TP from pancreatoduodenectomy for avoidance of postoperative pancreatic fistula, causing endocrine and exocrine insufficiency, remains controversial.

Salvage Complete Pancreatectomy for Complications After Partial Pancreatectomy

As described above, the mortality and morbidity rates of salvage TP for severe complications after partial pancreatic resections are extremely high, so this procedure should be avoided, if possible [12,17]. The significant decline in the use of salvage complete pancreatectomy relative to a pancreatoduodenectomy reflects a shift in the management of pancreatic fistula and postoperative hemorrhage, with radiologic drainage and arterial embolization now readily available and preferred to relaparotomy [24,54].

Limitations of Total Pancreatectomy

Although mortality rates after TP have dramatically decreased, perioperative morbidity rates remain substantial [10–13,16,17]. Especially in salvage completion pancreatectomy for severe complications after partial pancreatectomy, both mortality and morbidity rates remain extremely high [12,17], so this procedure should be avoided, if possible. Furthermore, postoperative endocrine and exocrine insufficient state could cause life-threatening complications [10,12,16,19,20,21]. Therefore, careful patient selection, considering the balance between clinical benefits and postoperative risks, and delivering information about postoperative management before and after TP are necessary to improve survival and QOL for patients who undergo TP.

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Minimally Invasive Resection for Pancreatic Cancer

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Introduction

As in many other fields of surgery, minimally invasive approaches have revolutionized the face of surgical practice since the first laparoscopic appendectomy was performed in 1980[1]. This approach has extended to complex hepato-pancreato-biliary (HPB) procedures, but the adoption of minimally invasive techniques in pancreas surgery has been sluggish, especially for pancreaticoduodenectomy (PD). This is mainly due to the complexity of the procedure, the steep learning curve, and the limitations of the laparoscopic approach.

The introduction of robotic surgical systems, the report of the first robotic PD in 2001, and the subsequent optimization of robotic techniques have resulted in a surge of minimally invasive pancreatectomy numbers over the last two decades [2]. Given the advantages of the robotic approach, such as three-dimensional stereotactic vision, tremor attenuation, optical magnification, high degree of articulation and improved ergonomics, minimally invasive complex pancreatic resection (MIPR) has evolved significantly to become a safe and feasible procedure with low morbidity and mortality when performed in high-volume centers [1,3]. The aim of this chapter is to provide an updated overview of current trends, surgical techniques, and outcomes data associated with minimally invasive pancreatic surgery for cancer, focusing on proximal (pancreaticoduodenectomy) and distal pancreatectomy.

Minimally Invasive Pancreatic Resections: Indications

Currently, the resectability of pancreatic cancers remains defined, primarily, by the level of celiac artery, hepatic artery, or mesenteric vessel involvement by the tumor [4]. The approach to be utilized depends on the experience of the surgeon and surgical team. In the hands of expert minimally invasive pancreas surgeons, most pancreas head tumors with resectable features are amenable for minimally invasive technique.

While our group and others perform robotic pancreatic resections on highly selected patients with vascular involvement (*borderline and locally advanced* cancers), we do not recommend it as standard of care unless surgeons are highly experienced. For surgeons at the early stages of their learning curve, and for patients with locally advanced tumors where superior mesenteric vein (SMV)/artery (SMA) or hepatic artery resection and reconstruction is anticipated, we recommend the open approach.

After a negative workup for metastatic disease, a robust preoperative assessment for vascular involvement is warranted. Imaging is crucial, and the combination of endoscopic ultrasound (EUS) and triphasic computed tomography (CT) scan helps identify the best candidates for MIPR. Preoperative diagnostic laparoscopy is also encouraged to look for occult peritoneal metastasis.

While there are no absolute contraindications for MIPR, potential contraindications exist such as patients with CO2-retaining conditions unable to undergo pneumoperitoneum, and patients with extremely high body mass index (BMI), previous upper abdominal operations with a prohibitive amount of adhesions, and multiple comorbidities.

As a general recommendation, the treatment plan and surgical approach must be thoroughly considered and discussed in a multidisciplinary team with the participation of surgeons, medical oncologist, gastroenterologist, and radiation oncologist among others. At our institution, all pancreas tumors are discussed in a multidisciplinary pancreatic cancer clinic.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Minimally Invasive Pancreaticoduodenectomy: Technique

Robotic Pancreaticoduodenectomy

The robotic platform offers a multitude of advantages allowing an improved dexterity and enhanced visibility, facilitating dissection and reconstruction without compromising quality of the intervention. For these reasons, our group favors this approach over conventional laparoscopy. Our technique and outcomes have previously been reported [3].

The patient is placed in a supine position, with arms tucked and on a split leg table that allows the bedside assistant surgeon to stand between the legs in an ergonomic position. Depending on the room size, disposition, and which Da Vinci® System (Intuitive Surgical, Sunnyvale, CA) is used, the operating room (OR) setup can vary.

Pneumoperitoneum is then created by inserting a 5 mm optical separator in the left upper quadrant. Open peritoneum or Veress technique are both acceptable alternatives. Trocars are placed afterwards as depicted in Figure 139.1 and the robotic arms are docked.

Our robotic pancreaticoduodenectomy (RPD) technique can be summarized in seven major surgical steps.

First comes the *mobilization* of the right colon and duodenum by dividing the gastrocolic, gastroepiploic, and hepatic flexure attachments as well as the Toldt's fascia planes. This is followed by an extensive Kocher maneuver where the ligament of Treitz (LOT) is dissected and the proximal jejunum is pulled under the mesenteric vessels and transected about 10 cm distal to the LOT using a laparoscopic/robotic linear stapler (Fig. 139.2). The anterior surface of the pancreas is separated from the posterior stomach, which is then divided using a laparoscopic or robotic linear stapler. The stomach is divided proximal to the pylorus in the classic approach and distal to the pylorus in the pylorus-preserving one.

The second step is the *porta hepatis dissection* that starts with the removal of the anterior common hepatic artery lymph node, allowing for better visualization of the common hepatic artery, gastroduodenal artery (GDA), and portal vein (PV) (Fig. 139.3). Using a linear vascular stapler, the GDA is transected. This is followed by a periportal and portocaval lymphadenectomy, keeping in mind a possible aberrant replaced or accessory right hepatic artery.

Cholecystectomy is the third step and is often performed in a top-down fashion using a robotic hook cautery. The common bile duct is then isolated and divided using a gastrointestinal linear stapler to avoid bile spillage unless the RPD is performed for a proximal or middle-portion cancer of the common bile duct, for which we prefer a sharp transection using robotic scissors, allowing us to sample and study frozen sections of the margins.

The fourth step is dissecting the SMV off the inferior border of the pancreas and creating a tunnel over the portal vein (Fig. 139.4), and then *dividing the neck of the pancreas* using electrocautery and scissors for the duct (Fig. 139.5). Additionally, this step involves the *uncinate process and posterior retroperitoneum dissection*. After freeing the uncinate process of the SMV, the pancreas head and uncinate are rotated clockwise on the cephalocaudal axis to dissect the SMA, which allows the surgeons to identify the first jejunal vein and the junction of the gastroepiploic towards the portal vein. The first jejunal branch should be preserved unless the tumor extends and invades it.

Dissection proceeds along the SMA by separating it from the uncinate process and the retroperitoneal tissue. Pancreaticoduodenal veins are identified, dissected, and transected using a vessel sealer.

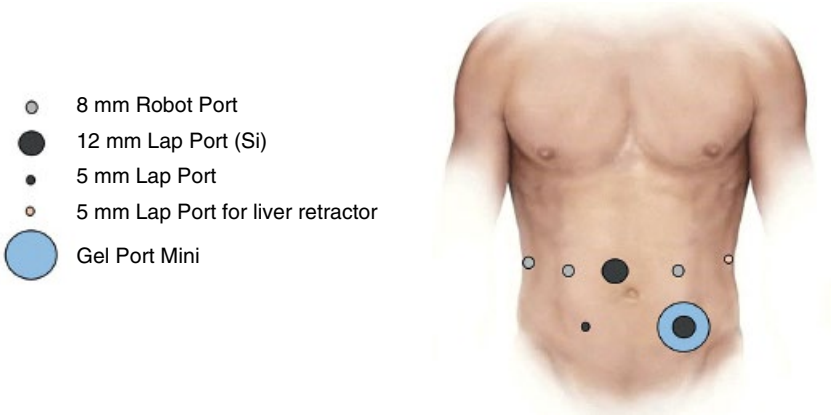


Figure 139.1 Schematic port placement for robotic pancreaticoduodenectomy.

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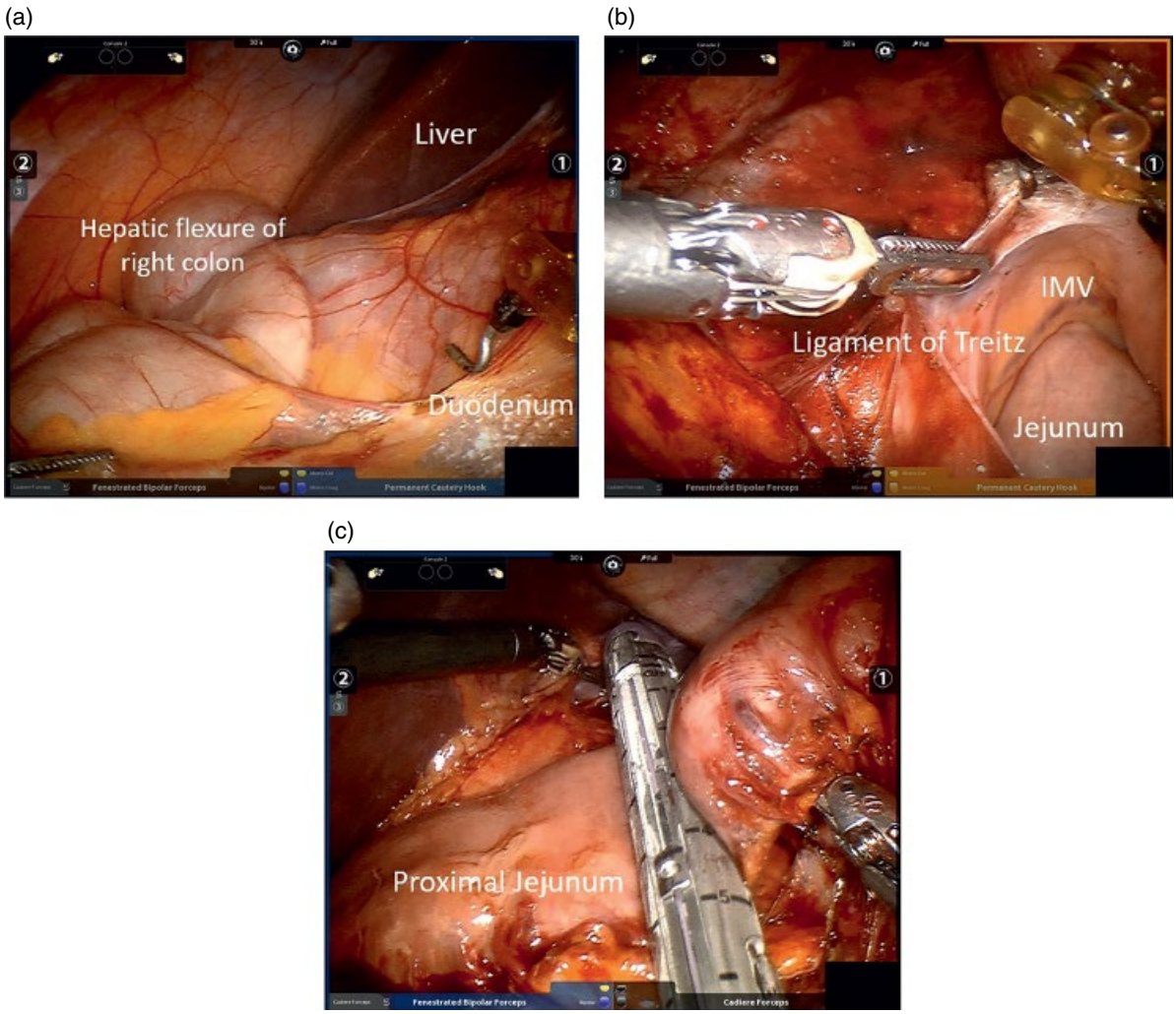


Figure 139.2 Mobilization of right colon (a) and duodenum, with dissection of ligament of Treitz (b) and division of proximal jejunum (c). IMV, inferior mesenteric vein.

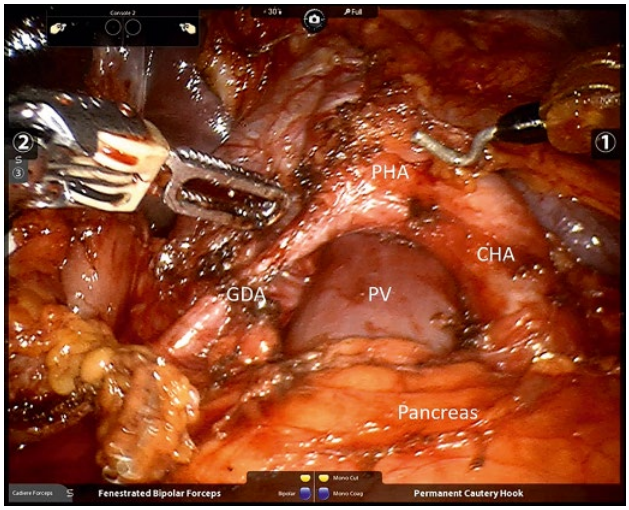


Figure 139.3 Suprapancreatic dissection of common hepatic artery (CHA), gastroduodenal artery (GDA), portal vein (PV), and proper hepatic artery (PHA).

The resection phase is complete at this point and the duodenum-pancreas-gallbladder specimen is collected in an endoscopic large bag and removed through the left lower bedside assist port that undergoes a 4–5 cm extension.

The fifth step marks the beginning of the reconstruction phase and is highlighted by *creating a two-layered end-to-side duct to mucosa pancreaticojejunal anastomosis* in a modified Blumgart technique (Fig. 139.6). The posterior mattress and anterior seromuscular bowel-to-pancreas approximations are performed using three 2-0 silks. The duct-to-mucosa anastomosis is performed with interrupted 5-0 PDS stitches. A ductal stent is used, especially when the duct is small, to confirm patency and facilitate anterior row stitching.

A *hepaticojejunal anastomosis* is then created and marks the sixth step (Fig. 139.7). After removing the stapled line of the common bile duct, the anastomosis is

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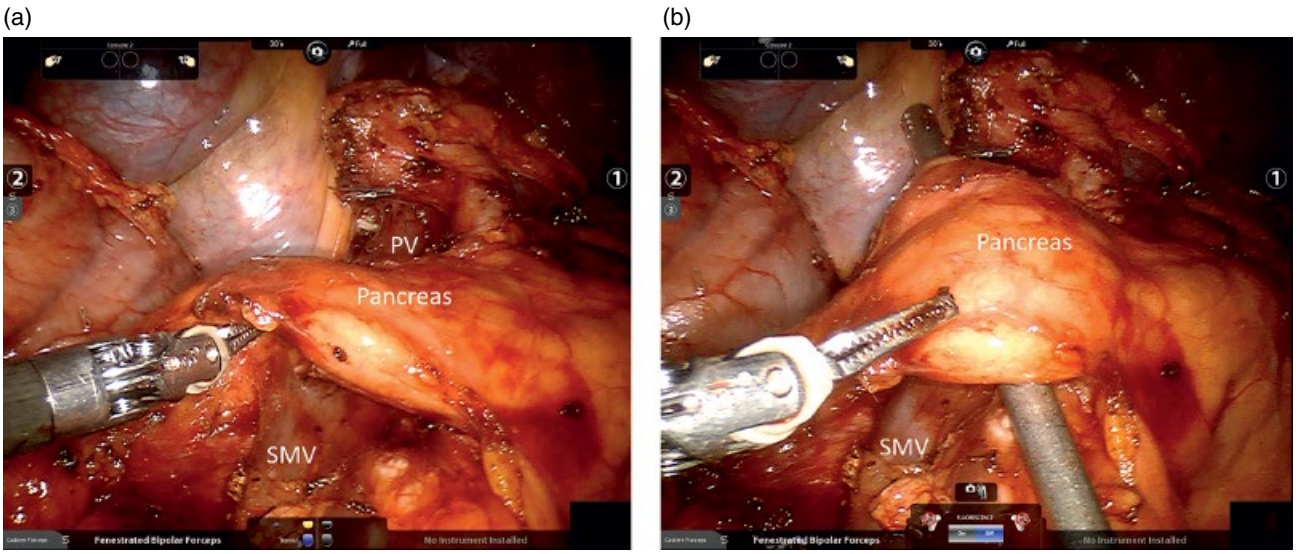


Figure 139.4 Retropancreatic dissection (a) PV, portal vein and creation of retropancreatic tunnel (b). SMV, superior mesenteric vein.

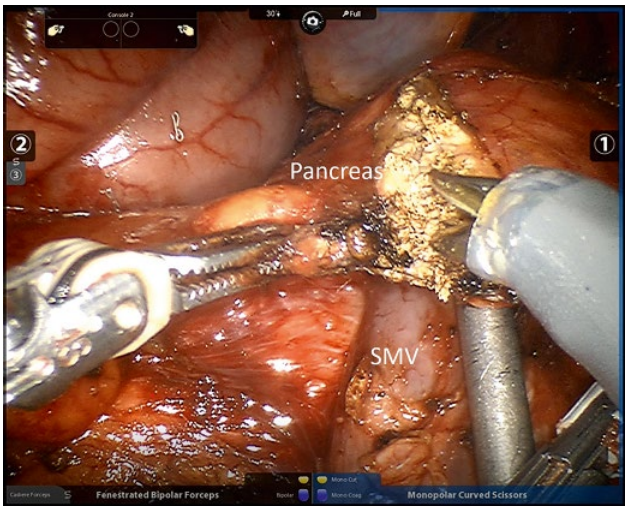


Figure 139.5 Pancreas transection. SMV, superior mesenteric vein.

performed using either interrupted or continuous stitching, depending on the width and thickness of the hepatic duct. For small ducts, 5-0 PDS interrupted sutures are used whereas for large and thick-walled ducts, running sutures with absorbable 4-0 barbed sutures are preferred for the anastomosis.

Creation of a *gastrojejunostomy* marks the last step of reconstruction and the end of this procedure (Fig. 139.8). It is performed using the loop of proximal jejunum roughly at 60 cm from the hepaticojejunostomy. A two-layered end-to-side gastrojejunal anastomosis is created using 3-0 absorbable barbed sutures. If the pylorus is preserved, a duodenojejunal anastomosis is fashioned with 4-0 absorbable barbed sutures in a two-layer running suture. Following the anastomosis, we create a pedicled falciform ligament flap that we place carefully over the GDA stump to prevent direct contact with pancreatic secretions and enzymes in case a pancreatic leak occurs.

Finally, depending on surgeon preference, one or two (anterior and posterior to pancreaticojejunostomy) 19 French drains are usually placed, trocars are removed under direct visualization, and wounds are closed.

Laparoscopic Pancreaticoduodenectomy

Laparoscopic PD (LPD) technique has previously been described by multiple institutions around the world [5–8]. The following steps summarize the procedures mostly used. Patients are preferably positioned in split leg supine position, pneumoperitoneum is achieved through the left upper quadrant, and trocars are placed in a semilunar shape facing the duodeno-pancreas region. After ruling out the presence of occult metastatic peritoneal tumor implants, the surgery proceeds in a fashion similar to the open and robotic approach. The right colic flexure is mobilized, and an extensive Kocher maneuver is carried out followed by a division of the LOT and the gastric antrum with a linear stapler. Cholecystectomy, dissection of the hepatic artery and the GDA, and division of the GDA are the next steps. The retropancreatic tunnel is then created between the pancreatic neck and the portal vein, and the pancreas is divided using electrocautery and laparoscopic scissors for the duct.

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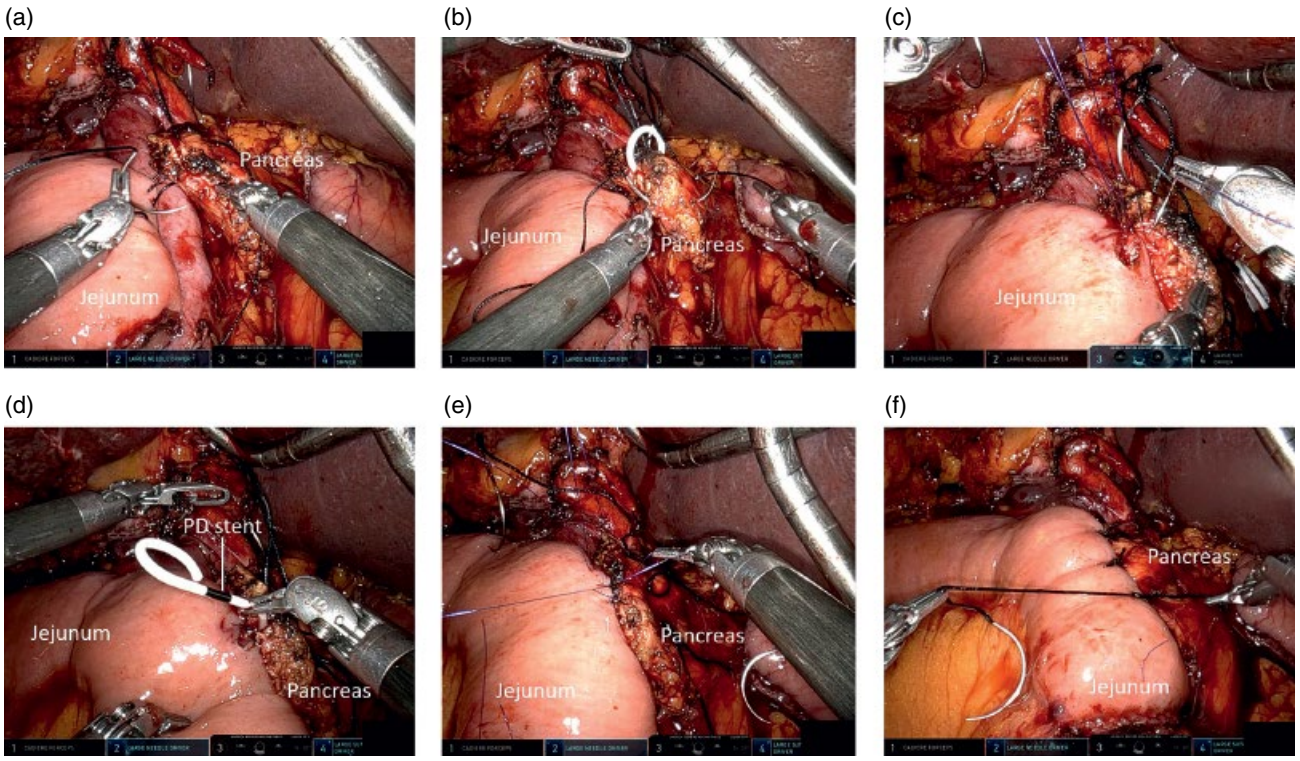


Figure 139.6 Pancreaticojejunostomy with modified Blumgart technique. Posterior seromuscular stitching with 2/0 silk (a,b), posterior row of duct-to-mucosa stitching with 5/0 PDS (c), 4 Fr Pancreatic duct (PD) stent placement (d), anterior row of duct-to-mucosa stitching with 5/0 PDS (e), anterior seromuscular stitching with 2/0 silk (f).

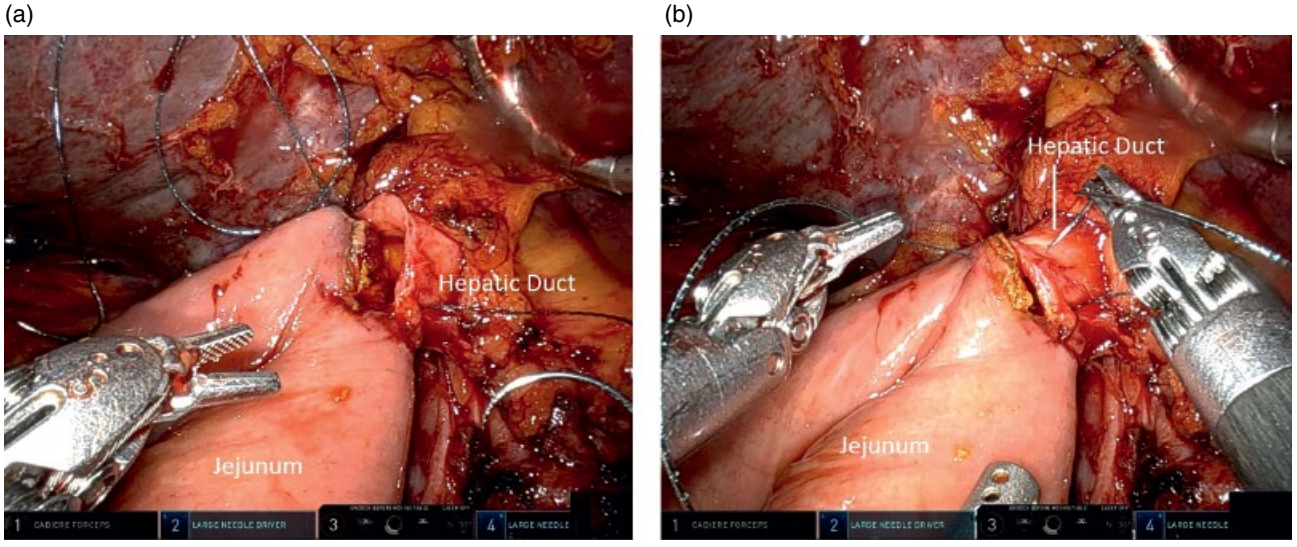


Figure 139.7 Hepatojejunostomy with running stitches of 4/0 barbed absorbable suture. Posterior row (a), anterior row (b).

The specimen is extracted through a right lower quadrant incision.

The reconstruction phase proceeds with a two-layer duct-to-mucosa pancreatojejunostomy, a single-layer hepaticojejunostomy (with 4-0 running or interrupted monofilament), and a two-layer antecolic gastro/duodenojejunostomy. One or two drains are left in the pancreatojejunostomy area prior to closure.

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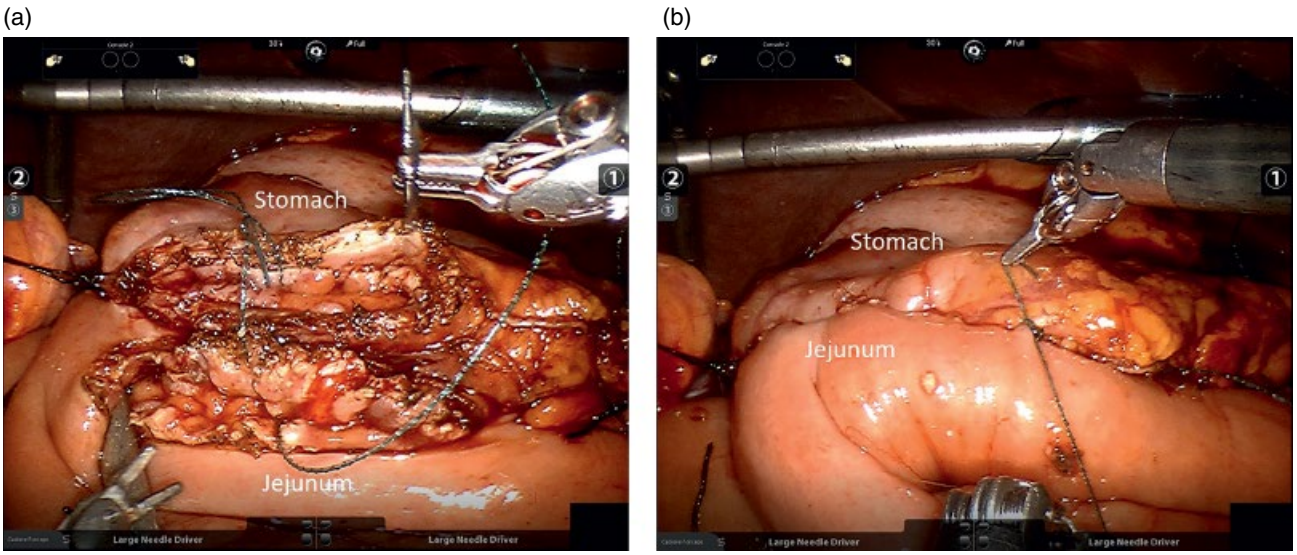


Figure 139.8 Gastrojejunostomy with two layers of running 3/0 barbed absorbable suture. Posterior row (a), anterior row (b).

Minimally Invasive Pancreaticoduodenectomy: Outcomes

Perioperative Outcomes

Robust data have been published so far, including large institutional series of MIPD, metaanalysis, systematic reviews, and randomized trials, and showed that minimally invasive pancreaticoduodenectomies are feasible and safe when performed by high-volume centers and expert surgeons who have overcome their learning curve.

Although initial experience with LPD was concerning, later reports described the safety and feasibility of LPD. In the largest series of laparoscopic pancreaticoduodenectomy, including 130 patients, Palanivelu et al. demonstrated the feasibility and advantages of the MI approach when performed by high-volume expert surgeons [9]. They reported a mean operative time of 310 minutes, mean estimated blood loss of 110 mL, average hospital stay of eight days and one conversion to open surgery. The postoperative pancreatic fistula, overall postoperative morbidity, and overall mortality rates were respectively 8.5%, 30%, and 1.5%.

Systematic reviews and metaanalyses have consistently shown that MIPD is associated with comparable postoperative morbidity in terms of pancreas-specific complications (i.e., pancreatic fistulas and delayed gastric emptying), perioperative morbidity and postoperative mortality, with a decrease of length of stay (LOS) and blood loss but increased OR time for MIPD when compared to open [10,11]. Using a propensity-matched analysis in a US national dataset, our group reported that patients with MIPD (excluding conversions) have a lower rate of prolonged LOS, decreased wound complications and transfusions, and no differences were noted in morbidity and mortality, when compared to the open approach [12].

In the largest documented cohort of RPD, the University of Pittsburgh group reported their 10-year experience of 500 consecutive RPDs [3]. In this series, the authors report an 8% rate of clinically relevant postoperative pancreatic fistula, with major complications occurring in less than 24% of patients and a median LOS of eight days. The 30- and 90-day mortality rates were 1.4% and 3.1%, respectively. These optimal outcomes were highlighted owing to the structured implementation and adoption of a robust robotic pancreas surgery program. Subsequent retrospective propensity-matched analysis of institutional and large national datasets has corroborated the association of RPD with a decreased rate of clinically relevant postoperative pancreatic fistula (CR-POPF) [13–15]. See Table 139.1 for selected case series of laparoscopic and robotic PD, and Table 139.2 for selected comparative studies of RPDs and open pancreaticoduodenectomy (OPD).

At least four randomized control trials comparing OPD and LPD have been published in recent years. The outcomes of two completed single-center nonblinded RCTs (PLOT and PADULAP) comparing LPD to OPD have demonstrated clear advantages for MIPD in terms of blood loss, functional recovery, and LOS with an increased operative time and comparable or reduced postoperative complications [16,17]. However, the LEOPARD-2 trial, a multicenter, patient-blinded phase II/III RCT comparing LPD against OPD, raised concerns of increased 90-day postoperative mortality rate of 15%

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Table 139.1 Selected case series of laparoscopic and robotic pancreaticoduodenectomies.

Author	Year	Technique	N (total)/N (malignant)	OR time (min)	EBL (mL)	CR-POPF rate	Mortality rate	Oncologic outcomes (R0 rate, LN)
Kendrick and Cusati [8]	2010	Lap	62/45	368	240	18%	1.6%	89%, 15
Palanivelu [9]	2015	Lap	130/130	310	110	8.5%	1.5%	91%, 18
Wang [55]	2015	Lap	31/30	515	260	3.2%	0%	100%, 13
Zureikat [38]	2013	Robot	132/106	527	300	1.5%	1.5%	88%, 19
Liu [56]	2018	Robot	417/320	300	171	9.35%	1%	97%, 15
Zhang [29]	2019	Robot	100/93	357	171	11%	-	100%, 7
Zureikat [3]	2021	Robot	500/413	415	250	8%	1.8%	85%, 34

OR, operating room time; EBL, estimated blood loss; CR-POPF, clinically relevant postoperative pancreatic fistula; LN, lymph node.

Table 139.2 Selected comparative studies of robotic versus open pancreaticoduodenectomies

Author	Year	N (RPD/OPD)	Cancer (n)	LOS (days)	OR time (min)	EBL (mL)	CR-POPF	Morbidity (%)	30-day mortality (%)	Oncologic outcomes (R0 rate, LN)
Li [57]	2015	60/120	60/120	20/25	410/323	400/500	8.3/15	35/40	1.7/2.5	98, 14/96, 13
Zureikat [58]	2016	210/817	70/452	8/8	402/300	200/300	13.7/9	23.7/23.9	1.9/2.8	50, 28/69, 19
Wang [28]	2018	87/87	72/78	24/24	420/360	120/250	3/14	44/54	-	97, 14/94, 13
Shi [26]	2020	187/187	123/130	22/26	280/300	297/415	10/14	-	2.1/3.7	95, 17/93, 16
Van Oosten [59]	2021	96/1417	34/707	8/9	474/345	150/487	5/12	63/73	2.1/0	- / -

RPD, robotic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LOS, length of stay; OR, operating room time; EBL, estimated blood loss; CR-POPF, clinically relevant postoperative pancreatic fistula; LN, lymph node.

(3/20 patients) in the LPD arm that led to the early termination of the trial [18]. While this study is commended for being the first multicenter blinded and randomized trial, questions were raised regarding the learning curve of surgeons participating in this trial and the adoption of a laparoscopic technique for PD. The lack of technical expertise specific to the LPD could have resulted in the unfavorable outcomes observed, as described by Strobel and Büchler [19]. A more recent Chinese randomized trial comparing these two approaches, with 328 patients in each arm, confirmed that LPD decreased LOS while other perioperative outcomes remained comparable among groups [20]. In this study, the surgeons have a documented preceding experience of over 100 LPD.

Currently, no RCT comparing either RPD to OPD or RPD to LPD has been published but ongoing trials are being performed (Table 139.3). Notably, the DIPLOMA-2 trial lead by the Dutch Pancreas Study Group will enroll 288 patients in a randomized international multicenter study comparing the morbidity and mortality of RPD and OPD (ISRCTN27483786). Similarly, the Robotic Versus Open Pancreaticoduodenectomy for Pancreatic and Periampullary Tumors (PORTAL) study is a phase III multicenter noninferiority RCT that aims to enroll 244 participants to compare RPD and OPD using time to functional recovery as main outcome [21]. See Table 139.3 for a summary of selected ongoing randomized trials comparing RPD and OPD.

Until further data are provided by these ongoing trials, we recommend that MIPD be performed in high-volume centers by surgeons with formal training in minimally invasive approaches who have clearly surpassed their learning curve. In their hands, MIPD is safe and feasible and provides an acceptable alternative to OPD with several potential benefits regarding blood loss, transfusions, length of stay, and fistula rates. The learning curve for RPD is steep and difficult to overcome as described by a US high-volume institution that demonstrated in a retrospective analysis a decrease in blood loss, fistula rate, and operative time after 20, 40, and 80 cases respectively [22].

While both laparoscopic and robotic approaches are good alternatives in experienced hands, we believe that RPD technique is more reproducible and may allow the completion of more complex pancreatic surgeries with a lower number of conversions. Our suggestion is based

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Table 139.3 Completed and ongoing randomized controlled trials on minimally invasive pancreaticoduodenectomies.

Study	Country	Status	Year	Arms	Design	N	Primary outcome	Outcomes
PLOT [17]	India	Completed	2017	LPD vs OPD	Single center Nonblinded	32 LPD vs 32 OPD	LOS	↓ LOHS = R0 rate 3% conversion
PADULAP(16) ISRCTN93168938	Spain	Completed	2018	LPD vs. OPD	Single center Non-blinded	34 LPD vs. 32 OPD	LOS	↓ LOHS = R0 rate = complications 23.5% conversion
LEOPARD-2 [18] NTR5689	Netherlands	Early terminated	2019	LPD vs OPD	Multicenter Patient-blinded	50 LPD vs 49 OPD	Morbidity, mortality and TTFR	↑ 90-day complication-related mortality ↑ TTFR ↑ LOHS 20% conversion rate
TJDBPS01 NCT03138213	China	Recruiting	Expected 2022	LPD vs OPD	Multicenter Triple-blinded	656 Participants	LOS	NA
PORTAL [21] NCT04400357	China	Recruiting	Expected 2024	RPD vs OPD	Multicenter Patient-blinded	244 participants	TTFR	NA
NCT04171440	USA	Recruiting	Expected 2025	MIPD vs OPD	Single center Patient-blinded	240 participants	TTFR	NA
LOPA trial NCT03747588	China	Not yet recruiting	NA	LPD vs OPD	Single center Nonblinded	100 participants	POPF, intraabdominal infection and bleeding, overall complications	NA
DIPLOMA-2 ISRCTN27483786	International	Recruiting	Expected 2026	MIPD vs OPD	Multicenter Patient-blinded	288 participants	Comprehensive complication index	NA
TJDBPS07 NCT03785743	China	Recruiting	Expected 2027	LPD vs OPD	Multicenter	200 participants	Five-year OS and DFS	NA

MIPD, minimally invasive pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LPD, laparoscopic pancreaticoduodenectomy; RPD, robot-assisted pancreaticoduodenectomy; TTFR, time to functional recovery; LOS, length of stay; POPF, postoperative pancreatic fistula; OS, overall survival. DFS, disease-free survival; NA, not available.

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on our previous experience, clinical observations, and reported findings of significantly lower conversion rates for RPD (11%) when compared to LPD (27%) in a national cohort of patients [23].

Oncologic Outcomes

Based on previously published retrospective single-center, multicenter, and national database analyses [24–29], and after critical review of these data by a group of pancreatic surgery experts, the Miami International Evidence-Based Guidelines on minimally invasive pancreatic resection addressed the question of whether MIPD should be used to treat pancreatic head tumors. This group concluded that both minimally invasive and open approaches are valid for patients with malignancies and show no major differences in perioperative outcomes and survival [30].

A recent systematic review and metaanalysis included 18 nonrandomized trials and performed an analysis on 13 636 patients with periampullary malignancies who underwent either RPD (N = 1593) or OPD (N = 10 046). The authors found that R0 resections and lymph node harvest rates were comparable between the two approaches [31]. Another metaanalysis by Da Dong et al., with focus on the resection rate as primary outcome, included 12 579 patients from 24 previous studies and showed that RPD provides better histopathologic outcomes. The authors found that R1 rates were significantly lower in robotic PD (15.6% vs 19.9%) [32].

While most of the studies included in the metaanalysis showed similar oncologic results, Kendrick and collaborators from the Mayo Clinic hospitals showed that patients undergoing LPD had longer progression-free survival. After comparing 108 LPD to 214 OPD, they found that LPD was associated with shorter length of stay, faster recovery, and less delay in adjuvant therapy delivery, which could explain the better survival outcomes [33].

When comparing RPD to LPD and using a national cohort of 1623 patients with pancreatic adenocarcinoma from the National Cancer Database, our group reported no significant differences in lymph node harvest, margin status, and overall survival between both approaches [34]. A recent review and metaanalysis identified 3426 patients (1025 RPD and 2437 LPD) from 44 studies, of which six were nonrandomized comparative studies. The authors reported no differences in R0 rates [35].

In summary, while there is a paucity of prospective randomized data reporting oncologic outcomes of MIPD and based on large retrospective series and US national data, we conclude that the minimally invasive approach has comparable results with the open approach when performed for periampullary malignancies.

Minimally Invasive Distal Pancreatectomy: Technique

Robotic Distal Pancreatectomy

Our standard technique has been previously reported [36]. Patients are positioned supine in a split leg table with arms tucked, in 14–16° of reverse Trendelenburg and with 4–6° of tilt towards the patient's right side (left side up). The peritoneum is accessed via an optical separator through the left upper quadrant and staging laparoscopy is performed to rule out occult metastatic disease in the peritoneum or elsewhere. Four robotic ports are then placed across the abdomen with the addition of one or two bedside assist ports.

Dissection begins by entering the lesser sac through the gastrocolic omentum and exposing the entire distal pancreas and the anterior aspect of the tumor. Cauterization and division of the short gastric vessels are performed and the splenic artery and left gastric pedicle are identified. The splenic artery and vein are dissected and isolated followed by the creation of a retropancreatic tunnel medial to the lesion. Note that intraoperative ultrasound is helpful with tumor identification or in case of uncertain vascular anatomy. The splenic artery and veins are then transected using a vascular load stapler followed by division of the pancreas using a linear stapler.

The remainder of the procedure follows the steps of a radical antegrade modular pancreato-splenectomy (RAMPS). The anterior Gerota's fascia, pancreas tail, spleen, and short gastric vessels are resected. A lymphadenectomy is carried out starting from the left side of the SMA laterally and including nodal regions 10 (supra-pancreatic) and 18 (infrapancreatic), as per the ISGPS guidelines [37]. The spleen is then mobilized from the splenocolic ligaments, the pancreas separated from the spleen, and both are placed in different laparoscopic bags and extracted. A drain is routinely placed before closure.

Based on our experience, the robotic approach confers an advantage if large tumors are encountered and involve the colon or the fourth portion of the duodenum as it allows fine *en bloc* resections with elaborate reconstructive techniques comparable to the open approach [38].

Laparoscopic Distal Pancreatectomy

Previous reports have described similar techniques for LDP [39,40]. The patient is placed in a supine position, legs apart, with 20–25° reverse Trendelenburg and tilted 15–20° to the right. With an optical separator inserted in the left hypochondrium, pneumoperitoneum is induced, metastatic disease is assessed and followed by the

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insertion of four trocars. The lesser sac is then accessed, allowing the exploration of the pancreas. A laparoscopic ultrasound is helpful in assessing the exact level of resection and to check for potential liver metastasis. The short gastric vessels are resected, and the splenic flexure is mobilized, exposing the inferior border of the pancreas for dissection. The pancreas is then moved out of the retroperitoneum by creating a subpancreatic tunnel.

The following dissection is focused on exposing, isolating, and dividing the splenic vessels, allowing a safer pancreas transection that is then performed with a linear stapler or harmonic scalpel. By excising its suspending ligaments, the spleen is mobilized and placed in a bag extracted through an access incision. Drains are kept next to the resection bed before closure.

Minimally Invasive Distal Pancreatectomy: Outcomes

Perioperative Outcomes

Minimally invasive distal pancreatectomy is a safe and feasible approach for pancreatic cancer resection, as has been shown in multiple studies [41]. Although these reports are mostly comparative and retrospective, MIDP has become a routine practice in many institutions around the world. See Table 139.4 for selected case series of MIDPs.

In a patient-blinded, multicenter RCT performed by a Dutch group (LEOPARD trial), 108 patients with left-sided pancreatic tumors were randomized to either MIDP (N = 51) (laparoscopic or robotic) or ODP (N = 57). Patients in the MIDP arm had significantly reduced blood loss (150 vs 400 mL), time to functional recovery (4 vs 6 days), grade B/C delayed gastric emptying (6% vs 20%) and an increased OR time (217 vs 179 min) [42]. Another unblinded, single-center RCT performed by a Swedish group, the LAPOP trial, enrolled 29 patients in the LDP arm and 29 in the ODP arm. The analysis showed a significant reduction of LOS in the LDP arm, time to functional recovery, blood loss, and comparable OR time [43]. See Table 139.5 for a summary of selected ongoing randomized trials comparing MIDP and ODP.

Focused analysis and trends are currently aiming to compare the robotic and laparoscopic approaches. A recent European multicenter analysis included 1551 patients (407 RDP and 1144 LDP) and matched 402 patients from each group. No differences were noted in terms of postoperative major morbidity and CR-POPF, which highlights the fact that both approaches are equally safe and feasible. Interestingly, RDP showed significantly fewer conversions to open surgery (6.7% vs 15%), lower rates of readmission (11% vs 18%), and higher rates of spleen preservation (81% vs 63%). However, RDP was associated with longer LOS (8.5 vs 7 days) and OR time (285 vs 240 min) [44].

Similarly, Guerrini et al. found in their review and metaanalysis of 813 patients that RDP, compared to LDP, had a significantly lower rate of conversion (8.2% vs 21.6%) and a significantly higher rate of spleen preservation (49% vs 27). This metaanalysis, contrary to the previous described multicenter study, showed that RDP was associated with a shorter LOS (7 vs 9 days). Finally, both groups showed similar outcomes in terms of major morbidity and POPF rates [41].

Oncologic Outcomes

While postoperative outcomes of MIDP have been well published, data regarding the oncologic outcomes remain scarce. In a recent Chinese single-center retrospective comparative analysis, no major differences between LDP and ODP groups were noted in terms of time to adjuvant therapy (50 vs 52 days), rate of adjuvant therapy (71% vs 66%), R0 rates (97% vs 91%), and survival rates. Differences were noted in lymph node retrieval favoring the LDP approach over ODP (14.4 vs 12.7) [45].

Table 139.4 Selected case series of laparoscopic and robotic distal pancreatectomies.

Author	Year	Technique	N (total)/N (malignant)	OR time (min)	EBL (mL)	CR-POPF rate	Mortality rate	Oncologic outcomes (R0 rate, LN)
Kooby [39]	2008	Lap	82/13	230	370	26%	0%	93%, –
Jayarman [60]	2010	Lap	107/16	293	150	16%	–	97%, 6
Zureikat/Zeh [38]	2013	Robot	83/60	256	150	36%	0%	97%, 16
Shakir [51]	2015	Robot	100/70	246	150	18%	0%	95.7%, 13
Liu [56]	2018	Robot	428/139	170	152	7.7%	0.23%	98%, 12

OR, operating room time; EBL, estimated blood loss; CR-POPF, clinically relevant postoperative pancreatic fistula; LN, lymph node.

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Table 139.5 Randomized controlled trials on minimally invasive distal pancreatectomies.

Study	Country	Status	Year	Arms	Design	N	Primary outcome	Outcomes
LEOPARD [42] NTR5188	Netherlands	Completed	2019	MIDP vs ODP	Multicenter Patient-blinded	51 MIDP vs 57 ODP	Time to functional recovery (TTFR)	↓ TTFR ↓ LOHS ↓ DGE
LAPOP [43] ISRCTN26912858	Sweden	Completed	2020	LDP vs ODP	Single center Nonblinded	60 LDP vs 58 ODP	LOHS	↓ LOHS ↓ Blood loss ↓ TTFR
DIPLOMA ISRCTN44897265	International	Recruiting	Expected 2022	MIDP vs ODP	Multicenter Double-blinded	258 participants	R0 rate	NA
NCT03792932	China	Recruiting	Expected 2024	LDP vs ODP	Multicenter Nonblinded	306 participants	Two-year DFS	NA
DISPACT-2 DRKS00014011	Germany	Recruiting	NA	MIDP vs ODP	Single-center	294 participants	Comprehensive complication index	NA
DAVID NCT02269683	Germany	Withdrawn	NA	RDP vs LDP	Single center Double-blinded	–	R1 rate	NA
NCT03957135	Korea	Recruiting	Expected 2025	LDP vs ODP	Multicenter Nonblinded	244 participants	Two-year survival	NA
NCT00988793	USA	Terminated	NA	LDP vs ODP	Single center Nonblinded	128 participants	LOHS, blood loss, overall complication rate	NA

MIDP, minimally invasive distal pancreatectomy; ODP, open distal pancreatectomy; LDP, laparoscopic distal pancreatectomy; RDP, robot-assisted distal pancreatectomy; TTFR, time to functional recovery; LOHS, length of hospital stay; DGE, delayed gastric emptying; DFS, disease-free survival; NA, not available.

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A recent metaanalysis of 11 studies included 4829 patients and found better oncologic outcomes with MIDP over ODP in terms of R0 margin rates (odds ratio [OR] = 0.71, 95% confidence interval [CI] 0.56–0.89; $P = 0.003$), but no difference in three-year and five-year overall survival outcomes [46].

Another recent metaanalysis of 21 studies included 11 246 patients and concluded that MIDP was comparable with ODP with respect to R0 resection rate and use of adjuvant therapy. However, the lymph node yield was lower with MIDP. In this study, fewer patients in MIDP received neoadjuvant chemotherapy and radiation therapy. In addition, MIDP patients were more likely to have smaller tumors, less perineural invasion, and less lymphovascular invasion. This generated an allocation bias and could not conclude on the oncologic efficacy of MIDP [47].

A pan-European propensity score-matched study included 1212 patients from 34 centers in 11 countries and that underwent either MIDP or ODP for PDAC. This study revealed comparable overall survival between groups (28 vs 31 months), with significantly higher R0 resection rates (67% vs 58%) but lower lymph node yield (14 vs 22) with MIDP [48]. This study paved the way for an international blinded RCT (DIPLOMA) that will compare R0 resection rates (primary outcome) between patients with PDAC undergoing MIDP versus ODP. Currently, this trial has just completed enrollment of all 258 patients from 34 centers.

Using the National Cancer Database, Raoof et al. analyzed 605 patients who underwent LDP versus 99 who underwent RDP. No major differences between these two approaches were noted in lymph nodes examined (12 vs 11), margin-positive rate (15% vs 16%), overall survival, time to chemotherapy (50 vs 52 days; $P = 0.65$), and mortality rates (1% vs 0%; $P = 0.28$) [49].

Learning Curve of Minimally Invasive Pancreatic Surgery

One of the biggest challenges in the adoption of minimally invasive surgery in pancreatic surgery is the steep learning curve (LC) needed to achieve optimal outcomes. The significant difference in the level of complexity of distal and proximal pancreatectomies is also reflected in the LC for the minimally invasive approach. As expected, the LC of MIDP is significantly shorter than for MIPD as reported by Chan et al. in a systematic review of 32 studies [50].

In our initial experience of 100 consecutive RDP, we reported that the LC for RDP includes 20 cases for an initial reduction of operative time and noted a subsequent significant reduction after 40 cases. Additionally, we noted an improvement of readmission rates and grade B/C pancreatic fistulas after 40 cases [51].

The LC for RPD also varies based on the outcome to be analyzed. Boone et al. reported our initial experience of 200 consecutive RPDs at the University of Pittsburgh. The main findings included that 20, 40, and 80 cases were needed to decrease the rate of conversions, blood loss, and operative time, respectively [52]. Another case series of 100 patients from Zhang et al. had undergone RPD by a single surgeon. CUSUM analysis showed two phases in the LC with a cut-off of 40 cases. [29].

We strongly recommended that any minimally invasive pancreatic resections should be performed at high-volume centers with expert surgeons. In that regard, and after critically reviewing the available data, the experts of the Miami Consensus Guidelines recommended an annual minimum of 20 LPD or RPD per year to optimize outcomes [30].

Besides the volume factor, it is extremely important to emphasize the need for formal training to mitigate the LC of these complex procedures. We support the use of a step-wise and proficiency-based simulation training as reported by Hogg et al. for training surgical oncology and hepato-pancreato-biliary trainees [53]. Moreover, based on individual hospital resources and access to robotic simulation and training systems, we endorse the early exposure and training of surgical residents [54]. Besides virtual reality and inanimate simulation, surgical coaching and proctoring is essential to achieve ideal results. Incorporating these elements and training tools will allow for an even safer adoption of the robotic technology for pancreatic resections or any complex procedures.

Conclusion

Minimally invasive pancreatic resections are safe and feasible for benign and malignant indications in the hands of experienced surgeons who have overcome their learning curve and achieved proficiency. Current data suggest that minimally invasive pancreatectomies could be associated with a quicker recovery, reduced blood loss, and equivalent oncologic outcomes compared to the open approach. Ongoing trials comparing the robotic to the open approach for PD will further define the role of minimally invasive surgery in this complex operation. While the adoption of robotic technique includes a steep learning curve, this could be mitigated by structured proficiency-based training.

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Robotic Resection for Pancreatic Cancer

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Introduction

Pancreatic cancer is a fatal disease, and it is becoming an increasingly common cause of cancer mortality [1]. Despite five-year survival rates of 10–25% for patients who can undergo surgical resection, surgery remains the most important treatment that offers curative potential [2]. Pancreaticoduodenectomy was described and popularized in 1935 by Allen et al. The Whipple procedure, which was initially a two-stage procedure, has been refined into the single-stage procedure that we use today [3]. Since its inception, pancreatic surgery has resulted in high morbidity and mortality, which has prevented its widespread use for many years [4].

Minimally invasive techniques have begun to revolutionize the surgical management of benign and malignant pancreatic diseases. In 2001, the first cases of robotic distal pancreatectomy (RDP) and robotic pancreaticoduodenectomy (RPD) were performed by Melvin et al. and Giulianotti et al., respectively [5,6]. RDP and RPD are increasingly being utilized for pancreatic malignancies because of the perceived benefits of stereotactic vision, magnification, platform stability, and favorable ergonomics [7–9]. Robot-assisted approaches to pancreatic surgery have been shown to be safe and feasible in high-volume centers of excellence performers [10,11].

Compared with their open counterpart, robotic resections have now been shown to be superior in perioperative outcomes with lower intraoperative blood losses and shorter durations of hospitalization [12]. Additionally, the robotic resection approach has been demonstrated to improve the traditionally high morbidity rates and has similar oncologic outcomes to its open counterpart [13].

We present in this chapter a description of robotic resection techniques for pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), focusing on the current data on techniques, safety, morbidity, oncologic outcomes, and learning curve.

Robotic Pancreaticoduodenectomy

Technique of RPD

In the current literature, the definition of RPD has not been standardized, since in many studies the technique was defined as robotic, robotic-assisted, robotic-assisted laparoscopic, or robotic hybrid. Therefore, the current chapter aims to evaluate the current state of total robotic PD, which includes robotic dissection, resection, and reconstruction.

Brief Procedure of RPD [14]

The patient should be placed in a supine position with the legs parted and the table placed at 20° in the reverse Trendelenburg position and tilted to the left side. The robotic surgeon should operate from the dVss console, while the laparoscopic surgeon should stand between the patient's legs. The ports should be placed as shown in Fig. 140.1.

After the diagnostic laparoscopy, the gastrocolic ligament should be opened from left to right until the right colonic flexor is mobilized. The right gastroomental blood vessels should be identified and cut with Hem-o-lok®. The gastroduodenal artery should be ligated with a double proximal end and separated. The common bile duct should be separated using a ligation or clip to avoid overflow of the bile duct, and a frozen section of the edge of the bile duct should be sent for histologic examination.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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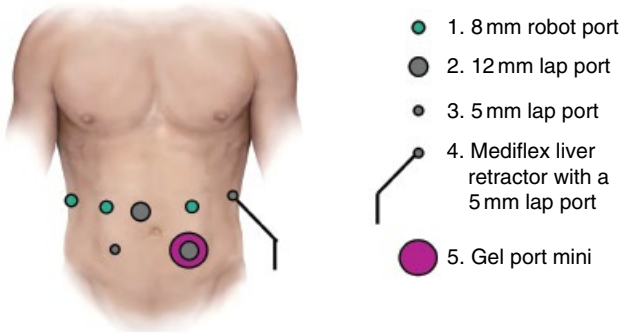


Figure 140.1 Port configuration for robotic pancreaticoduodenectomy.

A Kocher operation should be performed until the first loop of the jejunum is brought to the right of the upper mesenteric vessel by lifting and retracting the duodenum to the left. The pancreatic neck should be separated from the superior mesenteric vein (SMV) and portal vein (PV), the upper and lower borders of the glands sutured, and the glands separated with scissors. A frozen section of the margin of the pancreas should be sent for histologic examination. When the duodenum is retracted to the right, it should be peeled from the distal end to the proximal end along the peripheral plane of the SMA. The pancreaticoduodenal artery and vein should be ligated.

Reconstructive surgery should be performed in the same manner as a laparotomy. The intestinal loop should be rebuilt when the anastomosis is performed. First, the pancreatic stump should be anastomosed with the jejunum. The two-layer end-to-side pancreaticojejunostomy invagination or a catheter-mucosal technique should be used. The hepatic-jejunal anastomosis should be side-to-side, double-layered, and approximately 7–10 cm away from the jejunal limbs and the pancreas-jejunal anastomosis. Duodenojejunostomy or gastrojejunostomy should be performed in two layers, 40 cm downstream of the hepatic jejunostomy.

Outcomes of RPD

Robotic surgery assists surgeons in overcoming many obstacles to the widespread application of laparoscopic pancreatic surgery. The superior visualization, improved three-dimensional imaging, enhanced dexterity, improved ergonomics, and restoration of hand–eye coordination help surgeons complete complex procedures and reconstructions, with results that are at least equivalent to the open approach [7].

Robotic procedures lead to faster recoveries, reduced respiratory complications, reduced wound infections, and shorter postoperative stay compared to open surgeries [15]. Several case–control studies and case series that aimed to evaluate the outcomes of RPD have been conducted, and these showed a significantly lower estimated blood loss (EBL). In addition, the length of hospital stay was significantly shorter in the RPD group with no increase in operative mortality compared to the open cohort. None of the studies to date have demonstrated an improvement in overall morbidity, postoperative pancreatic fistula (POPF) rates, or operative times (Table 140.1).

However, despite the small number of studies demonstrating the feasibility of robotic surgery for PD, safety outcomes must be rigorously scrutinized, and the learning curve needs to be identified for safe use of this platform and to allow for comparisons with other techniques [16–19] (Table 140.2).

Table 140.1 Analyses of RPD studies.

No.	Author	year	Operative time mean[a], min	EBL, mL[a]	Fistula rate (grade B/C)	Clavien-Dindo ≥3	Mortality rate (90-day)	N (total)/N (malignant)	LOS, days[a]	Readmission (90-day)
1	Zhou [25]	2020	401.1±127.5		9 (22.0)	14 (26.4)	2 (4.9)	41/33	23.6 ± 19.1	1 (2.4)
2	Marino [26]	2020	415±85	220±253	3 (5)	12 (20.0)	3 (5)	60/52	11±7.4	10 (16.7)
3	Shi [21]	2020	309.6 ±86.7	419.0 ±285.8	44 (9.8)	32 (7.1)	12 (2.7)	450/232	22.2 ±14.9	
4	Zhang [27]	2019	357.9±93.3	171.1±144.5	11 (11)	22 (22%		100/78	18±13.46	7 (7)
5	Beane [28]	2019			28 (7.4)	89 (23.4)	13 (3.5)	380/380	7 [6-11]	
6	Shyr [18]	2018	438±14	161±135	7 (11.5%)	6 (10.8)	0	61/47	26±15	
7	Takahashi[19]	2018	498 ±144	150 [25–600]	2 (3.1)	7 (10.8)	0		7 [4–34]	16 (24.6)
8	Zureikat [29]	2016	402 [257–685]	200 [30–4500]	29 (13.74)	50 (23.7)	4 (1.9)	211/70	8 [4–58]	65 (30.81)

EBL, estimated blood loss; LOS, length of stay.
[a] Mean (SD) or median [IQR].

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Table 140.2 Studies evaluating the LCs for RPD and RDP.

No.	Author, year	Country	Study period	Type of resection	N	Assessment of LC analysis	Numbers needed to overcome LC	Numbers needed to overcome second point of LC	Numbers needed to overcome LC in conclusion
1	Shi, 2019 [21]	China	2010–2018	RPD	450	Operating time; EBL	100	250	100
2	Boone, 2015 [20]	United States	2008–2014	RPD	200	Operating time	80 to reach plateau phase	140 to reach steady improvement	80
3	Zhang, 2019 [27]	China	2012–2016	RPD	100	Operating time	40	NA	40
4	Napoli, 2016 [30]	Italy	2008–2014	RPD	70	Operating time	33	NA	33
5	Takahashi, 2018 [19]	United States	2012–2016	RPD	65	Operating time; any morbidity; major morbidity	Operating time: 10; any morbidity: 15; major morbidity: 30	NA	10
6	Shyr, 2018 [18]	Taiwan	From 2014	RPD	61	Operating time	20	NA	20
7	Marino, 2020 [26]	Italy	2014–2017	RPD	60	Operating time; EBL	Operating time: 32; EBL: 25	NA	30
8	Chen, 2015 [17]	China	2010–2013	RPD	60	Operating time; EBL	Operating time and EBL: 40	NA	40
9	Beane, 2019 [28]	United States	2011–2017	RPD	50	Operating time	8 to reach plateau	35 to reach improved operative time	35
10	Zhou, 2020 [25]	China	2016–2020	RPD	41	Operating time	8	NA	8
11	Zhang, 2018 [31]	China	2013–2017	RPD	20	Operating time; EBL; duration of stay	Operating time: 10	NA	10
12	Shakir, 2015 [23]	United States	2008–2013	RDP	100	Operating time	20 to first inflection point	40 to continuous gradual improvement	40
13	Shyr, 2018 [18]	Taiwan	From 2011	RDP	70	Operating time	37	NA	37
14	Takahashi, 2018 [19]	United States	2012–2016	RDP	43	Operating time; EBL; any morbidity	Operating time: 5	NA	NA

LC, learning curve; RPD, robotic pancreaticoduodenectomy; EBL, estimated blood loss; RDP, robotic distal pancreatectomy.

To date, one of the largest series of RPDs has been that reported by Boone et al. from the Pittsburgh Center in 2015 [20]. They conducted a retrospective review of a prospectively maintained database of 200 consecutive patients who underwent an RPD in a large academic center from October 3, 2008, to March 1, 2014. In addition, the important metrics of quality were evaluated. Their data showed that the 90-day mortality rate for the entire period was 3.3%. The mean (SD) operative time was 483 (113) minutes, and the median estimated blood loss was 250 mL (interquartile range, 150–500 mL). Conversion to open surgery was required in 13 patients (6.5%). Thirty-four patients (17.0%) developed a pancreatic fistula (ISGPF grade A, 17 [50.0%]; B, 10 [29.4%]; or C, 7 [20.6%]). Complications occurred in 135 patients (67.5%) with major complications (Clavien–Dindo classification ≥3) occurring in 52 (26.0%) patients. The median length of hospital stay was nine days, with a 90-day readmission rate of 29.2%. An R0 resection was performed in 184 patients (92.0%), with the median number of lymph nodes harvested being 22. No statistically significant differences in mortality or major morbidity rates were observed in this study. As the learning curve increased, statistically significant improvements in

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the estimated blood loss and conversion to open surgery occurred after 20 cases (600 mL vs 250 mL [P = 0.002] and 35.0% vs 3.3% [P <0.001], respectively), decreased incidence of pancreatic fistula was seen after 40 cases (27.5% vs 14.4%; P = 0.04), and a shortened operation time was observed after 80 cases (581 min vs 417 min; P <0.001). Although a continuous improvement in complication rates, lengths of hospital stay, and readmission rates was observed, these did not reach statistical significance. The outcomes of the last 120 cases, which represented optimized metrics beyond the learning curve, showed a mean operative time of 417 minutes, median estimated blood loss of 250 mL, conversion rate of 3.3%, 90-day mortality of 3.3%, clinically relevant pancreatic fistula (grade B/C) rate of 6.9%, and median length of hospital stay of nine days.

Shi et al. conducted a retrospective study on 450 consecutive patients who underwent robot-assisted RPD between May 2010 and December 2018 at Shanghai Ruijin Hospital [21]. The mean operative time and EBL were 309.6 ± 86.7 minutes and 419.0 ± 285.8 mL, respectively. Five cases of conversion to open surgery occurred because of massive bleeding (three cases) and severe vascular invasion by the tumor (two cases). An R0 resection was achieved in 418 (92.9%) patients, with the mean number of lymph nodes harvested being 16. Thirty-nine (8.8%) patients developed biochemical pancreatic leaks. Grade B or C POPF occurred in 44 patients (9.8%). A total of 181 (40.2%) patients developed complications, with severe complications (Clavien–Dindo ≥3) in 32 (7.1%) patients. Seventeen (3.8%) patients underwent reoperation, and the 90-day mortality rate was 2.7% (12 patients). The mean postoperative length of hospital stay was 22.3 ± 14.9 days. As the learning curve increased, the operative time decreased gradually over time from 405.4 ± 112.9 minutes (case 1–50) to 273.6 ± 70 minutes (case 301–350) (P <0.001), and the EBL reduced from 410 ± 563.5 mL (case 1–50) to 149.0 ± 103.3 mL (case 351–400) (P <0.001), respectively. According to the CUSUM curve, three phases were observed in the RPD learning curve. The inflection points were observed in cases 100 and 250. The incidence of a pancreatic leak (fistula) in the last 350 cases was significantly lower than that in the first 100 cases (30.0% vs 15.1%; P = 0.003).

Robot Distal Pancreatectomy

Technique of RDP

After the peritoneum is accessed in a similar fashion to that obtained using the laparoscopic approach, additional trocars should be placed, and the robot docked

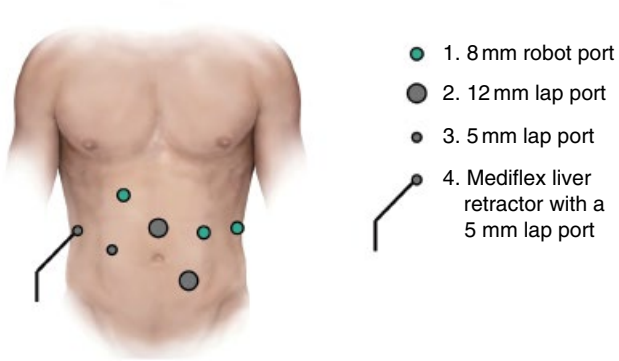


Figure 140.2 Port configuration for robotic distal pancreatectomy.

(Fig. 140.2) [22]. The splenic artery should be isolated at its take-off from the celiac trunk and divided with a vascular stapler. A lymphadenectomy should then be performed, starting from the left side of the SMA laterally, taking out the posterior pancreatic fascia *en bloc*, with a complete celiac lymphadenectomy being performed. With large tumors involving the fourth portion of the duodenum or colon, the robot allows meticulous *en bloc* resections with reconstructions performed in a similar fashion to the open technique [22] (Table 140.3).

Outcomes of RDP

In contrast to open distal pancreatectomy, patients who underwent RDP had decreased length of hospital stay, reduced blood loss, and equivalent complication rates [16]. In view of the need for complex operational requirements, RDP should be carried out in high-volume centers [13].

At the University of Pittsburgh, Shakir et al. studied 100 RDP patients and found precipitous reductions in the operative time from an initial time of 331–266 min and 210 min, after the first 20 and 40 cases, respectively (P <0.0001) [23]. The likelihood of readmission decreased significantly after the first 40 cases (P = 0.04). Nonsignificant reductions were observed in the occurrence rates of major (Clavien–Dindo Grade III or higher) morbidity and Grade B/C pancreatic fistula, as well as the length of hospital stay.

Daouadi et al. retrospectively compared the outcomes of LDP and RDP in a matched cohort [24]. Patients who underwent RDP had comparable age, sex, race, American Society of Anesthesiologists score, and tumor size with those who underwent LDP. The postoperative length of hospital stay and rates of pancreatic fistula, blood transfusion, and readmission were not statistically different. However, patients in the RDP group showed lower

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Table 140.3 Analyses of RDP studies.

No.	Author	Year	Operative time mean[a], min	EBL, mL[a]	Fistula rate (grade B/C)	Clavien ≥3	Mortality rate (90-day)	N (total)/N (malignant)	LOS, days[a]	Readmission (90-day)
1	Takahashi[19]	2018	242 ±78	50 (25–800)	4 (9.3)	4 (9.3)	1 (2.3)		5 [2–19]	8 (18.6)
2	Shyr [18]	2018	188±93	183±263	16 (22.9)	1 (1.4)	0	70/20	11±9	
3	Liu [32]	2017	207.1±65.5	100 (50–200)	7 (6.9)	5 (4.9)	0	102/26	7.67±2.19	
4	Xourafas [33]	2017	243 [91–1089]		42 (21)		1 (0.5)[b]	200/108	5 [0–36]	

EBL, estimated blood loss; LOS, length of stay.
[a] Mean (SD) or median [IQR].
[b] 30-day.

conversion rates to open surgery and less blood loss than those in the LDP group.

Shyr et al. reported a prospective study which included 70 patients who underwent RDP [18]. They found that 37 cases were required to get ahead of the learning curve. The median console time (112 minutes vs 225 minutes, P <0.001) was significantly shorter, and the median blood loss was significantly less (30 cc vs 100 cc; P = 0.003) at the late stage. The clinically relevant pancreatic fistula rate was 22.9%, with 32.4% at the early stage and 12.1% at the late stage (P = 0.043).

Conclusion

Early adopters have guaranteed the safety and feasibility of robotic resection for pancreatic cancer. It is recommended that to perform robotic pancreatic surgery in high-volume pancreatic centers, the volume is as important as the outcomes, and decreasing the learning curve for new centers that may be interested in performing robotic pancreatectomy is critical for the successful and sustainable dissemination of such techniques.

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Extended Radical Surgery for Pancreatic Cancer

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Introduction

Surgery is possible in only 15–20% of all patients suffering from pancreatic ductal adenocarcinoma (PDAC), by the time of diagnosis, which offers the chance of long-term survival in 20–25% when combined with adjuvant chemotherapy [1,2]. With the ongoing development of specialization and centralization for pancreatic surgery since the late 20th century, not only has postoperative mortality been considerably decreased but also the borders of resectability have been extended [3–7]. This has led to the development of so-called "extended resections" which exceed the standard historic approaches of partial pancreatoduodenectomy and distal or total pancreatectomy. In particular, extended lymphadenectomy, resection of adjacent vessels (superior mesenteric and/or portal vein, celiac axis, superior mesenteric artery) and organs have been performed and investigated in a large number of studies [8–18].

These developments raised the need for a definition and standardization of local resectability to better compare publications on this topic and to establish pathways for the diagnostic and therapeutic management of these patients. Today, the only situation that represents a clear contraindication for surgery is the finding of systemic spread, especially peritoneal carcinomatosis or diffuse liver metastases [19,20]. Regarding limited metastatic PDAC (i.e., single liver metastasis), resections are technically possible and several small case series have been reported [21]. Despite some encouraging results in these studies, surgery in metastatic PDAC remains a highly individual concept and the oncologic outcome is unclear to date [21].

The definition of "extended resection" in PDAC is closely correlated with the definition of "resectability." The critical anatomic structures to evaluate for local resectability in PDAC are the arterial and venous vessels located close to the pancreatic head and body, namely the superior mesenteric (SMV)/portal vein (PV) and the celiac axis (CA) as well as the superior mesenteric artery (SMA).

Resectability is defined as primary resectable PDAC, borderline resectable (BR-PDAC) or irresectable PDAC according to the criteria published by the International Study Group for Pancreatic Surgery in 2014 [16], which are mainly based on the recommendations of the National Comprehensive Cancer Network (NCCN) [11]. Besides these two recently published definitions, two other classifications are in clinical use, namely the definition of the AHPBA/SSO/SSAT published in 2009 [17] and the MD Anderson criteria, published in 2006 [18].

All these definitions are similar with regard to resectable PDAC. This implies that the tumor does not involve any vascular structures (no distortion of SMV or PV and clearly preserved fat planes towards CA and SMA).

Borderline resectable PDAC is characterized by a distortion/narrowing or occlusion of the respective veins but with a technical possibility of reconstruction on the proximal and distal margins of the veins (Fig. 141.1). PV involvement according to the MD Anderson definition does not include contact or narrowing of the vein, but gives occlusion as the criterion for BR-PDAC. With regard to the arterial structures, all definitions describe a semi-circumferential abutment (≤180°) of the SMA or an attachment at the hepatic artery (HA) without contact towards the CA as borderline resectable.

Unresectable PDAC is defined as a more extended involvement of the SMA, CA, aorta or inferior vena cava as well as a SMV/PV venous involvement without a possibility for surgical reconstruction of the venous tract due to lack of a suitable luminal diameter of the feeding and/or draining vein. This situation is most likely to be

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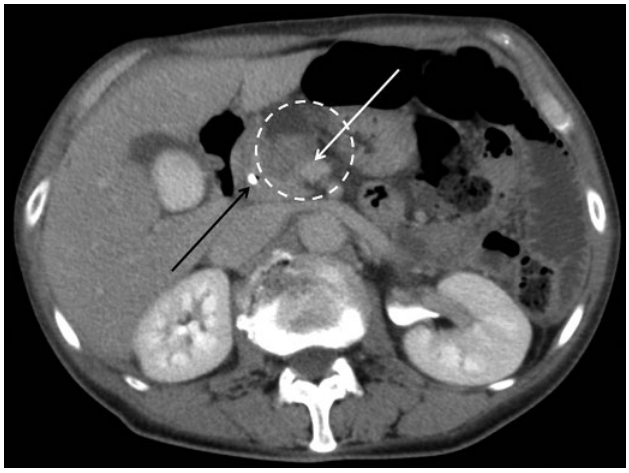


Figure 141.1 Contrast-enhanced CT scan (transversal, venous phase) showing a hypointense PDAC (white circle) with PV contact (white arrow); borderline resectability according to the ISGPS criteria. Stent inserted in common bile duct (black arrow).

associated with tumor-related portal cavernous transformation. Beyond the topic of vascular tumor involvement, the involvement of adjacent organs, i.e., mesocolon, colon, stomach, adrenal gland or kidney, may require extended radical resection approaches. There is international consensus that these extended approaches are feasible in terms of surgical and oncologic outcome and organ involvement should not be considered an obstacle for resection as long as a radical tumor removal is possible [21].

All the above-mentioned definitions of resectability are based on anatomic and technical aspects, but it has become obvious that such considerations do not include tumor- and patient related factors that determine long-term oncologic outcomes to a great extent. As a consequence, these factors have been evaluated and included in a more recent definition of resectability, published by the International Association of Pancreatology (IAP) in 2018 [22]. This consensus includes the pretherapeutic criteria "A: anatomic" (comparable to all other definitions), "B: biological" (depending on level of CA 19-9 and suspicion or proof of positive lymph nodes), and "C: conditional" (defined by the patient's ECOG status), and recommends that patients may be classified as "borderline resectable" based on categories B or C despite given resectability in category A. This may lead to a change in clinical decision, namely offering a neoadjuvant therapy (i.e., in case of unfavorable findings in category B) instead of upfront surgery.

Besides the classification of resectability, the operative procedures themselves have been classified in terms of the extent of surgery. This comprises four-tier classifications for partial and total pancreatectomies, which are specifically defined as "standard" (type 1), additional venous resection (type 2), additional organ resection (type 3), and additional arterial resection (type 4) [23,24]. This classification is based on the fact that procedure-specific complications as well as mortality are significantly different between these four types and allows a standardized reporting of the respective operations and outcomes.

Surgical Procedures and Outcomes

Lymphadenectomy

Lymph node spread is one of the most important prognostic factors for long-term outcome after PDAC resection [25,26]. The extent of lymphadenectomy during PDAC surgery is well defined and included in national guidelines and international consensus statements [27,28]. In partial pancreatoduodenectomy, the lymph nodes of the hepatoduodenal ligament, those along the common hepatic artery, portal vein and the cranial portion of superior mesenteric vein as well as right-sided lymph nodes of the celiac trunk and along the superior mesenteric artery are evaluated [28]. In distal pancreatectomy for tumors of the body and tail of the gland, tumor spread is mainly observed in the lymph nodes attached to the pancreas [29]. Further frequent metastatic sites are the nodes along the splenic artery, the paraaortic area and along the inferior margin of the pancreas as well as along the superior mesenteric artery. These lymph nodes should be routinely removed [30,31].

Lymphadenectomy during total pancreatectomy can be regarded as a combination of the approaches of lymph node dissection in partial pancreatoduodenectomy and distal resection. It includes dissection of the hepatoduodenal ligament, the lymph nodes along the hepatic artery, both sides of the celiac trunk, the splenic artery, and the inferior pancreatic margin. This procedure will usually result in approximately 30–50 lymph nodes included in the resected specimen. The most commonly reported extended approach in lymphadenectomy is the dissection of interaortocaval and paraaortic lymph nodes, especially when these are macroscopically suspicious during exploration [14–18].

Although there are differences between the studies with regard to the total number of harvested lymph nodes and outcome of certain subgroup analyses, there is no evidence that extended lymphadenectomy results in a better oncologic outcome or survival. This is confirmed by a recent metaanalysis including 13 studies and demonstrating that positive paraaortic lymph nodes are associated with significantly worse survival [32]. Furthermore, extended lymphadenectomy is associated with a significantly increased surgical morbidity (i.e., chyle leakage and fluid collections) and decreased quality of life (i.e.,

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diarrhea and intestinal discomfort) in the postoperative follow-up [18]. Consequently, the concept of extended lymphadenectomy during PDAC resection is not recommended as an uncertain oncologic value is achieved at the price of a high postoperative morbidity.

Vascular Resections

Historically, major vessel involvement has been a contraindication for PDAC resection. In 1973, Fortner described a surgical approach of regional pancreatectomy with *en bloc* resection of peripancreatic soft tissue, regional lymph nodes, and PV resection (type I), or resection and reconstruction of a major artery (type II) [33]. These initial extended resections, which were associated with a high morbidity (67%) and mortality (23%) as well as low survival rates (three-year-survival rate 3%), discouraged generalized adoption of major vessel resection and reconstruction [33]. However, major advances in radiologic and surgical techniques improved preoperative staging and reduced surgical morbidity and mortality [2,3,34].

Venous Resections

Resection of the PV and/or SMV during PDAC surgery can be performed without an increased perioperative morbidity or mortality and with good oncologic outcome compared to standard resections [6–9,11,12,34]. This has been demonstrated in a large number of studies and metaanalyses and has consequently been implemented in national guidelines and consensus recommendations [19,20,35].

Venous resection can be done by either a tangential or a segmental resection [6–9]. A small defect can be closed by direct suture if the vein is not narrowed as this may cause thrombosis in the postoperative course. If a tangential resection defect needs to be augmented, this is possible by an autologous peritoneal patch [36]. In case of segmental resection, the reconstruction requires an end-to-end anastomosis (Fig. 141.2). Depending on the length of the resection, either a direct suture is possible or an autologous venous/prosthetic graft must be inserted. For this purpose, autologous grafting (e.g., renal vein, saphenous vein, internal jugular vein) is possible but requires venous harvesting before clamping and resection [37,38]. Alternatively, a synthetic graft, i.e., a 10–12 mm ringed Gore-Tex® prosthesis, can be chosen to bridge the resected vein segment [39].

When resection of the venous confluence is required during partial PD, the splenic vein should be reinserted by an end-to-side anastomosis as long as this does not create any lateral tension on the anastomosis. This avoids left-sided portal hypertension and restores free drainage

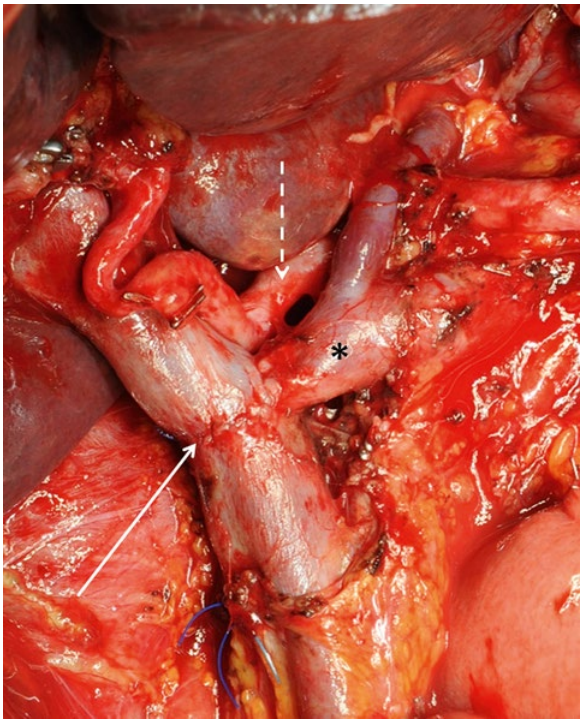


Figure 141.2 Intraoperative situs after PV confluens resection. End-to-end anastomosis (white arrow) between SMV and PV under preservation of the gastric coronary and splenic vein (black star). Celiac axis with splenic artery (broken white arrow) and hepatic artery.

of the stomach. In case of total pancreatectomy with splenectomy, stomach drainage is an important topic as well. In this situation, the gastric coronary vein may be preserved or reinserted, if necessary [40].

Another important aspect during PV/SMV resection is the diameter of the distal venous vessel, especially in tumors located in the uncinate process. The presence of a SMV branch of a sufficient diameter has to be confirmed before resection as otherwise it may be impossible to restore small bowel drainage afterwards, which may be a technical limit for resectability. Furthermore, for all attempts at venous resection, the mesenteric root should be mobilized completely by resolving the attachment of the right hemicolon to the retroperitoneal adhesions (Cattell–Braasch maneuver) [41]. This allows bridging of long distances after resection of the vein, and graft interposition can often be avoided by this approach.

When other surgical outcome parameters are considered, it has been demonstrated that both resection with a direct anastomosis and interposition of a graft can be performed safely. Numerous authors have reported a mortality rate below 5% in patients undergoing venous resection with PD, similar to that of standard PD [6–9, 37–39]. A systematic review [8] of outcome of synchronous PV/SMV resection during pancreatectomy included

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52 studies encompassing 1646 patients undergoing venous resection mainly together with partial PD (71%) or total PD (24%). The median morbidity rate for patients undergoing PD with venous resection was 42 %, and the mortality rate was 6% with a median survival of 13 months and one-, three-, and five-year overall survival rates of 50%, 18%, and 8%. Another more recent metaanalysis [9] included 19 studies and compared 661 patients with and 2247 patients without venous resections. Both groups showed similar surgical outcomes without any difference in overall survival. Furthermore, in terms of oncologic results, no difference in overall survival between both patient collectives was found, resulting in a five-year survival rate of 12.3%, certainly superior to palliative treatment. This demonstrates that resection of the PV or SMV is potentially curative and that involvement of the SMV or PV seems to be a consequence of the tumor being located close to these structures rather than a reflection of an uncommonly aggressive tumor biology.

Arterial Resections

Arterial resection during PDAC surgery has remained an area of controversy since Fortner first introduced the concept as part of regional pancreatectomy. Many authors regard invasion of the hepatic artery and celiac axis of the SMA as a contraindication for surgery because of the high morbidity and mortality rates associated with arterial resection and reconstruction as well as assuming a rather poor oncologic outcome [11–13,42].

Recently, with the introduction of effective neoadjuvant and adjuvant therapies, attention is being refocused on the potential benefit of removing the primary tumor, even in the setting of complex arterial abutment or encasement, when this is the only site of disease. Although in some patients, arterial invasion is considered as borderline resectable according to the ISGPS consensus statement, an upfront resection is rarely recommendable, even if it can technically be performed [35]. Furthermore, arterial invasion usually predicts extensive involvement of the mesenteric neural plexus with an inability to achieve a negative resection margin even with radical extended surgery. However, there is growing evidence that patients after neoadjuvant therapy should be subjected to surgical exploration as long as no signs of systemic tumor spread are present. Using this approach, in 33–50% of all primarily unresectable patients, a radical resection might be possible and R0 resection rates comparable to standard resections can be achieved [43–49]. An artery-first approach with evaluation of the SMA and celiac axis should be routinely used early during surgical resection in order to explore arterial as well as retroperitoneal tumor invasion [50–53]. Various artery-first approaches during PD can be carried out, either through a right-sided route after Kocher maneuver or through a left-sided route after lowering the duodenojejunal flexure or by an infracolic route [50]. These techniques offer several oncologic benefits, such as facilitating interaortocaval lymphadenectomy at the origin of the SMA and checking resectability at the retroperitoneal margin.

The first comprehensive metaanalysis on arterial resections included 26 studies with 366 patients undergoing arterial resection and 2243 patients without arterial resection [42]. This analysis showed median perioperative morbidity of 54% and mortality of 12%, respectively. Survival analysis did not show a benefit compared with patients who underwent only venous resection. However, compared with patients who underwent only palliative treatment, the one-year survival was favorable, being threefold greater for patients with arterial resection, especially when resections of the hepatic artery or CA were considered.

Another metaanalysis focusing specifically on SMA resection included a total of 70 patients. It confirmed that the resection is technically possible and various types of reconstruction (i.e., end-to-end anastomosis or grafting with the saphenous vein) are possible [54]. However, as these approaches were burdened by a high morbidity and oncologic outcome finally equalled a palliative therapy with FOLFIRINOX (median survival 11 months), the authors concluded that SMA resections should not be performed.

Despite these initially disappointing results, arterial resection in PDAC surgery has been reappraised in recent years with regard to several larger series that have been published. A single-center cohort study reported that pancreatectomy with artery resection can be performed without increased postoperative mortality and results in five-year survival rates of 23%, clearly superior to palliation alone for patients with locally advanced tumors [55]. Another recent study covering nearly 40 years of experience showed that any type of arterial resection was performed at a frequency of 6% (44/730 patients) but confirmed the safety and efficacy of these operations, additionally suggesting neoadjuvant therapy before arterial resection as a mandatory concept for locally advanced pancreatic cancer [56]. Two more important aspects of such surgical approaches were shown in the two largest single-center collectives of 111 and 195 patients, respectively [57,58]. Both of these studies underline the importance of selecting patients properly as well as gaining sufficient surgical experience demonstrated by the impact of the surgical learning curve to safely perform such procedures.

Overall, these recent publications justify the approach of pancreatectomy with arterial resection and reconstruction. From the technical point of view, after celiac axis or hepatic artery resection reconstruction can be

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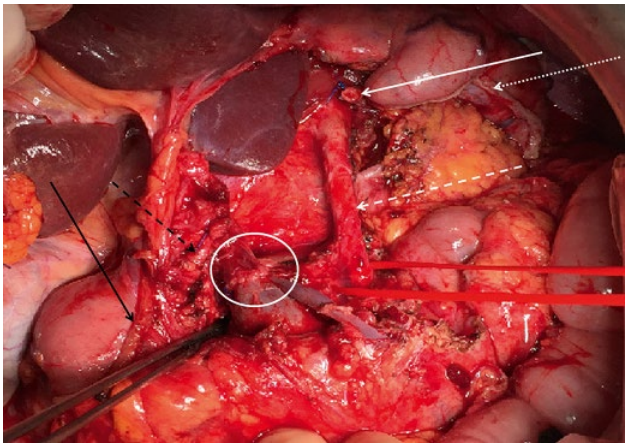


Figure 141.3 Intraoperative situs after modified Appleby resection for PDAC of the pancreatic body combined with PV resection (white circle). Cut CA basis (white arrow), dissected SMA (broken white arrow), subcardial cut margin of the stomach (dotted white arrow), cut margin of the duodenum (black arrow), preserved gastroduodenal artery for hepatic perfusion (broken black arrow).

carried out by direct anastomosis, by interposition of a venous graft (i.e., reversed saphenous or internal jugular vein) or with a prosthesis. The celiac axis might be resected down to its aortal orifice in PD as well as in DP or total pancreatectomy. As long as the proper hepatic artery can be preserved, a reconstruction is possible. An arterial graft (i.e., splenic artery) can also be used [59].

Regarding DP, celiac axis resection without revascularization (modified Appleby procedure) is an option for tumor removal as long as the proper hepatic artery is preserved and a sufficient arterial inflow via the gastroduodenal artery is present (Fig. 141.3). Numerous case series have described this procedure with reasonable results in terms of surgical and oncologic outcomes which seem to be nearly equal to the standard approaches [60–67]. According to the larger series in the literature, including more than 10 patients, these procedures can be carried out with mortality rates of 0–7% and an average overall morbidity of around 50%. Median survival in these reports ranges between 10 and 25 months; in the majority of publications approximately 20 months can be achieved. According to these retrospective studies, the modified Appleby procedure seems to be a good option in terms of postoperative and long-term outcome, but no high-level evidence is available to support these findings.

Combined Vascular Resections

Data on combined vascular procedures (venous and arterial resection) are scarce. There is only very limited literature published on this topic, and no conclusive evidence with regard to perioperative morbidity and oncologic outcome is available. The approach is technically feasible, but is not recommended as a standard procedure and must be based on individual decisions.

Arterial Divestment

A novel approach following neoadjuvant therapy is the concept of "arterial divestment" [68,69]. The idea of this technique is the observation that, despite pretherapeutic visible arterial abutment or even encasement, an arterial resection can often be avoided by sharp dissection in the subadventitial layer, as in many patients only fibrous tissue without any viable tumor is found after pretreatment. Consequently, tumor removal without resection of the artery itself is possible without compromising radicality (Fig. 141.4). As this technique has only been introduced recently, there are few data on the oncologic long-term outcome, but postoperative histopathologic workup supports this concept in terms of R0 resection rates.

Multivisceral Resections

If adjacent organs are affected by locally advanced PDAC (i.e., colon, stomach, left adrenal gland, small bowel or left kidney), complete tumor removal requires partial or total resection of these organs, which also fulfills the

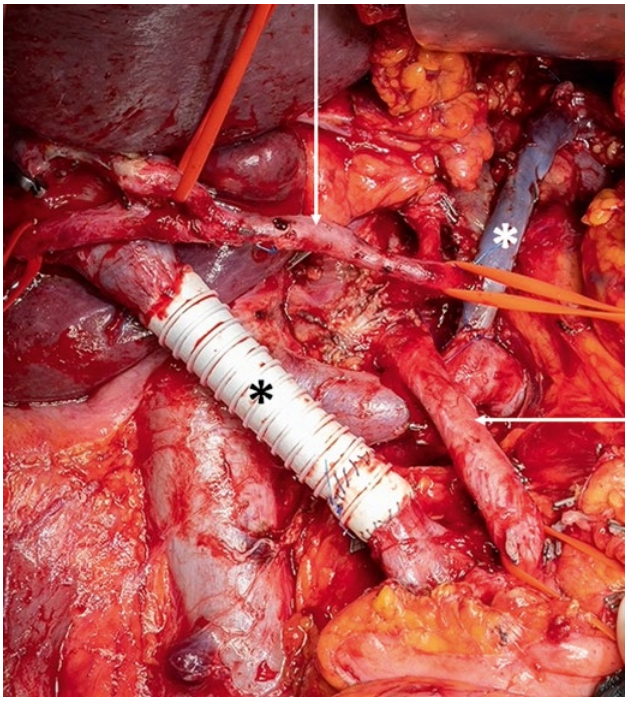


Figure 141.4 Intraoperative situs after total pancreatectomy with divestment of the SMA and hepatic artery (white arrows). Resection of the PV/SMV axis with ringed allograft reconstruction (black star). Reinsertion of the coronary vein into the left renal vein (white star).

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criteria of "extended resections" defined by the ISGPS in 2014 [35]. A neoadjuvant treatment is not indicated if technically a complete resection can be achieved based on the preoperative cross-sectional imaging. In larger series, between 20 and more than 270 patients are included and the most commonly resected organs are the colon and stomach [5,10,70–72]. In many patients also PV/SMV resections are often performed synchronously, reflecting local extension of the tumor and the close anatomic relationship of these venous structures.

Multivisceral resections have been investigated in large patient collectives and are associated with increased postoperative morbidity predicted by a long operation time and the resection of two or more additional organs [10,70–72]. Postoperative mortality is not increased unless patients show a relevant preoperative comorbidity. Regarding oncologic outcome, survival is similar to standard resections and in approximately 10–15% of these patients, five-year survival can be achieved, which is clearly superior to any palliative treatment options.

These results underline that extended surgery is a feasible approach if patients are accurately selected for these procedures, as certain subgroups seem to have a much greater benefit from surgery than others. For this purpose, common cross-sectional imaging is not sufficient and other markers need to be defined in the future. Tumor markers, especially CA 19-9, are used in clinical practice. A cutoff value of 400 U/mL has been identified as the threshold for a poor oncologic outcome and may help to stratify patients preoperatively [73].

Metastases Resection

According to international guidelines and clinical practice, stage IV PDAC patients are generally referred to palliative treatment by chemotherapy [2,19,20]. With the administration of modern chemotherapy regimens, a median survival of 11 months can be achieved in a palliative setting [74]. However, these regimens are often associated with severe side-effects that can impair patients' quality of life and no long-term survivors have been reported.

Although it remains unquestionable that PDAC with diffuse tumor spread to the liver, peritoneum or the lung is a situation in which surgery is not indicated, the approach of a surgical resection or liver-directed therapies in oligometastatic situations has been performed in a limited number of studies in the past with partly conflicting results [67–79]. An older metaanalysis published in 2007 [21] showed no clear benefit for resection of metastases. As the study was based on small case series, the level of evidence was highly limited. Previous studies showed more encouraging results with a median survival of 12 months [80], which was superior to historically reported survival times of 6–7 months following palliative monochemotherapy (i.e., gemcitabine) but did not exceed modern palliative multidrug protocols (i.e., FOLFIRINOX). However, especially when such protocols are applied and an additional metastases resection can be performed after induction therapy, the picture has changed and properly selected patients may benefit from metastases-directed surgery, either syn- or metachronously, and achieve up to two years median survival [81].

In addition and most importantly, in contrast to the palliative setting, the addition of metastases-directed surgery to the multimodal approach can enhance the possibility of long-term survival, with five-year survival rates of 10%, which is impossible without surgery in stage IV PDAC and underlines the importance of an interdisciplinary approach and proper patient selection of surgical candidates with stage IV PDAC. Besides synchronous resection in an oligometastatic situation, metachronous approaches to liver metastases have also been reported [76–78,80]. In this context, the interval between the initial and the consecutive operation or liver-directed therapy may be useful as an additional criterion for patient selection, and probably best reflects the tumor biology and potential prognosis of the individual patient. In general, clinical experience suggests that a time interval of 12 months can probably be regarded as a reference, although not based on high-level evidence. As this observation period cannot be used for synchronous resection of liver metastases, the decision for surgery in this situation is even more challenging and additional studies and markers are warranted for prognostic patient stratification and to evaluate these approaches in the future.

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Palliative Pancreatic Resection: Is It Justified?

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Introduction

While surgical removal of the tumor remains the only curative treatment option for patients suffering from pancreatic ductal adenocarcinoma (PDAC), only a minority of diagnosed cases are amenable to undergo resection with curative intent. The main reason is that PDAC is mostly diagnosed in an advanced stage or even with distant metastatatic disease at diagnosis [1]. Another issue is that despite the increasing centralization of pancreatic surgery, referral to a specialized center is often delayed, which provoked claims in recent years that pancreatic cancer should be treated as a medical emergency [2].

For localized or regional stages, resection of the primary pancreatic tumor together with regional lymphadenectomy remains the treatment of choice with the intention to cure. However, if strict pathology assessment is applied, rates of margin-positive resection (R1) are remarkably high (>70%) [3,4]. Nonetheless, in PDAC surgery R1 resection especially on the medial margin is not actually considered as "palliative resection" because a survival benefit and even long-term survival may be observed in these cases. Therefore, the term "palliative resection" is usually only used in cases of gross R2 tumor debulking procedures [5]. The current literature does not support such "palliative resections," or debulking procedures for PDAC, as no improvement of survival has been observed despite substantial morbidity of such procedures [6–9]. Thus, surgical palliation of advanced PDAC should avoid tumor resection and palliation of symptoms should be achieved by interventional procedures and/or bypass surgery [10,11].

Definition of Palliative Resection

Although substantial progress in imaging procedures has been achieved, it remains one of the greatest clinical challenges to accurately evaluate whether a PDAC is in fact locally confined or advanced. While metastases are usually found before treatment initiation, the local resectability is more difficult to assess. Therefore, standardized criteria have now been widely implemented including specific findings of cross-sectional imaging enhanced with biomarkers and conditional factors as criteria of biologic resectability [12]. These criteria can help to guide treatment decisions and avoid unnecessary surgical exploration.

While putative invasion of the superior mesenteric/portal vein axis can be managed surgically in order to achieve margin negativity (at least at the vein margin), tumor extension towards the superior mesenteric artery (SMA) is at times hard to determine in preoperative scanning and in some cases is only detected intraoperatively or even in the final pathology specimen. Similarly, the medial margin (the so-called "mesopancreas") is frequently at risk but can mostly only be judged definitely when the resection has been performed. Thus, exploratory laparotomy followed by dissection of the superior mesenteric artery axis (and/or celiac axis) is sometimes necessary to determine local resectability.

Review of the Literature

The development of higher resolution in cross-sectional imaging and the advance in surgical techniques have led to an increase in patients receiving surgery. A cohort

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study including over 16 000 patients receiving pancreatic resection identified an in-hospital mortality of 5% [13], illustrating both the risk of pancreatic surgery and the rising standard of intraoperative and postoperative treatment. However, a multidisciplinary approach and surgical pancreatic expertise are essential in order to allow best patient care and treating these patients successfully. This is essential for initial assessment of tumor resectability, which determines further therapy approaches.

Difficulties of Imaging and Preoperative Staging and Surgical Approaches to Avoid Incomplete Resections

Contrast-enhanced helical computed tomography (CT) (triphasic pancreatic-protocol CT) and/or magnetic resonance imaging (MRI) of the abdomen and pelvis represent the essential diagnostic techniques for preoperative tumor staging and assessment of resectability [14,15]. Involvement and invasion of major abdominal vessels including the SMA, superior mesenteric vein (SMV), portal vein, and celiac axis are crucial determinants of local operability and possible extension of surgery beyond classic procedures such as the Whipple operation.

While venous and/or portal vein involvement are not strict contraindications for a potentially curative approach [16], tumors with advanced arterial involvement are regarded as locally incurable [17]. In such cases, true R0 resections are technically difficult to achieve, and extension of surgery, in terms of major arterial resection, may increase morbidity and mortality. On the other hand, a recent study comparing pancreatectomy with arterial resection to palliative surgery for borderline resectable or locally advanced pancreatic cancer demonstrated a superior one-, three, and five-year survival in the resection group. This study suggests that arterial resection might be feasible and beneficial in highly selected patients [18]. However, such an approach should only be performed in selected cases within a multimodal treatment approach at specialized centers and preferably within clinical studies.

Another approach for locally advanced tumors with arterial involvement, which is currently being assessed in the trial setting, is to split arterial reconstruction and tumor resection into separate procedures. The aim is to reduce perioperative morbidity and mortality in comparison to simultaneous tumor resection with arterial reconstruction. In this trial, patients undergo visceral debranching/arterial reconstruction followed by neoadjuvant chemotherapy and subsequent tumor resection [19].

As an alternative to arterial resection, a novel technique, the so-called subadventitial divestment, has recently been described with promising results. With this technique, which might be of particular interest after neoadjuvant therapy, the periarterial soft tissue is fully cleared in the subadventitial plane, allowing for radical resection without the need for arterial resection [20,21].

The adherent posterior resection margin of the SMA is the most common location of microscopic tumor residues (R1 situation) [4]. Since neither of the cross-sectional imaging modalities provides high accuracy in predicting SMA infiltration, surgical exploration remains the only reliable diagnostic means. During classic pancreatoduodenectomy, the medial and posterior resection margins can only be reliably assessed after transection of the pancreas has been performed. These findings have led to the so-called posterior artery-first approach for locally advanced tumors [22], which allows for precise intraoperative assessment of the SMA before transection of the pancreas.

In addition to palpation and visual control, intraoperative ultrasonography (IOUS) has further increased the accuracy of resectability assessment [23,24]. This illustration of the diagnostic process, which in many cases only begins at the time of laparotomy, suggests that only specialized surgeons in high-volume centers should perform operations on borderline resectable and locally advanced tumors of the pancreas.

Perioperative Multimodal Therapy

Due to highly invasive growth and early-stage metastases, PDAC can almost always be considered a systemic disease. While surgery is the only curative option in early tumor stages, the systemic nature of advanced disease PDAC justifies the need for a multimodal therapeutic approach.

If local unresectability is confirmed intraoperatively, surgery is terminated and chemotherapy or chemoradiation may be initiated. Because FOLFIRINOX-based chemotherapy regimens have been shown to be the most effective, with considerable response rates [25–28], we advocate administering 4–6 cycles of FOLFIRINOX before restaging, followed by pancreas CT staging. If the tumor was primarily unresectable, resection rates after neoadjuvant therapy can be up to 40–50% [29,30] and in borderline cases can even reach >80% [31]. If no distant metastases occur during neoadjuvant therapy and preferably there is a decrease in CA 19-9, reexploratory laparotomy should be performed and resectability judged again, if the patient's performance status is good [32]. This approach has shown

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considerable local response to chemotherapy with margin negativity. However, intraoperative judgment is complex because of the remaining local fibrotic tissue, which cannot be differentiated from the presence of remaining cancer cells, resulting in a longer, more demanding operation compared to surgery without neoadjuvant treatment [33]. Intraoperative frozen sections may be helpful in distinguishing the fibrotic tissue from viable tumor tissue.

Another potential therapy approach is intraoperative radiotherapy, which is a treatment option when an intraoperatively obtained frozen section shows margin positivity. A recent systematic review on the topic suggests possible survival benefits for selected patients, but so far without reaching statistical significance [34].

Similarly, irreversible electroporation in patients with locally advanced PDAC has demonstrated promising results in a prospective multicenter study and in a recent systematic review, but higher quality evidence is still needed to finally elucidate its effectiveness [35,36].

Standardized Classification of Margin Status

Verdecke et al. demonstrated that after application of a standardized pathology protocol, a significantly higher number of patients (85%) had a positive margin [3]. Esposito et al. presented similar data and showed that most pancreatoduodenectomy specimens (surgery with curative intent) in their series of 111 patients had a locally incomplete resection (76% R1 resections) [4]. This led the authors to the assumption that a standardized protocol on tissue workup rather than the extent of surgery predominantly determines the R1 status.

An intriguing but difficult-to-prove hypothesis is that R1 status in resected PDAC may be linked to the underlying biologic phenotype. A more aggressive biologic tumor phenotype in R1 resected tumors with an elevated lymph node ratio and more microvascular invasion compared with R0 resected tumors was identified in a study by Kimbrough et al. [37]. This underlines the urgent need for a diagnostic approach reaching beyond macroscopic and microscopic description of the cancer towards a biologic model allowing for individualized, tumor-adapted treatment.

Palliative Surgery

In patients with jaundice and/or gastric outlet obstruction diagnosed with an unresectable tumor, bypass surgery is considered the therapy of choice (see Chapter 144) in order to ensure symptomatic relief. Because debulking is sometimes inevitable, there are a few studies evaluating outcomes after debulking procedures.

A systematic review performed by Gillen et al. [7] included four patient cohorts with a total of 399 patients. Of these patients, 138 received pancreatic resection (R2 status), whereas the others underwent surgical bypass (biliary and/or enteral). Operation time, morbidity, and mortality were significantly increased in the resection group, whereas overall survival was only minimally extended. In line with these results, another systematic review and metaanalysis demonstrated higher morbidity after R1/R2 resections compared to bypass surgery. While R1 resections resulted in improved survival, there was no such benefit for R2 resections compared to bypass surgery only [8]. Thus, both authors conclude that in the context of locally advanced carcinoma, planned incomplete resections should be avoided.

Management of Preoperatively Understaged Patients

Because of the limitations of contemporary diagnostic methods and the resulting vagueness in preoperative imaging, some patients are discovered to have locally advanced tumors during operation. Nevertheless, routine staging laparoscopy is not recommended, due to the limited detection rate and absence of benefit after switching from surgical to endoscopic palliation [38].

For patients without presence of distant metastasis but a locally unresectable primary tumor, surgery is terminated and neoadjuvant therapy indicated. Palliative bypass (biliary and gastric) operations in such patients depend on tumor extent and symptoms. For example, in patients with functional biliary stents, bypass operations are not recommended. However, if the patient has biliary obstruction, biliary and gastric bypass operations are performed. After completion of neoadjuvant therapy, patients are reevaluated. All patients without clear evidence of distant metastasis are offered surgical reexploration, with the intention of tumor resection. In case of intraoperative confirmation of metastases, exploration is terminated. All patients without metastases may receive, if available at the institution, another boost of intraoperative radiation therapy (15 Gy) regardless of resection status, and all tumors classified as resectable after neoadjuvant treatment are removed surgically.

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In patients without evidence of distant metastases and a resectable primary tumor, surgery of the tumor will be performed. In cases of tumor-positive margins in the intraoperative frozen sections, patients may receive intraoperative radiation, if available.

In the event of positive SMA and/or celiac trunk margin verification by frozen section after resection of the pancreas is performed, a careful surgical attempt is made in order to convert an R2 resection into an R1/R0 resection (it can also be argued that once tumor integrity is disturbed, it is no longer possible to achieve an R0 resection). It should be emphasized that such an attempt could create a domino effect that may ultimately necessitate the ligation of major vessels or rearterialization of the liver or bowels. Therefore, it should be kept in mind that such procedures may potentially increase morbidity and mortality rates, and they should not be attempted outside referral centers.

Conclusion

Standard palliative pancreatoduodenectomy in PDAC (i.e., with macroscopically positive margins) did not prove to be beneficial over nonsurgical treatment and should therefore not be performed. Nevertheless, with currently limited diagnostic tools, it is inevitable in approximately 10% of patients. Under such circumstances, most R2 resections may be converted to R1 resections with careful and diligent surgery. It should be emphasized that such an attempt is not based on evidence and should only be performed as part of a scientific study in tertiary referral centers. Nonetheless, aggressive surgical approaches are justified, since resection provides the only chance of cure for some, and the best palliation for most, of the patients. Further research to preoperatively stratify the patient cohorts is necessary to identify groups who would benefit from extended resections from those who do not.

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Outcome of Patients after R0 Resection for Locally Advanced Pancreatic Cancer Combined with Hepatic Metastasectomy: Indications and Limitations

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Introduction

Surgical resection of pancreatic cancer combined with systemic chemotherapy offers the only chance for cure of this disease. However, over 50% of patients diagnosed with pancreatic cancer are deemed to have unresectable disease because of distant metastases [1]. The liver is the most common site of pancreatic cancer metastases, accounting for over 50% of all cases [2]. In pancreatic cancer patients with liver metastasis, the prognosis is extremely poor, with a five-year survival rate of less than 1% [3]. Because of the dismal prognosis and the lack of high-quality evidence, surgical resection is generally contraindicated in the current guidelines when synchronous liver metastases are present at the time of surgery.

The only exception may be oligometastases, which are regarded as an intermediate stage between localized disease and widespread metastatic disease [4]. There has been increasing interest in exploiting the role of curative surgical resection, which has been used to successfully treat colorectal and neuroendocrinal tumors with liver oligometastases. Available data suggest that curative pancreatectomy in combination with metastasectomy may benefit some highly select patients with liver oligometastases. In a recent large international survey, 31.4% of the pancreatic surgeons interviewed would conduct surgical exploration and offer possible resection for oligometastatic liver metastases to patients with resectable disease who had an excellent response to neoadjuvant therapy [5]. However, in view of current evidence derived from retrospective analyses, case series, and case reports, questions regarding the surgical and oncologic outcomes, indications, and contraindications of hepatic metastasectomy have yet to be answered.

Outcomes

For pancreatic cancer patients with synchronous liver metastasis, resection with curative intent involves radical pancreatectomy with concomitant hepatic metastasectomy. It is clear that any possible benefit should be carefully weighed against the potential risk of such an aggressive surgical approach. This procedure would only be justified by a good safety profile in the short term and a survival benefit in the long term after surgery. However, currently available data regarding the outcomes of such procedures are from small retrospective cohorts and are deemed insufficient and inconclusive.

Survival

The first case series in the literature on synchronous resection of liver metastases and pancreatic tumors dates from 1996 [6]. In this report, curative R0 resection was achieved in 69% of patients with synchronous liver metastases (N = 16). The median survival time was 8.3 months after synchronous hepatic resection.

In the largest retrospective study conducted thus far, reported by Andreou et al., 76 patients who underwent resection for pancreatic cancer and concomitant hepatectomy for synchronous liver metastases were analyzed [7]. The one-, three-, and five-year overall survival (OS) rates were 41%, 13%, and 7%, respectively. The second largest study, conducted by Tachezy et al., enrolled 69 patients who underwent pancreatic resection and synchronous hepatic metastasectomy [8]. They reported that OS was prolonged in the group of resected patients (median 14 vs 8 months). Interestingly, in the subgroup analysis, only patients with tumors located in the

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pancreatic head benefited from surgery, while those with tumors in the pancreatic body and tail received no benefit from resection.

Another study, by Hackert et al., analyzed the outcomes of 85 patients after pancreatic and concomitant liver resection, of whom 62 patients underwent synchronous hepatic metastasectomy [9]. The median survival for the whole cohort was 12.3 months, and it was 10.6 months for patients undergoing synchronous hepatic metastasectomy. No significant difference in survival outcomes was observed between the synchronously and metachronously resected patients regardless of neoadjuvant treatment, tumor localization in the pancreas, number and size of liver metastases, and preoperative CA 19-9 levels.

The most promising survival outcome thus far has been reported by Frigerio et al. [10]. In their relatively small cohort (N = 24), only patients who achieved successful downstaging (disappearance of liver metastasis on radiologic examination, normalization or significant reduction in serum CA 19-9) after neoadjuvant chemotherapy were enrolled. Unsurprisingly, R0 resection was achieved in 88% of patients, and the median OS reached 56 months.

Although the above studies favor resection, there are also studies that failed to show a possible survival benefit following synchronous liver resection. Dünschede et al. reported on 14 patients who underwent synchronous liver resection for metastatic pancreatic cancer [11]. They found no differences in the survival outcomes of patients with synchronous liver metastases of pancreatic cancer treated either by resection of the primary tumor combined with partial hepatectomy or by gemcitabine (8 vs 11 months).

Safety

Although the safety of pancreatic resection has dramatically improved, it is still a challenging procedure. Undoubtedly, synchronous hepatic metastasectomy further increases the complexity of surgery and thus theoretically contributes to higher morbidity and mortality. This concern is indeed supported by some early reports [12,13]. However, reports over the last few years, including the three largest series, showed comparable surgical morbidity and mortality outcomes [7–9]. The safety of such extended resections seems acceptable provided that the procedures are performed in high-volume centers.

Indications

The currently limited evidence indicates that synchronous pancreatic and liver resection for metastatic pancreatic cancer can be carried out safely. It is still far from clear who is most likely to benefit from such extended resections. Thus, establishing criteria upon which patients can be selected to undergo synchronous pancreatic and liver resection is necessary. Based on the currently available data, a low metastatic burden and a good response to neoadjuvant therapy are generally considered potential indications for curative surgery.

Metastatic Burden

In metastatic pancreatic cancer, widespread or high-volume metastases contraindicate resection with curative intent. For liver metastasis, oligometastatic disease makes curative synchronous pancreatic and liver resection possible. Unfortunately, the term “oligometastases” in pancreatic cancer has been poorly defined in the literature [4,14]. Recently, Damanakis et al. proposed a new definition of oligometastatic disease from pancreatic cancer that incorporated biologic behavior into the criteria [15]. Patients with fewer than five metastases in a single organ, serum CA 19-9 baseline <1000 U/mL (with bilirubin <2 mg/dL), and responsive or stable disease after first-line chemotherapy were considered to have oligometastatic disease. In this study, 10 patients meeting the criteria had a significantly longer OS time (median 19.4 vs 7.2 months) than the remaining patients.

The combination of anatomic and biologic criteria may facilitate candidate selection for surgery. However, clinicians should still be prudent when making a diagnosis of oligometastatic disease. A thorough evaluation of tumor burden using multimodality imaging techniques, including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT, is warranted. Biomarkers including serum tumor markers, circulating tumor cells or DNAs, and gene mutations that may reflect the biology of the tumor should be taken into account if available. Recommendations for surgery should be made within the framework of a multidisciplinary panel.

Neoadjuvant Therapy

According to current guidelines [16], neoadjuvant therapy is recommended for patients with borderline resectable and locally advanced pancreatic cancer. The rationale for neoadjuvant therapy includes downstaging or downsizing of the tumor, elimination of occult micrometastases, and early assessment of tumor biologic behavior to facilitate the selection of patients who can potentially benefit from aggressive surgery [17].

For patients with potentially resectable pancreatic cancer, a good response to neoadjuvant therapy paves

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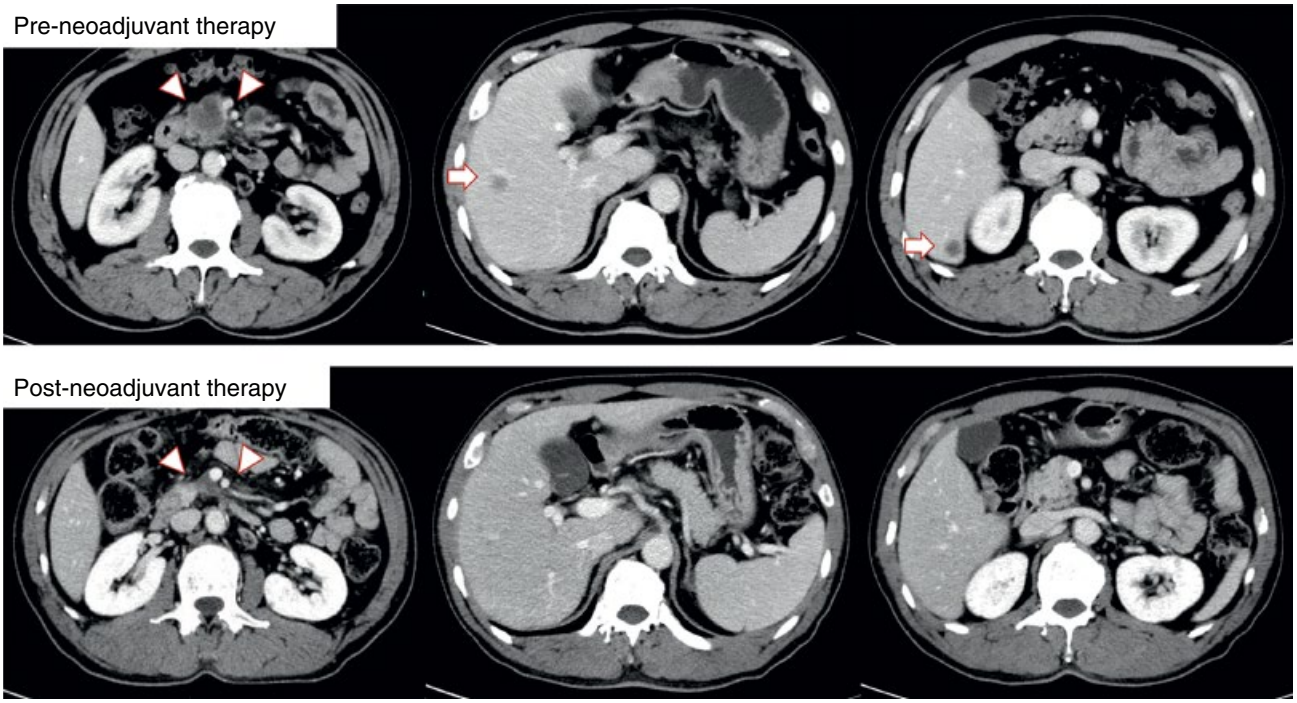


Figure 143.1 A case of locally advanced pancreatic cancer with multiple liver metastases. After six months of neoadjuvant therapy, the primary tumor (arrowheads) decreased in size, and all liver metastases (arrows) disappeared on imaging. Pathologic evaluation of resected specimens confirmed a complete response of the primary tumor and liver metastases.

the way for surgical resection. This may also be the case for patients with metastatic disease, as efficient neoadjuvant treatment may not only shrink the primary tumor but also control or even eliminate metastases in select cases (Fig. 143.1). This may at least partially explain why survival results from some older studies are dismal, while the results from other, mostly recent reports are promising. Indeed, most satisfactory survival data of synchronous pancreatic and liver resection come from cohorts in which neoadjuvant therapy was administered and a good response was achieved prior to surgery. In several small cohorts, patients who had a good response to neoadjuvant chemotherapy and underwent pancreatic and liver resection had a significantly longer survival time than patients who did not undergo subsequent resection [7,10,18]. In the report by Andreou et al., no preoperative chemotherapy was an independent predictor for worse OS in the multivariate analysis [7].

The criteria for surgical intervention after neoadjuvant therapy are also ambiguous. Although the potential benefit of neoadjuvant therapy in the setting of borderline and locally advanced disease is well established based on current knowledge, less evidence is available with regard to the timing of surgery when a good response to neoadjuvant therapy is achieved. As indicated in the NCCN guidelines [16], resection for locally advanced pancreatic cancer should be considered if there is a >50% decrease in the CA 19-9 level and clinical improvement in performance status, pain, early satiety, and weight/nutritional status. In the setting of metastatic pancreatic cancer, little if any evidence evaluating the timing of surgery is available. In particular, indicators of a favorable response and the time interval before surgery are far from being clarified.

In the study by Frigerio et al., indicators of successful downstaging for surgery included disappearance of liver metastasis and reduction in serum tumor marker CA19-9 [10]. In another study, conducted by Crippa et al., surgical resection was only considered if a major biochemical response and a complete or a major radiologic response of the liver metastases were observed [18]. It has been reported that changes in the CA 19-9 level could be used to improve the selection of borderline and locally advanced pancreatic cancer patients who can benefit from resection after primary chemotherapy [19]. However, for metastatic pancreatic cancer, large-scale studies are needed to clarify the role of CA 19-9 in surgical decision making.

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Conclusion

Along with advancements in preoperative evaluation, neoadjuvant therapy, surgical techniques, and adjuvant therapy in recent years, synchronous resection of pancreatic tumors and liver metastases in highly selected patients has been proven to be feasible and even to prolong patient survival in some small case series. Based on the current evidence, patients with a low metastatic burden, or so-called oligometastases, who show a good response to neoadjuvant therapy appear to benefit the most from such an aggressive surgical approach. However, no prospective trials have been conducted to confirm this notion. Thus, the exact oncologic benefit cannot be fully assessed beyond individual clinical experiences, and the selection of candidates who could benefit most from surgery remains challenging.

A thorough evaluation of the metastatic burden, both anatomically and biologically, and precise assessment of the response to neoadjuvant therapy should be performed in future studies.

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Bypass Surgery for Advanced Pancreatic Cancer

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Introduction

Irrespective of recent developments in multimodal therapeutic concepts, complete surgical resection is still the only curative therapy for pancreatic cancer [1]. However, most cases of pancreatic cancer are diagnosed at an advanced stage and thus, only a small percentage of patients are candidates for curative surgery [2]. At the time of diagnosis, approximately 50% of patients have distant disease, approximately 30% have regional or locally advanced disease, and only about 15–20% of patients are diagnosed in a localized stage eligible for potentially curative resection [3,4].

The five-year relative survival rate for all patients with pancreatic cancer remains around 10% [4]. Therefore, palliative therapy is needed in a considerable number of patients not eligible for curative-intent surgery to reduce or prevent symptoms [5]. Furthermore, histologic confirmation should be obtained in potentially palliative cases detected during exploratory laparotomy in order to guide further treatment. Palliative therapy primarily aims to reduce pain, obstructive jaundice and malignant gastric outlet or duodenal obstruction. The latter two are nowadays most frequently palliated using endoscopic and interventional methods, but can also be treated with bypass surgery.

However, the potential benefit of a surgical procedure must be weighed carefully against perioperative morbidity and length of hospital stay. This holds particularly true for patients with a presumed limited life expectancy. The decision to perform a surgical bypass procedure is made in patients in whom the tumor was initially deemed resectable, in those where endoscopic/interventional therapy is technically impossible, or in select cases with a potentially good prognosis (e.g., over one year of expected survival). This chapter focuses on the indications for surgical bypass procedures and the respective operative techniques and approaches.

Background

Before the mid-1980s, palliation of biliary and/or duodenal obstruction was provided primarily through surgical bypass [6]. In some series, up to 57% of patients with unresectable pancreatic cancer underwent surgical bypass [7]. Palliative surgical bypass of the gastrointestinal and biliary tracts has been the reference standard of therapy in many of these cases [8]. Due to great improvements in interventional and endoscopic therapies, palliation of jaundice and/or gastric outlet obstruction is nowadays mostly performed endoscopically.

Symptoms

While tumors in the body and tail of the pancreas mainly cause epigastric or back pain, those in the head of the gland cause a variety of symptoms including obstructive jaundice, gastric outlet or duodenal obstruction, and symptoms of exocrine insufficiency due to obstruction of the main pancreatic duct [9].

Biliary obstruction with jaundice is the most frequent presenting symptom [10]; it occurs in about 60–80% of patients with tumors of the pancreatic head. In patients with a carcinoma of the body or tail of the pancreas, it may occur in the late course of the disease and thus only rarely requires palliative bypass procedures. Because obstructive jaundice causes malaise, malabsorption and anorexia, severe and resistant pruritus, and impaired

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liver function leading to liver failure, its palliation is clinically important. Mechanical gastric outlet obstruction historically occurs in only 2–25% of patients without surgery, but with new advances in chemotherapy and radiation, the life expectancy of pancreatic cancer has increased and up to 38% of patients eventually develop symptomatic duodenal obstruction requiring duodenal stent or surgical bypass [11]. This rate will likely increase further in the upcoming years as patients survive longer with advances in multimodal therapy for pancreatic cancer. Yet, importantly, nausea and vomiting occur in the majority of pancreatic cancer patients without suffering from duodenal obstruction. This is attributed to retroperitoneal infiltration of autonomic nerve plexus leading to gastric dysfunction and cannot be sufficiently palliated by a bypass procedure [12].

Biliary Bypass Procedures

Endoscopic stenting through endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as the standard palliative treatment for patients with malignant biliary obstruction [13,14]. Due to the low invasiveness of the procedure, endoscopic stenting relieves biliary obstruction within a short period of hospitalization. Palliative endoscopic transpapillary drainage was first described in 1980 [15] and nowadays endoscopic decompression has a 99% technical success rate and low morbidity and mortality [16].

Although endoscopic stenting is the preferred method for treating bile duct obstruction, it is technically unsuccessful in a considerable number of patients because of altered anatomy or duodenal obstruction [17]. In such cases, biliary stenting can be performed via percutaneous transhepatic drainage (PTCD) or as endoscopic ultrasound-guided biliary drainage (EUS-BD). PTCD, which was initially described in 1974 [18], is a valid option, despite the higher risk of major complications (i.e., bleeding, biliary fistula, liver abscess) and its conflicting therapeutic success rate [19,20]. With EUS, technologic advances in recent years have rapidly translated into the shift of endoscopic ultrasound from a strictly diagnostic tool into an interventional and therapeutic option as well. EUS-BD is feasible with excellent technical success, limited adverse events, and a beneficial effect on cancer-associated pain [21].

Despite the success of endoscopic treatment of biliary obstruction, surgery continues to be an important alternative option for select patients. Surgery was historically the first option as a biliodigestive bypass procedure and the initial techniques were described as cholecystojejunostomy by Monastyrski in 1887, as choledochoduodenostomy by Sprengel in 1891, and as hepaticojejunostomy by Dahl in 1909 [22]. Cholecystojejunostomy is a relatively simple procedure but has low long-term patency rates, with 8–11% of recurrent jaundice compared to 0–3% after choledochojejunostomy [7]. In a large cohort study of 1919 patients, cholecystoenterostomy was significantly inferior to other bypass procedures [23]. Similarly, in a small randomized controlled trial (RCT) comparing cholecystoenterostomy to choledochoenterostomy, the latter resulted in fewer postoperative complications and fewer failures of the biliary bypass [24].

Occlusion of the cystic duct might explain the lack of long-term patency since the hepatocystic junction was located most frequently within 1 cm distance from the biliary obstruction. Because of this anatomic situation, cholecystojejunostomy was frequently found to be inadequate for the permanent relief of recurrent obstruction [25]. We believe that this procedure is only an option in cases where dissection of the porta hepatis is technically challenging, for example because of local variceal conversion due to portal hypertension/portal vein thrombosis. Hepaticocholecystojejunostomy is another potentially viable alternative to hepaticojejunostomy with similar functional results but a technically less demanding construction of the bypass [26,27].

While laparoscopic biliary decompression is feasible in principle, laparoscopy does not easily allow for judging resectability to the same extent as during open surgery. It is thus infrequently used and has not been established widely in clinical practice [28,29]. Robotic surgery may facilitate the judgment of resectability and also the technical procedure of minimally invasive biliary bypass, but there are very few reports about palliative robotic surgery in pancreatic cancer in the literature [30].

Gastroduodenal Bypass Procedures

The placement of a nasogastric tube or percutaneous gastrostomy is an option for palliative gastrostomy that reduces quality of life substantially and does not give nutritional support for the patient. The endoscopic method of bridging malignant stenosis with a (self-expandable) metal stent has been proven to be an alternative to surgical bypass [31]. Equally, EUS-guided gastroenterostomy has recently been shown to be a safe and effective method for malignant gastric outlet obstruction [32].

Surgical gastric bypass was initially described by Wölfler and Wosler in 1881 in an antecolic way. Retrocolic gastrojejunostomy was performed first by Courvoisier in 1883 with the patient not surviving the operation, while von Hacker performed it successfully in 1885. After years of debate about the value of gastrojejunostomy due to high morbidity and mortality, the results

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of gastroenterostomy have improved significantly [33]. Today's standard side-to-side gastrojejunostomy can be performed in antecolic or retrocolic fashion, with delayed gastric emptying still being a relevant clinical issue after the procedure [34]. Through developments in minimally invasive surgery the procedure can now be laparoscopically performed in suitable patients [32].

Prophylactic retrocolic gastrojejunostomy at diagnosis of unresectable disease during explorative laparotomy was studied by Lillemoe et al. [8]. They showed an increase in operation length as expected, but no differences in blood loss or transfusion or in postoperative morbidity and mortality, including delayed gastric emptying rate, length of hospital stay, and mean survival (8.3 months) compared to no gastric bypass. About 80% of patients received additional hepaticojejunostomy. Late gastric outlet obstruction appeared more frequently in the control group (19% vs 0%, $P = 0.01$) after a median of two months. Therefore, the authors concluded that prophylactic gastrojejunostomy should be performed routinely in patients with unforeseen unresectable periampullary cancer. This was later confirmed in a meta-analysis and systematic review [33].

Van Heek et al. [34] compared double bypass (hepaticojejunostomy and retrocolic gastrojejunostomy) to single bypass, finding no significant differences in terms of postoperative morbidity including delayed gastric emptying, length of hospital stay, survival, and quality of life. Gastric outlet obstruction occurred significantly more often in the single bypass group, leading to an increased rate of repeat gastrojejunostomy. A longitudinal analysis of quality of life after double bypass by the same authors showed that quality of life can be preserved for a considerable time [35]. Similarly, Jeurnink et al. demonstrated in a RCT of 39 patients with malignant gastric outlet obstruction (28 with pancreatic cancer) that surgical gastrojejunostomy resulted in better long-term results, while stent placement resulted in more rapid symptom relief. Thus, they concluded that gastrojejunostomy should be considered in patients with a life expectancy of >2 months [36]. If a palliative gastrojejunostomy is performed, a Roux-en-Y reconstruction should be considered, since it may result in lower rates of delayed gastric emptying and a shorter hospital stay, as shown in the trial by Szymanski et al. [37].

In 2018, a Cochrane review compared interventional and surgical palliation for malignant gastric outlet obstruction. The authors found that duodenal stent placement has the benefits of a quicker resumption of oral intake and a reduced hospital stay; however, it was also associated with earlier recurrence of symptoms and higher reintervention rates compared to surgery [38]. In another Cochrane review investigating prophylactic gastrojejunostomy in patients with periampullary cancer that were unresectable at exploratory laparotomy, the authors found a significantly lower rate of long-term gastric outlet obstruction. Thus, they concluded that surgical gastrojejunostomy remains the reference standard of care in this situation [33].

Comparison of Endoscopic Versus Surgical Approach

In general, surgical bypass has been linked to a higher risk of morbidity and mortality but better long-term patency [39]. In 2020, Fabian et al. published a meta-analysis comparing palliative double stenting for malignant duodenal and biliary obstruction with surgical double bypass [16]. Clinical success of endoscopic biliary stenting was higher than that of surgery and double stenting was associated with fewer adverse events but more frequent need for reintervention than double bypass. In line with these data, the incidence of recurrent jaundice in surgical patients is consistently lower than that in stented patients even though surgery itself tends to be associated with a higher early complication rate [40–42].

Apart from the biliary bypass, two randomized controlled trials demonstrated that an additional prophylactic gastrojejunostomy (i.e., double bypass) is effective in preventing the development of potential gastroduodenal obstruction without increasing surgery-related morbidity and mortality [8,34]. However, surgery itself is more extensive and may significantly affect the quality of life of patients with a short life expectancy. Advantages of surgical bypass increase with longer survival of the patient, avoiding frequent readmissions and recouping initial higher costs with fewer future management costs than in nonsurgical patients [43]. Thus, surgical bypass is a good option for those patients in whom unresectable cancer is found during surgery for planned tumor resection, and also occasionally for patients who have a relatively long life expectancy [8,44]. Several factors were found to predict early mortality following palliative bypass: presence of distant metastatic disease, poor tumor differentiation, severe preoperative nausea and vomiting, and lack of previous placement of a biliary stent [45]. These factors may be helpful in selecting appropriate interventions for this group of patients undergoing a palliative bypass procedure. Nevertheless, individual clinical judgment is still important when discussing options with the patient.

Importantly, the recent increases in survival even in Stage IV disease using polychemotherapy [46] may render surgical bypass a more frequently used procedure in the near future. Vreeland et al. recently published an analysis of patients who underwent surgical exploration with planned partial pancreatoduodenectomy after neoadjuvant therapy. Of 271 patients, 47 (17.3%) planned

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resections were intraoperatively aborted, of which six underwent hepaticojejunostomy and nine underwent gastrojejunostomy. Although 53% of patients without a biliary bypass required endoscopic biliary intervention and 37% required intervention for gastric outlet obstruction in the further course of their disease, all cases were manageable without palliative surgery. Thus, they concluded that prophylactic surgical bypass is not required during aborted partial pancreatoduodenectomies [47].

Current Approach and Future Perspectives

Given the current data, a double bypass procedure with gastrojejunostomy and hepaticojejunostomy should still be considered in symptomatic patients with pancreatic cancer that is deemed unresectable during surgical exploration to reach palliation of these symptoms in one definite procedure [48]. Patients with primarily unresectable disease should undergo endoscopic biliary drainage, but surgical bypass may also be considered in select cases with a presumed favorable survival time. However, constant improvement in preoperative staging in recent years has led to a significant reduction in the number of such bypass procedures. On the other hand, the progress in multimodality treatment may considerably increase survival time for many patients, which in turn may again increase the number of surgical bypass procedures as the definitive long-term palliation method. In order to keep the surgical trauma as well as postoperative morbidity as low as possible, the role of minimally invasive surgery and in particular the robotic approach needs to be explored in future trials.

Another crucial aspect, which is currently underrepresented in the literature, is the perspective of patients. Future research on this topic needs to assess patient-reported outcome parameters, e.g., quality of life, as a central aspect and in a structured way. Furthermore, individual patients' perspectives and wishes should be considered in detail in the decision-making process on palliative measures to tailor a personalized approach in each case.

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Endoscopic and Interventional Palliation of Pancreatic Cancer

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Introduction

Cases of pancreatic cancer have been rapidly increasing worldwide. The latest data show that the number of cases of pancreatic cancer has increased to more than 60 000 in the USA [1]. It is well known that most pancreatic cancers are usually in their advanced stage when they are detected. In fact, more than 80% of patients present with disease that is not surgically resectable [2]. Furthermore, most patients with advanced pancreatic cancer show resistance to adjuvant therapies such as chemotherapy, resulting in a mortality of more than 49 000 in the USA [1].

The main problem with unresectable pancreatic cancers is that they cause various complications, such as obstructive jaundice, gastric outlet obstruction, abdominal pain, pancreatic duct obstruction, and pancreatitis, according to cancer progression. This consequently delays the start of adjuvant therapy. Surgical interventions such as choledochojejunostomy and gastrojejunostomy in such patients are usually not indicated because they are more invasive. Surgical interventions may also cause delay in starting adjuvant therapy.

At present, nonsurgical interventions such as interventional endoscopy (IVE) and interventional radiology (IVR) allow palliative therapy in most cases. In terms of endoscopic therapy, endoscopic ultrasonography (EUS) has become widely used in selected institutions in addition to therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for the treatment of such complications. This chapter reviews the latest palliation in pancreatic cancer by IVE and IVR.

Biliary Obstruction

Malignant biliary obstruction, particularly in the extrahepatic bile duct, is the most common symptom in patients with advanced pancreatic cancer. The progression of biliary obstruction causes mainly cholestasis and jaundice, and rarely cholangitis, leading to fat malabsorption, malnutrition, and cachexia. Absence of therapy for obstructive jaundice leads to exacerbation of liver dysfunction and eventually liver failure.

Thus, biliary drainage has been traditionally performed to improve the quality of life of patients. For resectable pancreatic cancer with jaundice, preoperative biliary drainage (PBD) has been preferred to improve the postoperative morbidity and mortality rates. However, recent high-quality studies [3,4] have reported that PBD should not be performed routinely. However, there are several reports in the literature on the selection of drainage methods (mixed procedures, percutaneous transhepatic biliary drainage [PTBD], and endoscopic drainage by ERCP) and endoscopic stent selection (small-bore plastic stent). Recently, PBD using a large-bore metal stent has been reported as a preferable technique of biliary decompression with a low adverse event rate as a bridge to surgery [5].

Traditionally, biliary decompression in patients with unresectable pancreatic cancer has been conducted by ERCP and PTBD as nonsurgical and palliative interventions. The choice of drainage method depends on the preference of the principal physician and the presence of skilled ERCP endoscopists and interventional radiologists in each institution [6]. Recently, endoscopic

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ultrasonography-guided biliary drainage (EUS-BD) has emerged as a salvage therapy in cases of failed ERCP [7].

Palliation of Obstructive Jaundice by ERCP

(Table 145.1)

Conventional ERCP

Endoscopic plastic stent placement by ERCP is the most common procedure for biliary decompression since the first report by Soehendra and Reynders-Frederix in 1980 [8]. Early randomized controlled trials (RCTs) revealed that endoscopic plastic stent placement has a similar outcome in terms of technical success, morbidity, and mortality, or is more preferred to reduce morbidity (P = 0.02) and mortality (P = 0.01) in the palliation of biliary obstruction than surgical intervention [9,10]. Plastic stents are usually used for the initial biliary drainage because they are less expensive and can be removed easily while pancreatic masses are evaluated. On the other hand, self-expandable metal stents (SEMSs) were developed in 1989 for the palliation of biliary obstruction [11,12]. Theoretically, a large-bore stent (approximately 8–10 mm) allows long stent patency, reducing the number of reinterventions compared with small-bore plastic stents (7–10 Fr). Plastic stent occlusion occurs within four months compared with SEMS occlusion which occurs at about nine months to nearly one year. Thus, the Cochrane review suggests that SEMSs are preferable to plastic stents in patients with an expected survival period of more than four months because of lower numbers of stent failure, decreased total hospitalizations secondary to stent-related issues, a lower risk of cholangitis (relative risk [RR] 0.48), and overall low costs [13].

However, recent progress in adjuvant therapies such as chemotherapy has allowed prolongation of survival time. Furthermore, cholangitis due to stent occlusion causes an interruption of scheduled chemotherapy. Thus, SEMSs may be suitable for biliary decompression at the first session as a first-line stent once pancreatic cancer is definitively diagnosed and as long as standard chemotherapy is scheduled. In fact, Davids et al. [14] have suggested that the initial use of SEMSs results in a 28% decrease in overall procedures compared with the initial use of plastic stents. Even in the case of borderline resectable pancreatic cancer undergoing neoadjuvant therapy, SEMSs appear to be preferable to avoid preoperative serious complications [3,15]. A more recent RCT has demonstrated that endoscopic metal stent placement has a similar outcome for palliation of the biliary obstruction when compared with surgical bypass in patients with metastatic pancreatic cancer [16].

At present, two types of SEMSs are used: uncovered SEMSs and fully/partially covered SEMSs. Theoretically, as covered SEMSs can preclude tumor ingrowth, these stents have prolonged stent patency. In contrast, SEMSs have the possibility of inward and outward stent migration and may cause acute cholecystitis due to cystic duct obstruction. Recent metaanalyses have shown that the superiority of covered SEMSs is controversial compared with uncovered SEMSs [17,18]. However, a more recent RCT has demonstrated the usefulness of covered SEMSs [19]. The uncertain conclusion may be due to several biases such as heterogeneity of diseases and stent selection (i.e., stainless or nitinol, braided type or laser cut type, fully covered or partially covered, and with or without an antimigration system).

One of the most critical issues of endoscopic stenting is reintervention owing to stent dysfunction. Although a plastic stent is easily exchanged with a new stent, removal of SEMSs, particularly uncovered SEMSs, was usually not considered possible. Thereafter, the stent-in-stent technique (i.e., a new stent within the existing occluded metal stent) is performed using a plastic stent or an uncovered/covered SEMS. Theoretically, a large-bore second SEMS appears effective, but one study has demonstrated that plastic stent placement may be as effective as second SEMS placement [20]. These data suggest that an occluded first SEMS may impair the second SEMS.

Recently, a new concept of removal of SEMSs, that is, mostly covered SEMSs and rarely uncovered SEMSs, has emerged when stent occlusion occurs [21,22]. Furthermore, one study has demonstrated that covered SEMSs could be safely removed at the time of stent occlusion and that the patency rates were similar for the initial stent placement and the reintervention [23].

Table 145.1 Typical technique of nonsurgical biliary decompression.

- I) Endoscopic retrograde cholangiopancreatography (ERCP)
  - 1) External drainage (nasobiliary drainage)
  - 2) Biliary stenting
- II) Endoscopic ultrasonography (EUS)
  - 1) Hepaticogastrostomy
  - 2) Choledochoduodenostomy
  - 3) Antegrade biliary stenting
  - 4) Rendezvous
- III) Percutaneous transhepatic biliary drainage (PTBD)
  - 1) External drainage
  - 2) Internal drainage
  - 3) Internal-external drainage
  - 4) Rendezvous

Balloon Enteroscopy-assisted ERCP

Endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy in the setting of

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Roux-en-Y (RY) reconstruction, including RY gastrectomy and RY gastric bypass, is always a challenging procedure. Traditionally, conventional colonoscopy has been used in such patients but the success rate was not very high (<50%). Recently, single-balloon enteroscopy (SBE) and double-balloon enteroscopy (DBE) have allowed access to the papilla and successful endoscopic procedures in the setting of RY reconstruction [24–26]. Thus, most patients with biliary obstruction in the case of pancreatic cancer and RY reconstruction can be treated by balloon enteroscopy (BE)-assisted ERCP [27].

In patients following pancreatoduodenectomy (Whipple resection), malignant or benign stenosis of the hepaticojejunostomy site causes obstructive jaundice with or without intrahepatic bile duct stones. BE-assisted ERCP is also useful for resolving the stenosis by balloon dilation or stent placement in such patients [28].

Palliation of Obstructive Jaundice by EUS

Selective biliary cannulation by ERCP for biliary decompression is not always successful, even when performed by ERCP experts, for several reasons, including intradiverticular papillae, surgically altered anatomy, or gastroduodenal obstruction. Traditionally, in the case of failed ERCP, PTBD has been performed as a useful and safe salvage technique. EUS-BD has emerged as another salvage technique, reported by Giovannini et al. in 2001 [29]. EUS-BD includes several transmural approaches such as the EUS-rendezvous technique (EUS-RV), EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS) (Fig. 145.1), and EUS-guided antegrade stenting (EUS-AS). To date, many studies regarding each procedure have shown high technical and clinical success rates of more than 80–90% with moderate adverse event rates of 10–30% (e.g., bile leakage, bleeding, stent migration), although the severity of most adverse events was mild or moderate [30]. Recently, covered SEMSs have been frequently used to avoid unexpected adverse events (e.g., bile leakage) for biliary decompression, although accumulated data have shown no difference between plastic stents and covered SEMSs in the EUS-HGS procedure [31].

Of the EUS-BD procedures, EUS-RV appears to achieve minimum invasive drainage because conventional ERCP and even BE-assisted ERCP can be performed although it may be technically difficult compared with other procedures. Notably, the current data have been reported from high-volume centers with expertise in EUS. Furthermore, as each EUS-BD technique including accessories has not yet been established, EUS-BD has not become an alternative to conventional ERCP. However, a recent RCT has shown that EUS-CDS can be an effective and safe alternative to PTBD with a similar success rate, complication rate, cost, and patient quality of life [32]. Furthermore, EUS-CDS with a single-step delivery system using an electrocautery enhanced, lumen-apposing metal stent (LAMS) is associated with successful stent placement rates of over 90 percent in patients with malignant biliary obstruction [33,34]. Although larger studies with long-term outcome data are needed to compare its efficacy and safety with percutaneous drainage, EUS-BD may become an alternative to PTBD in failed ERCP cases in the near future.

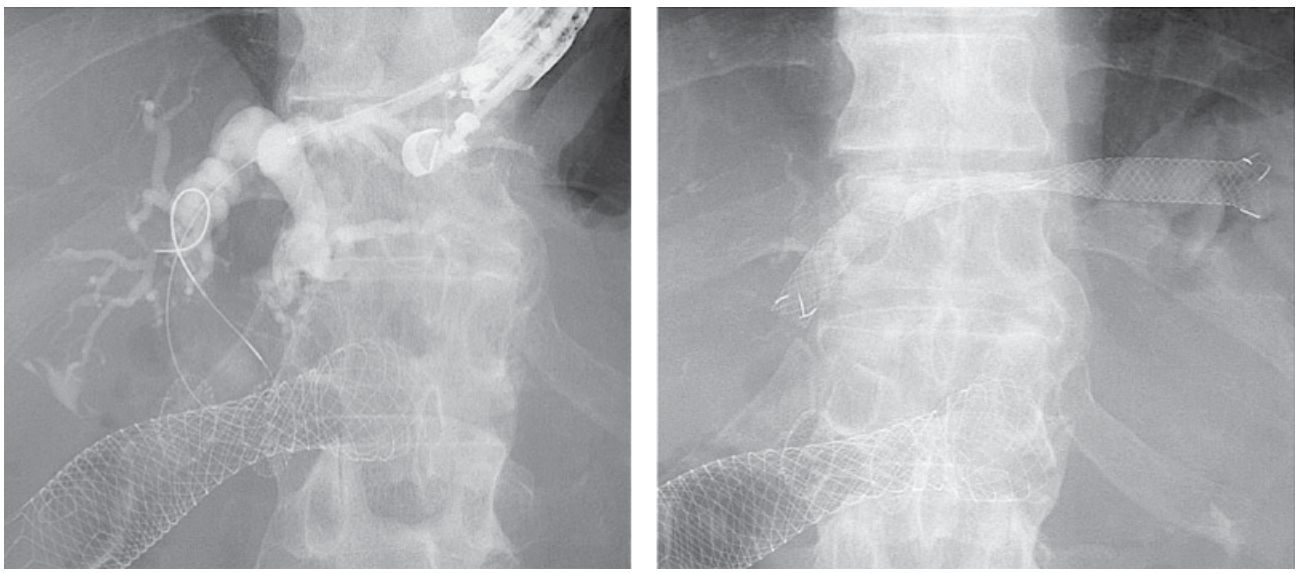


Figure 145.1 EUS-guided hepaticogastrostomy. The metal stent delivery system was inserted in the intrahepatic bile duct (left). Hepaticogastrostomy was completed using a metal stent.

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Palliation of Obstructive Jaundice by IVR

Percutaneous transhepatic biliary drainage has been performed traditionally by radiologists as one of the biliary decompression methods, although it is becoming less common due to the widespread use of endoscopic biliary drainage regardless of the choice of the plastic stent and SEMS by ERCP. PTBD is divided into three types according to the percutaneous tube condition in the bile duct across the stenosis, namely, external drainage, internal-external drainage, and internal drainage. A 7–8 Fr percutaneous tube is used which allows sufficient drainage for the therapy of obstructive jaundice. From the viewpoints of physiological bile flow, activities of daily living, and the quality of life of patients, internal drainage appears to be desirable. In most PTBD cases, eventually, internalization appears to be technically possible using several accessories such as a hydrophilic guidewire.

However, the most desirable procedure in patients undergoing percutaneous transhepatic therapy is percutaneous stenting without any percutaneous tube. In particular, the present percutaneous SEMS placement using a small-caliber (approximately 6–7 Fr) delivery system allows good efficacy, with few complications and reduced associated pain [35]. Similarly to ERCP, percutaneous covered SEMS placement provides long stent patency compared with percutaneous uncovered SEMS placement for the treatment of extrahepatic biliary obstruction [36]. However, an earlier RCT that compared percutaneous therapy with endoscopic therapy has demonstrated that the endoscopic method had a significantly higher success rate in relieving jaundice and a significantly lower 30-day mortality from complications associated with liver puncture [37]. Even at the time of writing, serious complications due to percutaneous stent placement are still common [38]. It is probable that needle puncture and tract dilation in patients who have coagulopathy and hemorrhagic tendency cause serious complications such as massive bleeding. Furthermore, needle puncture is not always successful even by skilled radiologists. Quality improvement guidelines for percutaneous transhepatic biliary cholangiography, biliary drainage, and percutaneous cholecystostomy have described that the success rate of needle puncture in a nondilated bile duct was lower than that in a dilated bile duct (63% vs 86%) [39].

Nonetheless, since PTBD is an effective and established technique, it should remain as a salvage therapy before shifting to surgical intervention, even at institutions with expertise in both ERCP and EUS [40]. In fact, PTBD is performed even in ERCP and EUS high-volume centers [41].

Malignant Gastric Outlet Obstruction

Malignant gastric outlet obstruction (MGOO), which is often caused by unresectable pancreatic cancer at the end stage, causes inadequate food intake with nausea and vomiting, leading to malnutrition and deterioration of the quality of life. Surgical gastrojejunostomy (GJ) under open laparotomy or laparoscopy, which has been the standard palliative treatment for MGOO, is associated with good functional outcome and long-term relief of symptoms. However, surgical GJ shows high morbidity and mortality [42,43].

Duodenal Metal Stent Placement

At present, duodenal stent placement using a 20–22 mm diameter SEMS under fluoroscopic guidance or, more recently, endoscopy owing to the development of a thinner 10 Fr delivery system for MGOO treatment, has been gaining popularity as an alternative to surgical GJ because the stent can be inserted through the accessory channel with a high technical success rate and less invasiveness [42–47]. A previous systematic review [42] revealed that the initial clinical success rate was higher after stent placement than after surgical GJ (89% vs 72%, respectively) with fewer minor complications (9% vs.33%, respectively). However, recurrent obstructive symptoms were more frequent after stent placement (18% vs 1%, respectively) owing to tumor ingrowth, preventing the patient from being able to eat soft solid food or a full diet.

These results suggest that endoscopic stenting might be preferable in patients with a relatively short life expectancy, whereas surgical GJ might be preferable in patients with a longer expected survival (>2 months) [42,43]. However, recent systemic chemotherapies for pancreatic cancers have shown marked improvements, making it harder to predict a patient's life expectancy. This may lead to an increase in cases of endoscopic stent occlusion, which often occurs during longer follow-up periods owing to tumor ingrowth. In this cohort, an additional stent is often placed within the original stent which can lead to early stent occlusion or stent-related adverse events such as perforation.

Thus, several investigators have recently attempted nonsurgical GJ for longer efficacy while maintaining a less invasive procedure using magnet compression anastomosis, interventional EUS, and natural orifice transluminal endoscopic surgery in animal models. In particular, EUS-guided GJ has been developed and one clinical study has demonstrated that EUS-guided GJ

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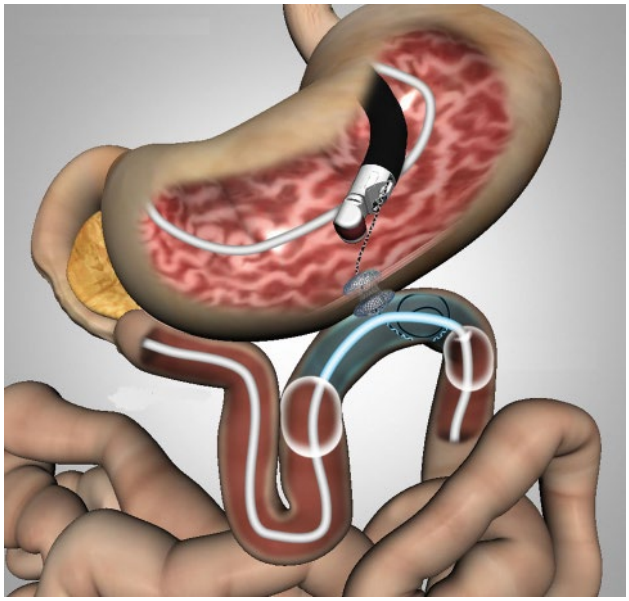


Figure 145.2 EUS-guided gastrojejunostomy. A lumen-apposing metal stent was placed over the wire using a dedicated double-balloon tube.

using a dedicated double balloon and a fully covered lumen-apposing SEMS (15 mm diameter) shows high technical and clinical success without causing serious adverse events (Fig. 145.2) [48]. Several systematic reviews and metaanalyses report on the safety and efficacy of EUS-guided GJ compared with other treatments [49–51]. While the data are promising, further studies are warranted prior to widespread adoption.

Duodenal and Biliary Stent Placement: Double Stenting

In patients with unresectable pancreatic cancer, progression of the cancer is accompanied not only by MGOO but also by biliary obstruction, which is usually a late manifestation. In such patients, both biliary stent placement and duodenal stent placement, so-called "double stenting," is often required. The methods and ease of the procedure vary according to the site and timing of the duodenal obstruction. In particular, the duodenal obstruction site appears to be more important in terms of planning the biliary stenting strategy.

The duodenal obstruction site is classified in relation to the position of the major papilla, namely, type I (the obstruction site is at the entrance of the principal papilla), type II (the obstruction site is somewhat convoluted with the papilla present in the second portion), and type III (the obstruction site is closer to the anal side than to the major papilla) [52]. In double stenting, biliary drainage with or without the rendezvous technique is performed using three kinds of approaches: percutaneous transhepatic approach, ERCP approach, and EUS approach. In double stenting by ERCP, if the duodenal obstruction site is convoluted around the major papilla (type II), the treatment is most complicated. Even if the balloon is stretched or the duodenal stent is placed first, cancer invasion makes it difficult to identify the major papilla and confirm the distance from the scope. In addition, it is very difficult to pass the biliary stent through the mesh gap of the duodenal stent. Thus, in type II cases, the traditional percutaneous transhepatic approach including biliary drainage and rendezvous appears preferable for double stenting than the ERCP approach.

Recently, the EUS approach has allowed biliary drainage including EUS-HGS, EUS-CDS, EUS-AS, and EUS-RV even in type I and type II MGOO. In type I and type II MGOO, EUS-HGS and EUS-AS appear to be suitable drainage techniques for the treatment of obstructive jaundice and can replace the percutaneous transhepatic approach because of the minimum invasive procedures involved [53].

Management of Pain Derived from Cancer

Pain due to cancer invasion of the celiac plexus is a major manifestation of pancreatic cancer, occurring in approximately 70% of patients with unresectable pancreatic cancer [54]. At present, pain is comparatively controllable by opioid analgesics, IVE, and/or IVR. Celiac plexus neurolysis (CPN) is a unique technique that can potentially improve pain control in pancreatic cancer to avoid further dose escalation of opioid medication. CPN is most often performed by injecting a local anesthetic followed by absolute alcohol into the celiac plexus neural network of ganglia with the intention of ablating the tissue transmitting pain from the pancreas and adjacent visceral organs. Interventions targeting CPN have been performed percutaneously with computed tomography or transabdominal ultrasound, while the EUS-guided approach has been increasingly utilized in clinical practice.

EUS-CPN

EUS-CPN has emerged as a promising approach to CPN that has the potential for better visualization of the celiac plexus through close proximity and real-time high-resolution ultrasound, possibly allowing for more precise and safer injections [55]. Standard EUS-CPN is

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performed using a 19–25 gauge EUS-guided fine-needle aspiration (EUS-FNA) needle. The needle is advanced anterior to the lateral aspect of the aorta at depiction of the celiac trunk. Then, after confirming the absence of backflow of blood, absolute alcohol is injected following local anesthetic injection. A previous metaanalysis demonstrated that pain was reduced in 80% of the patients following EUS-CPN for pancreatic cancer [56]. Although most adverse events of EUS-CPN are mild and include transient hypotension, diarrhea, constipation, and pain exacerbation, although serious and fatal adverse events appear to be occasionally inevitable [57].

Unilateral neurolysis is conducted by a single injection into the base of the celiac artery takeoff. In contrast, bilateral neurolysis is performed by injecting into both sides of the celiac plexus. A previous metaanalysis demonstrated the superiority of bilateral injection over central injection for pain reduction (85.54% vs 45.99%, respectively) [56]. However, an RCT comparing the two approaches in pancreatic cancer among 50 patients showed no significant difference in terms of pain control or adverse events [57].

Recently, EUS-guided celiac ganglia neurolysis (EUS-CGN) has been developed in which alcohol is injected directly into the celiac ganglia (detection rates of 80–90% by EUS). A RCT comparing EUS-CGN with unilateral EUS-CPN has shown significantly greater pain relief in the CGN group than in the CPN group (73.5% vs 45.5%, $P = 0.026$) with similar adverse events [58]. However, the latest trial indicated that EUS-CGN resulted in decreased survival without a pain control benefit compared with EUS-CPN (survival time 5.6 versus 10.5 months; hazard ratio 1.49; 95% confidence interval [CI] 1.02–2.19) [59]. In addition, a RCT showed EUS-CPN for patients with pancreatic cancer-associated pain did not appear to improve pain, quality of life, or opioid consumption compared with those who did not undergo EUS-CPN and medicated with oxycodone/fentanyl [60]. From those results, although EUS-CPN or CGN can be an option, it cannot be used routinely in clinical practice.

Anticancer Therapy

To date, several anticancer therapies for pancreatic cancers have been reported [61–66]. EUS-guided or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy has been used as first-line treatment for locally advanced pancreatic cancer in a phase III study [61]. However, this study demonstrated that although it was safe, it was not effective for prolonging survival. In terms of brachytherapy, EUS-guided interstitial implantation of 125I seeds has been performed and the obtained data suggested improvement in pain, but there was no long-term survival benefit [62].

Several investigators have performed EUS-guided radiofrequency ablation (EUS-RFA) of unresectable pancreatic

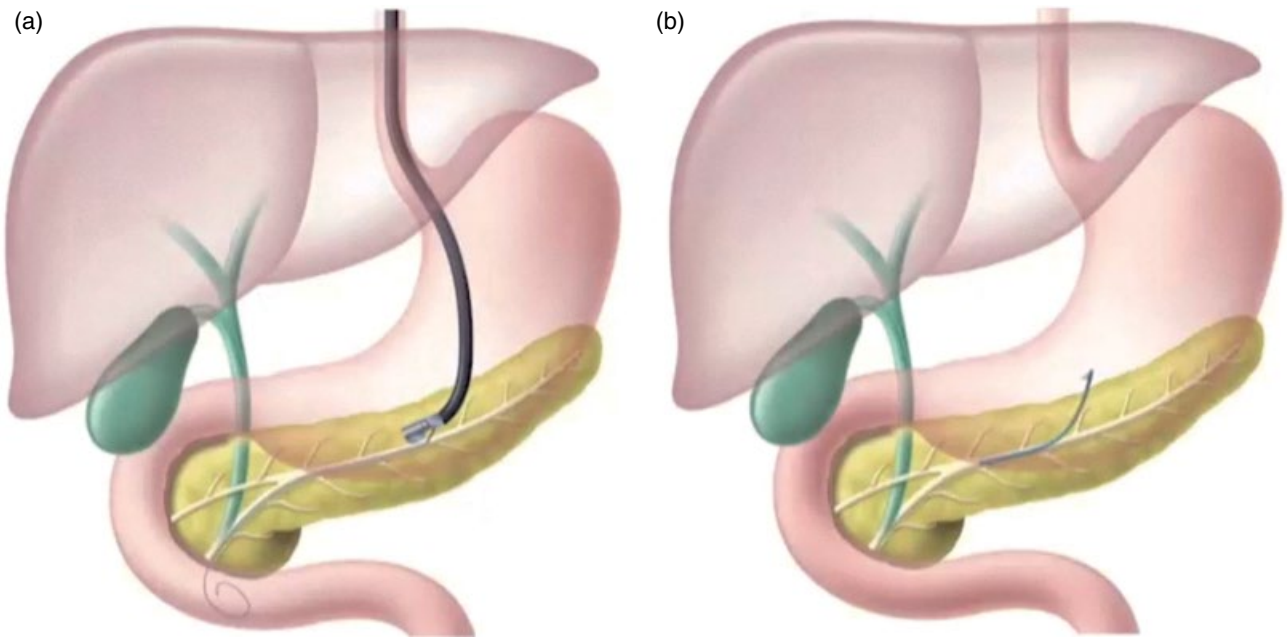


Figure 145.3 EUS-guided pancreatic duct stent placement. The mechanism of EUS-guided pancreatic duct stent placement using a plastic stent. A plastic stent was placed in the pancreatic duct (b) after insertion of a guidewire into the pancreatic duct under EUS guidance (a).

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cancer and concluded that it could be a technically feasible and safe option [63]. However, long-term efficacy should be evaluated in the near future. Currently, EUS-guided cryothermal ablation therapy [64] and EUS-guided dendritic cell injection therapy [65,66] have also been reported, but their efficacies are not apparent because the studies involved a small case series without a control group.

Miscellaneous

Patients with pancreatic duct (PD) obstruction which blocks the outflow of pancreatic juice owing to pancreatic cancer experience abdominal pain. Although this condition is infrequent in such patients, transpapillary PD stent placement is useful. In case of failed ERCP, EUS-guided PD stent placement is performed as salvage therapy (Fig. 145.3). Anastomotic stricture of pancreatojejunostomy causes pain and pancreatitis as a late adverse event after pancreatoduodenectomy for pancreatic cancer. EUS-guided PD stent placement is also effective for decompression of dilated PD [67]. Acute pancreatitis due to pancreatic cancer is rare but is observed in some patients. Pancreatic fluid collections, including walled-off necrosis and pseudocyst, require EUS and/or percutaneous drainage. Furthermore, endoscopic necrosectomy may be required to remove the infected necrotic tissue.

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Neoadjuvant Treatment of Pancreatic Cancer: Evidence for Treatment Effect

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Introduction

Neoadjuvant treatment (NAT) has long been established as leading to superior outcomes in other gastrointestinal malignancies, specifically rectal cancer and gastroesophageal cancers, compared with upfront surgery. In rectal cancer, a landmark randomized trial of preoperative chemoradiotherapy (CRT) followed by surgery compared with initial surgery and adjuvant CRT led to improvement in clinically meaningful endpoints with evidence of downstaging and treatment effect [1]. These included a higher chance of sphincter-sparing surgery, an increase in pathologic T1 with a concomitant decrease in T3 tumors (40% vs 60%), and a decrease in positive lymph nodes (LNs) (25% vs 40%). Pathologic complete responses occurred in 8% of resection specimens. In gastroesophageal cancers, the evidence for the benefit of NAT was also demonstrated. Similar to the experience in rectal cancer, NAT generated pathologic evidence of downstaging and treatment effect with lower T stages and lower rates of positive lymph nodes, in addition to longer overall survival (OS) [2,3].

For years, the standard approach to resectable pancreatic cancer was upfront surgical resection followed by AT [4–6]. Over time, it became apparent that the completeness of surgical resection, deemed the "R" factor, had prognostic implications. Better survival has generally been observed for patients undergoing complete resection with microscopically negative surgical margins (R0) [7–9]. Reports from several AT trials have consistently shown that R1 resections occur quite frequently with upfront surgery and confer a worse prognosis [7,10,11]. While high-quality cross-sectional imaging can predict the surgeon's ability to remove all gross tumor [12], the diffusely infiltrating nature of pancreatic adenocarcinoma often results in positive surgical margins, particularly with upfront surgery [13,14].

Defining Localized Pancreatic Cancer: Resectable, Borderline Resectable, or Locally Advanced?

High-quality imaging can distinguish between tumor/vessel interfaces with interposed fat planes (potentially resectable), from tumor/vessel contact (<180°) without encasement (BR), or evidence of tumor encasement of critical vascular structures (LA). Broadly defined, BR tumors represent a subset of localized pancreatic cancers that may be grossly resected, but pose high risk for positive margins with upfront surgical intervention based on a tumor's contact with surrounding vascular structures [15] Given the cumulative evidence demonstrating that NAT can produce local tumor regression in resectable disease, leading to higher R0 resection rates compared with upfront surgery, early reports of NAT in BR pancreatic cancer patients showed that a subset could undergo R0 resection with survival rates similar to those reported for patients with resectable disease [16,17]. Importantly, broader recognition of BR disease provides a framework for better defined, more homogeneous subsets of patients for entry into clinical trials of NAT [18]. This allows for three separate categories of localized pancreatic cancer: potentially resectable, BR, and LA pancreatic cancer, and prospective studies are now emerging on the role of NAT for these three distinct subsets.

Neoadjuvant Therapy for Resectable Pancreatic Cancer

The rationale for delivering NAT to patients with potentially resectable tumors is based on: (1) the potential to produce primary tumor regression, thereby improving

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the chances of an R0 resection; (2) early treatment of micrometastatic disease; (3) delivery of anticancer therapy prior to a complex procedure, avoiding the risk of prolonged surgical recovery, which delays delivery of AT; (4) providing a time interval to assess the underlying tumor biology, thus identifying patients for surgery who have the highest likelihood of benefit from it.

Downstaging Resectable Pancreatic Cancer

From a technical perspective, downstaging a resectable pancreatic cancer is not required to allow for tumor resection. However, despite advances in cross-sectional magnetic resonance imaging (MRI) and computed tomography (CT), and their proper interpretation, modern trials of AT continue to demonstrate the significant risk of an R1 resection with upfront surgery. For example, three of the most recent AT trials had R1 resection rates of 24–60% [13,14,19]. The discrepancy between radiographically resectable disease and achievement of an R0 resection may be in part explained by the findings of Verbeke et al. who found that tumor cell dispersion at the periphery of pancreatic head tumors was greater than observed in other gastrointestinal cancers [20].

Retrospective analyses from a variety of datasets show consistent benefit of NAT leading to lower rates of R1 resections, lower rates of positive lymph nodes and improved survival in potentially resectable pancreatic cancer in comparison with upfront surgery (Table 146.1) [21–24]. While "downstaging" resectable pancreatic cancer may be a misnomer, these results clearly suggest sufficient treatment effect from NAT to justify its use. Importantly, the criteria for surgical removal of a resectable tumor after NAT are based on the absence of disease progression rather than primary tumor response. This is distinct from the setting in BR and LA disease, where some evidence of treatment effect is usually required to attempt tumor resection.

Downstaging Borderline Resectable Disease with Neoadjuvant Therapy

A number of academic centers have reported on results with NAT for BR disease. An early retrospective report came from UTMDACC, where 160 patients were classified as having BR disease [16]. Among those patients, all of whom were treated with NAT, approximately 40% had some combination of clinical, serologic (drop in tumor marker), or radiographic response to therapy sufficient to attempt resection. For the patients who ultimately underwent resection, the R0 rate was 94% with a median overall survival of 40 months. Of note, the survival of patients who did not undergo surgery was consistent with patients having LA pancreatic cancer managed with nonoperative therapy (13 months). Other groups have also published results after NAT for BR tumors with resection rates around 60–65% [25,26]. More recently, prospective data from a multiinstitutional trial of

Table 146.1 Retrospective analyses of R0 resection rates and lymph node involvement comparing upfront surgery with neoadjuvant therapy followed by surgery using nonrandomized datasets.

Author Study details Year	Clinical stage	Number of patients	R0 resection rate (%)		Lymph node involvement (%)		Comments
			Upfront surgery	Neoadjuvant therapy	Upfront surgery	Neoadjuvant therapy	
Roland MDACC/Single institution 2015	R	307	85	92	74	50	Improved survival for NAT + resection
Youngwirth National Cancer Data Base 2017	R ("Clinical Stage II")	18 243	78	85	57	41	Clinical Stage II in most cases; more stage I at surgery with NAT
Mokdad National Cancer Data Base-propensity match 2017	R	15 237	76	83	77	48	Lower pathologic T-stage with NAT + surgery and > survival
Versteijne Metaanalysis 2018	R/BR	3484	67	87	65	44	Improved survival with NAT based on ITT and for resected subset

ITT, intention to treat; NAT, neoadjuvant therapy.

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FOLFIRINOX followed by capecitabine-based CRT for patients with BR disease were reported. Among the 23 patients enrolled, 68% underwent surgery with curative intent; the R0 rate was 93% [27]

In the recent past, a series of randomized trials from Korea, Japan, and Europe have compared NAT and subsequent surgery with initial surgery and AT, and all demonstrated clinical benefits using NAT, particularly for those patients with BR disease (Table 146.2) [28–31]. In patients with resectable pancreatic cancer, the survival benefits using NAT are mixed based on intention to treat (ITT) analyses. However, if survival results are analyzed among patients who ultimately underwent surgical resection with curative intent, the survival benefit of NAT becomes more evident for those patients with either resectable or BR disease. Note that in Table 146.2, the specific NAT regimens used in these reported trials are quite variable, with some delivering systemic therapy alone (gem + S1, gemcap, or FOLFIRINOX), while others have used 5FU-based or gem-based CRT alone, or before and after some systemic gem.

At the present time, the NCCN Pancreatic Cancer Guidelines subcommittee recommends NAT for patients presenting with BR disease [32]. In addition, for patients having potentially resectable tumors, the guidelines suggest consideration of NAT for those patients with high-risk features to include markedly elevated pretreatment CA 19-9 level, large primary tumor, enlarged regional LNs or excessive weight loss. The guidelines generally recommend NAT with combination chemotherapy such as FOLFIRINOX, gem/nab-p, or gemcap with or without CRT.

Downstaging Locally Advanced Disease with Neoadjuvant Therapy

The potential to downstage LA pancreatic cancer to potentially resectable disease has been touted in the medical literature for years. Single institutions have reported widely varying conversion rates ranging from 1% to as high as 68% [33,34]. Note that many of these reports were published in an era before BR tumors were defined as a distinct subset and the patients likely represent a heterogeneous population of those having tumors that would currently be considered BR and those defined as LA.

Recent reports of NAT in LA pancreatic cancer patients suggest a select subset may be considered for surgery after a period of preoperative treatment as shown in Table 146.3 [34–38]. A retrospective experience from investigators at Duke University analyzed patient cohorts treated from 1995 to 2000 and partitioned patients as either potentially resectable (53) or locally advanced (58) [35]. The resection rate among potentially resectable patients was 53% and 19% for the LA group; R0 resections were achieved in 72%. This was consistent with retrospective data from the Johns Hopkins Hospital using modern regimens of induction systemic therapy with 96% of patients also receiving CRT [36]. Within this cohort, 20% of patients underwent resection with an R0 rate of 89%. Recent data from LAPACT, a prospective phase II trial of gem/nab-p in 107 patients with LA disease, reported that only 16% of enrolled patients were able to undergo surgical resection with an R0 rate of 44% [38]. Of note, LAPACT was a multicenter trial not designed to investigate chemotherapy as a neoadjuvant strategy in patients with LA disease.

The results from Duke and Johns Hopkins coupled with the prospective data from LAPACT are at odds with recent results from Massachusetts General Hospital in which a select group of 49 LA pancreatic cancer patients received FOLFIRINOX and losartan followed by short- or long-course CRT [34]. In this study, the resection rate was almost 70% with an R0 resection rate of 88%. Somewhat similar results were reported from NEOLAP-AIO-PAK-0113 which was likewise designed as a neoadjuvant trial and delivered gem-based therapy alone or gem-based therapy followed by FOLFIRINOX [37]. Here, the resection rate was 40%, 67% of which were R0.

Taken together, the clear variability in resection rates and R0 resections demonstrates a spectrum of LA tumors, some unlikely to ever be resectable, with others potentially resectable after NAT. In a report from the Medical College of Wisconsin, the authors proposed a new classification of locally advanced disease to aid in the identification of patients more likely to benefit from eventual resection [39]. LA type A patients had anatomic tumor–vessel relationships which allowed for consideration of surgery after NAT; in LA type B patients, resection and long-term survival were far less likely.

Challenges of Neoadjuvant Therapy in Borderline Resectable and Locally Advanced Pancreatic Cancer

Despite keen interest, questions remain about tumor downstaging using a neoadjuvant approach.

- What is the best chemotherapy regimen?
- What is the optimal duration of NAT?
- What is the relative contribution of neoadjuvant systemic therapy and radiotherapy to tumor downstaging?
- What response criteria can identify patients most likely to benefit from surgical resection after NAT?
- Is total NAT better than perioperative therapy?

At the present time, only partial answers are available to these questions.

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Table 146.2 Randomized trials comparing upfront surgery and adjuvant therapy with neoadjuvant therapy (NAT) and surgery in patients with resectable (R) and borderline resectable (BR) pancreatic cancer.

Author Study title NAT Year	Clinical stage	Number of patients	R0 resection rate (%)		ITT median overall survival (months)		Resected patients median overall survival (months)		P value	Comments
			Upfront surgery	Neoadjuvant therapy	Upfront surgery	Neoadjuvant therapy	Upfront surgery	Neoadjuvant therapy		
Jang Korea Gem-based CRT 2018	BR	50	26	52	12	21	19.5	22.0	0.028 (ITT population)	Lower T-stage and LN + rate with NAT
Unno Prep-02/JSAP-05 Gem + S1 2019	R	362	NS	NS	26.6	36.7	NS	NS	0.015 (ITT population)	Lower T-stage and LN + rate with NAT
Versteigne PREOPANC Gem + Gem-based CRT 2020	R	133	59	66	15.6	14.6	19.8	35.2	0.029 (resected patients)	Lower T-stage and LN + rate with NAT
Versteigne PREOPANC Gem + Gem-based CRT 2020	BR	113	15	23	13.2	17.6				Lower T-stage and LN + rate with NAT
Ghaneh ESPAC 5F Gem/Cap or FOLFIRINOX or 5FU-based CRT 2020	BR	88	15	23	1 year survival 40%	1-year survival 77%	NS	NS	< 0.001	Lower T-stage and +LN rate for NAT Smaller tumors after NAT

CRT, chemoradiotherapy; ITT, intention to treat; LN, lymph node.

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Table 146.3 Retrospective reports and prospective trials of chemotherapy +/– chemoradiotherapy (CRT) in patients with locally advanced (LA) pancreatic cancer.

Study	Study period Study type	Number of patients	Regimen(s)	Resection rate (%)	R0 rate (%)	Survival (months)	
Duke	1995–2000 Retrospective	58	5FU-based CRT +/– MMC or cisplatin or both	19	72	NS	NS
Johns Hopkins	2013–2017 Retrospective	415	FFX or G + nab-p or both 96% received CRT	20	89	No resection 16.3	Resected patients 35.3
Massachusetts General	2013–2018 Prospective	49	FFX followed by short or long course CRT	69	88	Entire cohort 31.4	Resected patients 33.0
NEOLAP-AIO-PAK-0113	2014–2018 Prospective	130	Gem + nab-p or gem+ nab-p followed by FFX	40	67	No resection 13.9	Resected patients 27.5
LAPACT	2015–2018 Prospective	107	Gem + nab-p (with option for CRT and or surgery)	16	44	Entire cohort 18.8	Resected patients NS

5FU, 5-fluorouracil; FFX, FOLFIRINOX; MMC, mitomycin C; NS, not significant.

What is the Best Chemotherapy Regimen?

Two recent randomized trials suggest similar outcomes using FOLFIRINOX or gem/nab-p as part of perioperative or NAT [40,41]. S1505 was a cooperative group study that treated 103 patients with potentially resectable disease and randomized them to perioperative treatment with FOLFIRINOX or gem/nab-p [40,42]. The surgical resection rate (75%), R0 rate (85%), and two-year survival rate were all similar (47–48%). In a smaller randomized trial from Japan with 51 patients, no difference in outcomes were observed using FOLFIRINOX or gem/nab-p as NAT [41].

What is the Optimal Duration of Therapy Prior to Considering Surgical Resection?

Single-institutional data suggest that in BR and LA disease, longer durations of NAT provide greater benefit compared with shorter periods of treatment [43–45]. This appears to be supported by prospective trials. For example, in ESPAC 5F, patients randomized to NAT received just eight weeks of FOLFIRINOX or gemcap, or 5.5 weeks of capecitabine-based CRT [31]. If one assumes a four-week break thereafter for restaging and recovery from NAT, nonprogressing patients would undergo surgery within 10–12 weeks of initiating NAT. In that trial, the resection rate among patients randomized to NAT was 55%.

In the PREOPANC trial, patients randomized to NAT underwent laparotomy within 14–18 weeks from time of randomization, with a resection rate of 61% [30]. Lastly, Alliance A021101 (a US multiinstitutional trial), enrolled patients with BR pancreatic cancer with about a 24-week interval from start of treatment to surgery [27]. Here, the resection rate was 68%.

In the future, perhaps shorter courses of NAT will be devised for patients with resectable disease while longer courses are reserved for those with BR or LA pancreatic cancer.

What are the Relative Contributions of Systemic Therapy and Chemoradiation?

While many single-institutional efforts have routinely incorporated CRT as a component of NAT, multiinstitutional and cooperative group trials are beginning to present results in which patients with BR disease are being randomized to systemic therapy alone, to CRT alone, or some combinational approach. Preliminary results from ESPAC 5F showed that patients who received NAT CRT and surgery had a higher R0 resection rate compared with patients who underwent resection after receiving either gemcap or FOLFIRNOX [31]. In contrast, in Alliance A021501, patients with BR disease were randomized to eight courses of FOLFIRINOX with planned surgery thereafter (arm A) or to seven courses of FOLFIRINOX followed by five fractions of stereotactice body radiation therapy (SBRT) with subsequent surgery for nonprogressors (arm B). Preliminary results demonstrated an 18-month overall survival rate of 67.9% among patients randomized to arm A alone versus 47.3% in arm B. Among patients who underwent pancreatectomy, the 18-month OS rate was 93.1% for those assigned to arm A and 78.9% for arm B [46].

PREOPANC 2 is a randomized controlled trial of NAT in resectable and BR disease designed to compare NAT

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FOLFIRINOX (eight cycles) with gem and gem-based CRT. However, since the systemic therapy used in both arms is different, this trial will not provide a definitive answer as to the role of radiation in NAT for pancreatic cancer. In the setting of LA pancreatic cancer, for those patients who benefit from induction chemotherapy, NAT CRT is usually recommended, with surgical candidacy reassessed upon the completion of NAT.

What Response Criteria can Identify Patients Most Likely to Benefit from Surgical Resection After Neoadjuvant Therapy?

Prior studies have found that post-NAT imaging is unable to reliably identify tumor downstaging [25,47], likely related to tumor desmoplasia thwarting radiographic evidence of tumor shrinkage despite significant tumor destruction. Furthermore, it is rare to see a change in critical tumor–vessel relationships, particularly arterial abutment or encasement after NAT (Figure 146.1). Retrospective data from a few centers are now suggesting that normalization of CA 19-9 in response to NAT is associated with better long-term survival in resected patients in comparison with those patients who do not have a normal CA 19-9 level post-NAT [48,49].

Is Total NAT Better Than Perioperative Therapy?

Whether patients should undergo total NAT or perioperative therapy is an unresolved question. In other gastrointestinal tumors such as gastroesophageal and rectal cancer, both approaches have been utilized. In Prep-02/JSAP-05, ESPAC 5F, and PREOPANC, in patients assigned to NAT and underwent surgery, AT was also intended. Retrospective data from UTMDACC suggest a potential survival advantage for patients with resectable or BR disease who undergo NAT, surgery, and subsequent AT compared with those who undergo NAT and surgery only [50]. These results are based on a small number of patients who received perioperative therapy (36) compared to a larger number who did not (227). An interesting finding was that AT only benefited patients whose tumors had a positive lymph node ratio of 0.15 or less. This result may be useful in future trials of perioperative therapy as a stratification factor for randomized trials that deliver a uniform NAT regimen with randomization to AT or observation for patients who undergo resection.

In the future, postoperative therapy may be based on specific selection criteria such as pathologic staging, serum tumor markers, or as yet undefined biomarkers.

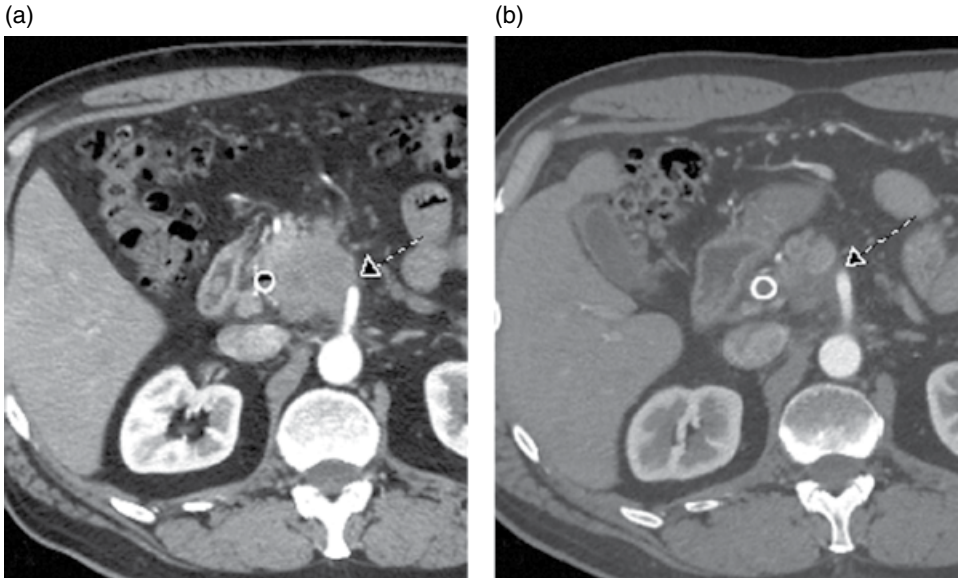


Figure 146.1 (a) Baseline CT image of a mass in the head of the pancreas from a 60-year-old man diagnosed with locally advanced pancreatic cancer. The arrow depicts tumor abutting the superior mesenteric artery by greater than 180°. (b) CT image obtained after treatment with induction FOLFIRINOX × 8 doses followed by capecitabine-based CRT delivered to 50.4 Gy. Note that while the tumor has reduced in size, the degree of arterial abutment has not changed (arrow). Patient underwent successful R0 resection with complete pathologic response. However, disease recurred locally approximately eight months postoperatively. He eventually died 34 months after his initial diagnosis.

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Diagnostic Innovations for Precision Medicine

CT Imaging Biomarkers

At UTMDACC, signal characteristics of tumor–parenchymal interface from pretreatment CT images were analyzed and characterized primary tumors as high-delta, with a well-defined interface between the tumor and surrounding parenchyma, or low-delta, with an ill-defined interface. Patients with high-delta tumors had inferior median PFS compared to those with low-delta tumors (7.5 months vs 23.5 months, P <0.01) and inferior OS compared to those with low-delta tumors (17.1 months versus not reached, P <0.01) [51]. If validated, these findings may allow for alternative treatment strategies in high-delta vs low-delta primary tumors.

Biopsy Material for Molecular Profiling

As precision medicine in pancreatic cancer slowly emerges, acquisition of sufficient primary tumor tissue for molecular profiling is desirable. In a small, randomized trial, 60 patients undergoing endoscopic ultrasound for biopsy of a pancreatic mass were randomized to undergo aspiration with a 25 gauge needle followed by biopsy with a 19 or 22 gauge needle or vice versa. The investigators found that needle biopsy material provided more DNA for molecular profiling than aspiration (P <0.01); adequate material was obtained for profiling in 78% of biopsies compared with 14% of aspirates (P <0.001) [52].

Circulating Tumor DNA-Liquid Biopsy

The power of ctDNA assays has implications in cancer management as a marker of tumor burden, molecular residual disease or relapse, detecting actionable mutations, and elucidating mechanisms of resistance to therapy. In a retrospective analysis of blood samples from 60 patients with pancreatic cancer (13 patients with localized disease and 47 with metastases), ctDNA was detected in 10% and 57% of samples, respectively. In localized disease, pretherapeutic ctDNA detection significantly correlated with the numbers of involved locoregional lymph nodes (P = 0.030) and was associated with shorter DFS (3.3 vs 18.1 months, P = 0.001). In another study with 112, KRAS mutated ctDNA was detected in 62% of preoperative and 37% postoperative cases. At a median follow-up of 38.4 months, ctDNA detection in the preoperative setting was associated with substantially inferior recurrence-free survival (RFS) (P = 0.002) and OS (hazard ratio [HR] 4.1, P = 0.015). Detectable ctDNA following curative intent resection was also associated with inferior RFS (HR 5.4, P <0.0001) and OS (HR 4.0, P = 0.003). Recurrence occurred in 13/13 (100%) patients with detectable ctDNA postoperatively [53].

Thus, in the setting of resectable, BR, and LA disease, ctDNA may prove to be a useful biomarker for prognostic purposes and to identify the patients most likely to benefit from surgical resection after NAT. In addition, detection of ctDNA postoperatively may influence the decision to deliver postoperative therapy.

Emerging Therapeutic Strategies

The complex biology of the microenvironment of pancreatic adenocarcinoma, with stromal elements that may act to both sequester malignant cells and protect them from cytotoxic therapy or immunologic attack, is steadily being elucidated. Important cellular components of the tumor microenvironment (TME) include CD8+ T cells with effector memory phenotype capable of cell killing, in addition to immunosuppressive myeloid cells and CD4+ regulatory T cells. Of note, conventional NAT by itself can alter the TME, generating a less immunosuppressive milieu [54,55]. NAT can lead to selective depletion of inhibitory CD4+ T cells and myeloid-derived immunosuppressive cells with enrichment of antitumor immune cells. Coupling conventional NAT with other therapeutic manipulations may tilt the balance from an immunosuppressive TME to one that is more susceptible to tumor cell death using a combination of cytotoxic therapy, targeting agents, and immune check point inhibitors.

Reports of agents designed to modulate the TME in nonmetastatic pancreatic cancer are being investigated in the clinic [56]. Recent efforts include the administration of the autophagy inhibitor HCQ or CD40 agonists to cytotoxic NAT [57,58], in addition to investigations of vaccines [59], and immune checkpoint inhibitors combined with chemotherapy or radiation to augment tumor killing from NAT.

Local Therapies

As discussed previously, while a randomized NAT trial failed to show an added benefit for SBRT after induction chemotherapy in BR pancreatic cancer [46], novel approaches to deliver higher doses of radiation therapy [60] or to enhance radiation killing while protecting surrounding tissues are being explored in patients with locally advanced pancreatic cancer [61].

Lastly, based on improvements in systemic therapy, more interest in local control to include aggressive surgical intervention is certain to develop. While venous resection with reconstruction is commonly performed in pancreatic cancer centers of excellence, there is renewed interest in performing arterial resections with reconstruction at the time of surgery. In a previous era, arterial

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resections were associated with poor outcomes. With modern chemotherapy regimens and improved CRT, encouraging results have been reported in small numbers of patients where arterial resection and reconstruction have been performed [62,63]. With increasingly active NAT regimens, greater numbers of patients with localized disease may be able to undergo surgery with curative intent.

Conclusion

Neoadjuvant treatment is a rational approach to therapy for localized, nonmetastatic pancreatic cancer. It is also a strategy to uncover aggressive tumor biology or frailty prior to surgical intervention. Radiographic evidence of tumor downstaging is not required in the setting of resectable pancreatic cancer, but NAT may lead to pathologic downstaging and improve the likelihood of an R0 resection. In borderline resectable disease, which places the patient at high risk for an R1 resection, treatment with NAT is sufficiently active in 40–60% of patients to ultimately allow for surgical resection. For those with locally advanced pancreatic cancer, although the chances of ultimately undergoing surgery with curative intent are lower than in resectable or BR disease, newer drug therapies intended to alter the TME or enhance immunologic cell killing may expand the proportion of patients who can be considered for surgery.

Lastly, the recognition of and formalized definitions for BR disease which is intermediate in the spectrum of resectable and LA/unresectable pancreatic cancer will allow for more reliable comparison of results in clinical trials of various neoadjuvant regimens.

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Locally Advanced Pancreatic Cancer: Does the Addition of Stereotactic Body Radiation Therapy to Neoadjuvant Chemotherapy Lead to a Significant Survival Improvement after R0 Resection?

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Neoadjuvant Treatment in Pancreatic Cancer Patients

Long-term survival of patients who undergo surgical resection for pancreatic cancer (PC) has significantly improved over the last few decades but remains below that of other tumors [1]. One of the major contributors to the improvement of PC prognosis has been the implementation of more effective systemic treatments [2,3]. Neoadjuvant chemotherapy has become the standard of care for the multimodal treatment of borderline resectable (BR) and locally advanced pancreatic cancer (LAPC). Unlike other types of cancer, neoadjuvant treatment (NAT) very rarely causes downstaging of PC. Radiologic response to the most commonly used NAT, FOLFIRINOX, is seen in a minority of cases. However, absence of a radiologic response does not necessarily equal absence of pathologic or biologic response [4]. In contrast to chemotherapy, the use of neoadjuvant radiation therapy (RT) is not universally accepted or standardized across geographical regions [5].

Given the limited number of patients with downstaged disease after NAT, the main goal of NAT in PC is not to downstage local disease, but rather:

- biologic selection of the best candidates for surgical resection (e.g., patients who do not have progression of disease during NAT)
- determining the optimal neoadjuvant chemoradiation therapy in combination with surgery (especially considering that a significant percentage of patients cannot receive adjuvant treatment postoperatively due to surgical complications)
- early systemic control of the disease.

In a recent analysis of the role of neoadjuvant RT in a large cohort of patients from the National Cancer Data Base, the retrospective study did not show any survival advantage for patients who received neoadjuvant chemoradiation compared with patients who received neoadjuvant chemotherapy alone. This is despite RT being associated with a significant higher rate of R0 resections. In contrast, single-center, retrospective studies of LAPC have reported impressive results in terms of long-term survival with preoperative chemoradiation therapy followed by surgery [6].

Use of Stereotactic Body Radiation Therapy in Borderline Resectable/ Locally Advanced Pancreatic Cancer

The authors group BRPC and LAPC due to the lack of significant difference in prognosis in the literature [7]. We previously published a retrospective analysis of 103 patients (85 BRPC and 18 LAPC) who underwent preoperative chemotherapy followed by SBRT. For patients who underwent resection in this series, the rate of R0 was 97.3% and complete pathologic response was seen in 7%. The median overall survival of the resected group was 24 months [8]. Another recent retrospective study reviewed 155 patients (64 BRPC and 91 LAPC) who underwent preoperative chemotherapy followed by SBRT. Patients who underwent surgical resection achieved an R0 resection in 96% for BRPC and in 88% for LAPC. However, the median overall survival was 18.7 months from the end of SBRT [9].

Another study retrospectively comparing patients affected by BRPC and LAPC who underwent either neoadjuvant chemotherapy or neoadjuvant chemoradiation demonstrated an advantage in the radiation group in achieving RO resection (92% vs 70%), node-negative disease (59% vs 42%) and a complete pathologic response

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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(7% vs 0). However, there was no observed benefit in overall median survival (22.1 vs 24.5 months) [10].

However, all these studies were retrospective and exposed to several biases. For this reason, a multicenter, prospective, randomized trial (Alliance A021501) was designed in the US. The study sought to compare the use of neoadjuvant FOLFIRINOX chemotherapy with combined neoadjuvant chemotherapy and SBRT. Patients who received chemotherapy alone had a better overall median survival than those who received chemoradiation (31 vs 17.1 months) [11].

Interpretation of the Data Behind Neoadjuvant SBRT in Pancreatic Cancer

The majority of data in the current literature suggest a higher rate of R0 resections and complete pathologic response. However, despite these promising results, they do not show any improvement in survival. In contrast, in the only prospective, randomized trial performed so far, the opposite trend appears to emerge. Addition of SBRT to neoadjuvant chemotherapy was associated with a decrease in median overall survival.

In the authors' view, the role of neoadjuvant SBRT for the treatment of BRPC and LAPC remains unclear. Pancreatic cancer is a systemic disease. For this reason, local control is not the only important aspect of treatment. Distant disease recurrence occurs in at least 80% of the cases in most of the recent series [12]. Even if SBRT can help achieve a more radical resection from a pathologic perspective, this local effect of treatment may not have any influence on tumor biology and overall prognosis.

On the other hand, a negative result from a single prospective, randomized trial is probably not sufficient to say that there is no role for SBRT in the treatment of pancreatic cancer. Future studies will better clarify SBRT's role in the multimodal treatment of pancreatic cancer.

The authors caution against, however, the use of preoperative radiation therapy in patients with LAPC that have the potential to undergo arterial resection and reconstruction. Even though solid evidence is lacking, we believe that the possibility of actinic arteritis caused by radiation may increase the risk of complications during arterial reconstruction [13].

Conflict of interest

Dr. Del Chiaro has been awarded an industry grant (Haemonetics, Inc) to conduct a multi-center study to evaluate the prognostic implications of TEG in pancreas cancer.

Dr. Del Chiaro is a co-PI of a sponsored Boston Scientific study on the use of intra-operative pancreatoscopy in IPMN's patients.

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Adjuvant Chemotherapy in Pancreatic Cancer: First Line and Second Line Treatment—Benefits of Survival

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Introduction

Pancreatic ductal adenocarcinoma remains the most common malignancy of the pancreas, and is the fourth highest cause of cancer death in the developed world. An estimated 367 000 new cases were diagnosed worldwide in 2015, and it is likely to become the second leading cause of cancer mortality within the next decade, overtaking deaths from breast cancer [1,2].

The majority of patients with pancreatic cancer present with advanced disease. Surgery remains the only potentially curative option, but even in specialized centers just 10–15% of patients are suitable for resection [3]. The mortality associated with major pancreatic surgery has reduced considerably in recent years, and is now routinely reported as less than 5% [4]. Following surgery alone, prognosis remains dismal with a median survival of around 13 months and only 10% surviving for five years [5]. Increasingly radical resections that include extended lymphadenectomy or total pancreatectomy have been employed in an attempt to improve long-term outlook, but prospective trials comparing these more radical resections with classic surgical techniques have failed to demonstrate any survival benefit, with significant disadvantage in terms of postoperative quality of life [6].

Around 70% of patients undergoing curative intent surgery succumb to distant metastases rather than local recurrence [7] and so attention has turned to additional therapies that may delay or prevent the development of recurrence in an effort to improve long-term outcome. Adjuvant therapy is used with the aim of reducing these occult micrometastases and the results from contemporary randomized studies provide the most compelling evidence so far to support its use after surgery for pancreatic cancer.

This chapter aims to provide a summary outline of key trials in adjuvant therapy, as well as to highlight potential future avenues to improve outcomes in this deadly disease.

Rationale for Adjuvant Therapy

The first randomized trial assessing the role of adjuvant treatment for pancreatic cancer was the small 1985 Gastrointestinal Tumor Study Group (GITSG) study, where 43 resected patients were randomized to receive either 5-fluorouracil (FU) concurrent with radiation (50 Gy) followed by maintenance 5-FU, or observation alone. The trial closed prematurely because of failure to recruit, but despite these problems, median survival was considerably longer for the adjuvant therapy arm (20 months vs 11 months, $P = 0.04$) (Table 148.1) [8]. It was impossible to tell whether it was systemic chemotherapy or radiotherapy that led to this improvement.

Subsequent to this, a larger European study (EORTC 40891) assessed concurrent 5-FU and radiation (40 Gy) versus observation alone for 120 patients with resected pancreatic head cancer and periampullary tumors but demonstrated no difference in median or long-term survival, even when the pancreatic head group was evaluated independently [9,10].

The European Study Group of Pancreatic Cancer (ESPAC)-1 trial provided a further challenge to the value of chemoradiation and suggested that chemotherapy alone provided the primary survival benefit seen in

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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Table 148.1 Summary of major trials of adjuvant therapy for pancreatic cancer.

Trial	Year	Regimen	Median survival (months)	*P*	Five-year survival (%)	*P*
GITSG [8]	1985	Observation	11	0.04	13.6	NR
		5-FU/50 Gy	20		4.7	
EORTC 40891 [9,10]	1999	Observation	19	0.2	22	NS
		5-FU/40 Gy	25		25	
ESPAC-1 [11,12]	2001	Chemotherapy (bolus 5-FU)	20.1	0.009	21	0.009
		No chemotherapy	15.5		8	
		Chemoradiotherapy (50 Gy)	15.9	0.05	10	0.05
		No chemoradiotherapy	17.9		20	
CONKO-001 [13]	2007	Gemcitabine	13.4	<0.001	20.7	0.01
		Observation	6.7		10.4	
ESPAC-3 [14]	2010	5-FU/leucovorin	23.0	0.39	15.9	NS
		Gemcitabine	23.6		17.5	
EORTC 40013 [15]	2010	Gemcitabine	24.4	NS	–	–
		Gemcitabine/50.4 Gy	24.3	–		
ESPAC-4 [16]	2016	Gemcitabine	25.5	0.03	28.8	0.032
		Gemcitabine/capecitabine	28.0	16.3		
JASPAC-01 [17]	2016	S1	–	–	44.1	<0.0001
		Gemcitabine	–	24.4		
PRODIGE [18]	2018	FOLFIRINOX	54.4	0.03	63.4 (3 yrs)	–
		Gemcitabine	35.0		48.6 (3 yrs)	–
APACT [19]	2021	Nab-paclitaxel/gemcitabine	41.8	0.0091	38	–
		Gemcitabine	37.7		31	–

NS, nonsignificant; NR, not reported; –, data not available.

GITSG [11,12]. The study used a 2 × 2 factorial design to stratify patients undergoing curative intent surgery for pancreatic adenocarcinoma by center, type of tumor, and resection margin status. Patients were then randomized to one of four arms: (i) chemoradiation (50 Gy split course), (ii) six months of systemic chemotherapy (bolus 5-FU), (iii) combination chemotherapy and chemoradiotherapy, or (iv) observation. A total of 289 patients from across Europe were randomized. At a median follow-up of 47 months, five-year survival was significantly higher for those receiving chemotherapy versus those who did not (21% vs 8%, $P = 0.009$). Median survival for those treated with chemotherapy was 20.1 months compared to 15.5 months for those without ($P = 0.009$). Median survival was also significantly longer in the group who did not receive chemoradiotherapy (17.9 vs 15.9 months, $P = 0.05$), which translated to an estimated five-year survival rate of 10% for those treated with chemoradiation compared to 20% for those who did not ($P = 0.05$) (Fig. 148.1) [11,12]. The survival rates for patients treated with chemoradiation in ESPAC-1 were broadly in keeping with those from other series, and the superior outcomes seen after systemic chemotherapy led to a move away from adjuvant radiotherapy in favor of systemic chemotherapy across Europe.

The promising results of ESPAC-1 led other researchers to question whether the use of more active systemic chemotherapies would translate to improved long-term outcome. The Charité Onkologie (CONKO)-001 trial compared six cycles of systemic gemcitabine with observation alone in 368 patients who had undergone resection, and found a significant improvement in median disease-free survival (13.4 vs 6.7 months, $P < 0.001$), which also translated into improved five-year survival (20.7% vs 10.4%, $P = 0.01$) [13,20]. This benefit was consistent irrespective of tumor stage, nodal status, and margin status. However, patients with a postoperative CA 19-9 level >92.5 KU/L were excluded from trial entry, meaning the patient population included were a prognostically more favorable group.

Both ESPAC-1 and CONKO-001 therefore confirmed the role of adjuvant therapy as standard of care after

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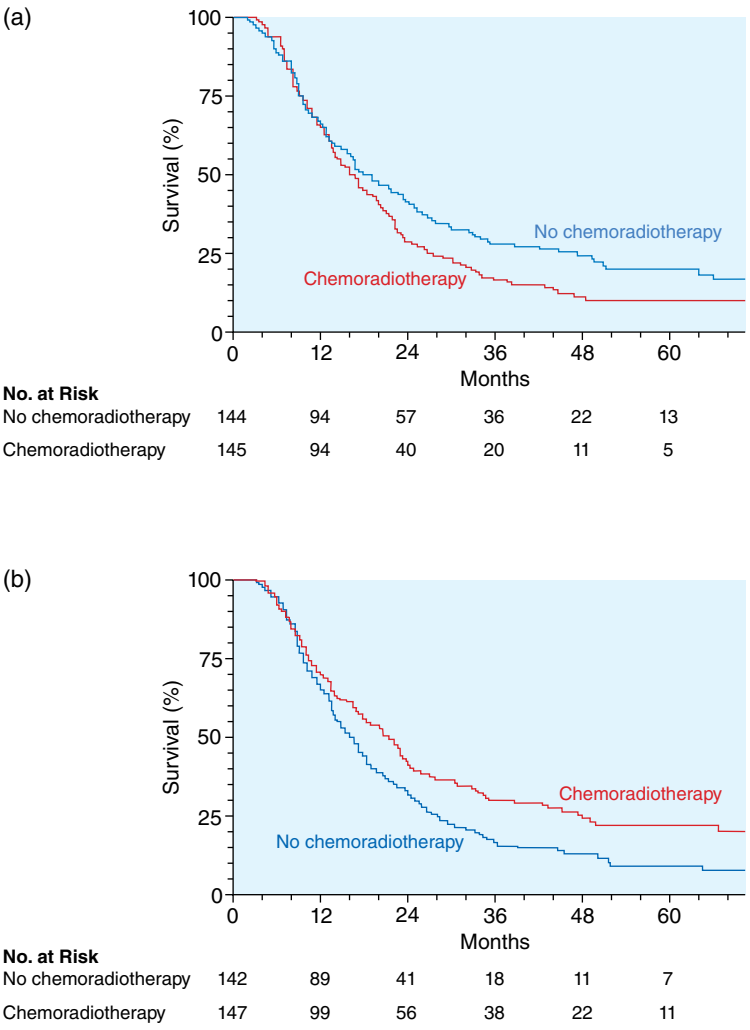


Figure 148.1 Overall survival from the ESPAC-1 trial. *Source:* Reproduced from [12]/With permission of Massachusetts Medical Society.

curative resection, and led to an almost doubling in the five-year survival after surgery.

ESPAC-3 built on these findings by randomizing 1088 patients to observation, bolus 5-FU/leucovorin, or bolus gemcitabine for six months after surgery [14]. The observation arm was closed when the final results of ESPAC-1 were published. Final analysis at a median follow-up of 34.2 months demonstrated equivalence in median survival (23.0 months for 5-FU/leucovorin vs 23.6 months for gemcitabine, $P = 0.39$) (Fig. 148.2) but significantly lower grade 3/4 toxicity in the gemcitabine arm (7.5% vs 14%, $P < 0.001$). These results defined gemcitabine as the optimal adjuvant monotherapy for patients who had undergone curative resection.

The Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)-01 trial assessed S-1 (a 5-FU analogue with marked efficacy in the Japanese population) versus gemcitabine in the adjuvant setting. This noninferiority study randomized 385 Japanese patients, and found overall survival at two years of 70% for the S-1 group compared with 53% for the gemcitabine group, with a five-year overall survival of 24.4% in the gemcitabine group and 44.1% in the S-1 group (P <0.0001 for noninferiority, P <0.0001 for superiority) [17]. While these results are impressive, it remains unclear whether they are applicable to a non-Japanese population with different S-1 metabolism where efficacy is lower and toxicity higher. In addition, randomized patients were a prognostically favorable group with only 13% having an R1 resection and only 21% having a raised CA 19-9. As such, the results may have limited applicability in a real-world Western population.

Combination therapy with gemcitabine and capecitabine has become increasingly common in the palliative treatment of metastatic pancreatic cancer, with good response rates and acceptable toxicity [21,22]. The ESPAC-4 study therefore assessed whether these improved response rates translated to improved overall survival in the adjuvant setting. A total of 732 patients were randomized to six cycles of intravenous gemcitabine

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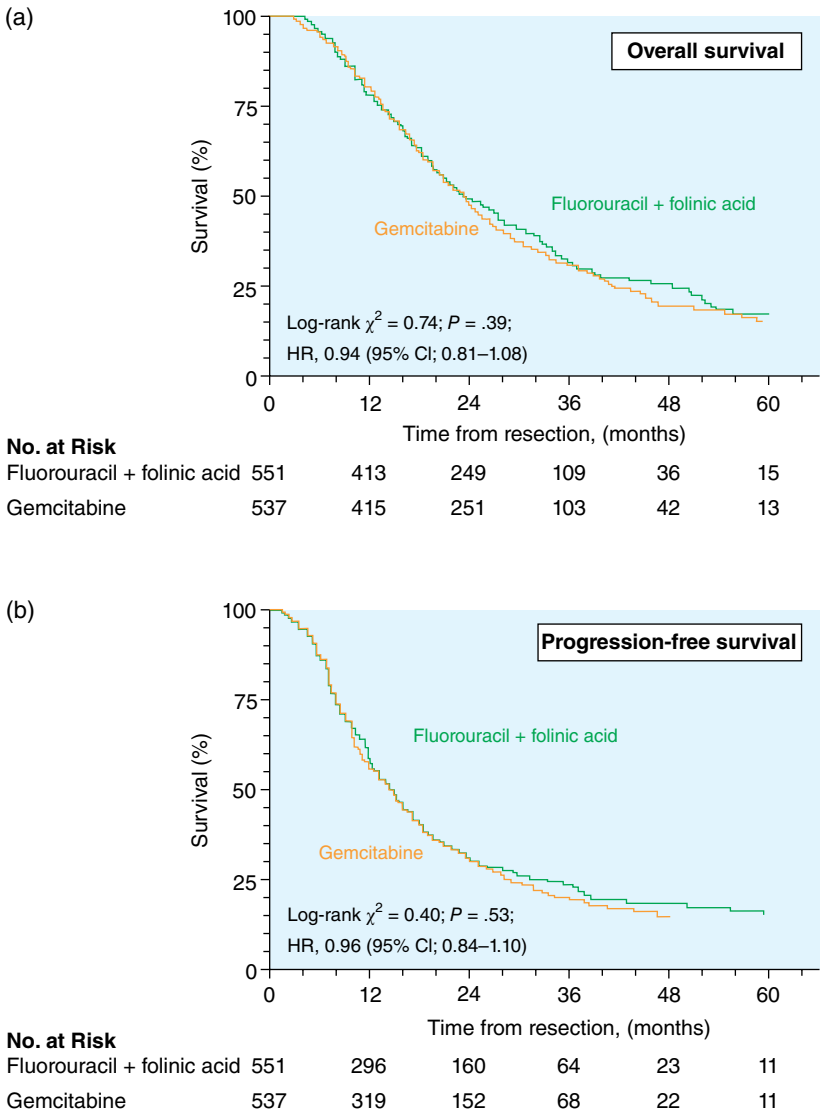


Figure 148.2 Overall survival from the ESPAC-3 trial. *Source:* Reproduced from [14]/With permission of American Medical Association.

with or without oral capecitabine. Median survival was slightly longer in the combination therapy arm (25.5 vs 28.0 months, $P = 0.03$). However, the five-year survival rates were considerably higher for patients receiving dual therapy rather than gemcitabine alone (28.8% vs 16.3%) (Fig. 148.3) [16]. Severe toxicities were similar, and both regimens were well tolerated. It is also important to note that ESPAC-4 recruited a wider variety of patients than other studies (Table 148.2). For example, patients with raised postoperative CA 19-9 and without immediate preadjuvant imaging were eligible for inclusion. These findings suggest that combination therapy with gemcitabine/capecitabine is proving more effective than single agent gemcitabine and is a standard of care for this patient population.

The PRODIGE and Canadian cancer trials group (PRODIGE 24 - ACCORD) randomized 493 patients with resected pancreatic cancer to receive adjuvant modified FOLFIRINOX (oxaliplatin, irinotecan, leucouvorin, and fluorouracil) or gemcitabine [18]. After a median follow-up of three years the median disease-free survival was 21.6 months in the FOLFIRINOX group compared to 12.8 months in the gemcitabine group ($P < 0.001$), with a disease-free overall survival of 39.7% vs 21.4% respectively. Median overall survival was 54.4 months and 35 months in the FOLFIRINOX and gemcitabine groups respectively [18]. The striking increases in survival are partly explained by inclusion criteria. ages of patients being maximally 79, WHO performance of 0 or 1, patients with high CA 19-9 (>180 U 21 days before randomization) and those with an incomplete resection (R2). The adverse events of grade 3 and 4 occurred in 75.9% of patients treated with FOLFIRINOX and 52.9% of patients treated with gemcitabine. The

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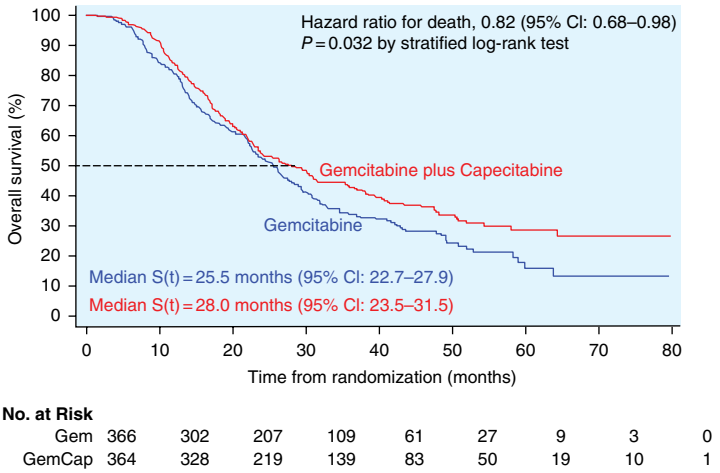


Figure 148.3 Kaplan–Meier plot for overall survival in the ESPAC-4 trial.

Table 148.2 Comparison of patient populations in JASPAC-01, CONKO-01, and ESPAC-4 trials.

Prognostic factor	JASPAC-01 [15] (N = 377)	CONKO-01 [12] (N = 368)	ESPAC-4 [18] (N = 730)
WHO PS 0	68.7%	–	42.2%
PS 1	31.3%	–	54.9%
PS 2	0.0%	–	2.9%
Grade 3	–	35.9%	40.4%
LN positive	62.9%	67.9%	80.4%
R1 positive	13.0%	16.6%	60.3%
Postop CA 19-9 > 37 KU/L	21.0%	–	31.7%
Postop CA 19-9 >92.5 KU/L	–	0.0%	17.1%

toxicity of the multiagent FOLFIRINOX precludes older and comorbid patients from receiving treatments. This explains the inclusion criteria but still demonstrates the significant benefit FOLFIRINOX has over gemcitabine as a adjuvant treatment agent.

The APACT phase III trial compared 866 patients with resected pancreatic ductal adenocarcinoma randomized into two adjuvant groups: nab-paclitaxel plus gemcitabine (nab-P + Gem) vs gemcitabine (Gem) alone in six 28-day cycles. The study did not reach the primary endpoint of independently assessed disease-free survival. The median follow-up was over five years and there was a median overall survival of 41.8 and 37.7 months (P = 0.009, nab-P + Gem vs Gem) with the nab-P group having a five-year survival of 38% compared to 31% in the Gem group [19].

The use of FOLFIRINOX and gemcitabine/capecitabine has become routine in patients with good performance status. FOLFIRINOX and nab-paclitaxel have yet to be compared in a trial setting. Gemcitabine may be preferable in older patients with poor performance status. The side-effect profile and chemotherapy regimen schedules are important considerations for patients and should be discussed with the oncologist, for fully informed decision making [23].

Adjuvant Chemoradiotherapy

The data presented from the CONKO-001, JASPAC-1, and ESPAC-1, -3, and -4 trials provide compelling evidence to support systemic chemotherapy for six months after surgical resection as standard of care. The role of additional adjuvant chemoradiotherapy remains less clear, with no randomized trial providing clear benefit in terms of overall survival.

Although the previously described GITSG and EORTC 40891 trials provide some evidence, they do not allow direct comparison of chemotherapy versus chemoradiotherapy. Concerns about the long-term survival benefit of additional adjuvant radiotherapy are supported by retrospective reviews and metaanalyses. Merchant et al. performed a pooled analysis of 646 patients from seven high-volume centers, 299 of whom were treated with surgery followed by chemoradiation and 347 with surgery alone [24]. Median overall survival was 20 months for the adjuvant chemoradiation arm, versus 14.5 months for surgery alone (P = 0.001). The investigators found a significant survival advantage only in patients with lymph node-positive disease. Somewhat surprisingly, they also identified reduced disease-free survival in patients with lymph node-negative disease who received adjuvant chemoradiotherapy (14.5 months vs 18.6 months, P = 0.034). These findings were further supported by another large retrospective series that

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compared 1130 patients treated with surgery, with or without adjuvant chemotherapy or chemoradiotherapy, at eight major US centers over 10 years. The authors identified reduced local recurrence after chemoradiation, but no impact on distant recurrences (in contrast to systemic chemotherapy) and therefore no impact on overall survival [25].

The first attempt to directly compare systemic chemotherapy with systemic chemotherapy and additional radiotherapy was the 2010 EORTC 40013 study, which randomized 90 patients to four cycles of gemcitabine versus gemcitabine with concurrent chemoradiation (50.4 Gy). Median overall survival was the same for both arms at 24 months, with comparable toxicity profiles. Eighty-seven percent of patients treated with gemcitabine alone completed all planned treatments, compared to 73% undergoing combination therapy [15]. Supporting previous retrospective series, local recurrence as site of first progression was 24% for the chemotherapy arm compared with 11% in the chemoradiotherapy arm. However, this did not translate into a long-term survival benefit.

In 2005, Stocken et al. performed a metaanalysis assessing the impact of adjuvant chemoradiation and chemotherapy on survival and included patient-level data from five randomized trials of adjuvant therapy [26]. Individual patient data were available in four of the five studies (94% of patients). Analysis demonstrated a 25% reduction in the risk of death (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.90, $P = 0.001$) with chemotherapy compared to no chemotherapy but no significant difference between chemoradiation and no chemoradiation (HR 1.09, 95% CI 0.89–1.32, $P = 0.43$). On subgroup analysis, chemoradiation was more effective and chemotherapy less effective in patients with positive resection margin.

In 2013, Liao et al. performed an updated metaanalysis of adjuvant 5-FU versus gemcitabine versus chemoradiation with 5-FU or gemcitabine, and showed that chemotherapy alone with either 5-FU (HR 0.65, 95% CI 0.49–0.89) or gemcitabine (HR 0.59, 95% CI 0.41–0.83) was associated with significant overall survival benefit. By contrast, adjuvant chemoradiation was associated with worse overall survival when compared with 5-FU (HR 1.69, 95% CI 1.12–2.54) and gemcitabine (HR 1.86, 95% CI 10.4–3.23) as monotherapy with significant additional toxicity [27].

The results of the RTOG 0848 phase III trial are still anticipated. Between 2009 and 2014, 856 patients who had a pancreatoduodenectomy for ductal cancer were randomized to receive either gemcitabine or gemcitabine with erlotinib for five cycles. After the final cycle, the patients were imaged and a further randomization step was performed to enter a no radiotherapy arm or a chemoradiotherapy arm using intravenous 5-FU or capecitabine as a radiotherapy sensitizer. Recently, the trial published a phase II report of the trial of 336 patients to answer the question of adjuvant erlotinib, reporting no additional benefit of the drug. They report there are no adverse effects of chemoradiation but maturation and analysis still await [28].

The role of adjuvant chemoradiotherapy therefore remains unclear, with benefit seeming to be limited to a subset of patients yet to be fully elucidated.

Timing and Duration of Adjuvant Therapy

The optimal timing of adjuvant therapy after surgery remains unclear. Patients need sufficient time to recover from the physiologic insult, whilst treatment needs to commence soon enough to prevent the establishment of micrometastatic deposits.

Valle et al. assessed the optimal timing to start therapy in the ESPAC-3 trial. A total of 985 patients were included, of whom 486 received gemcitabine, 675 (68.5%) received all six planned cycles of adjuvant therapy, and 457 (46.4%) started treatment within eight weeks of surgery. Overall survival was much better in those who received the full six cycles of treatment (28 months vs 14.6 months) (HR 0.516, 95% CI 0.443–0.601, $P < 0.001$) whilst time to start of treatment did not predict overall survival (HR 0.985, 95% CI 0.956–1.015, $P = 0.99$). However, for the subgroup of patients who did not complete all six cycles of treatment, the time to initiation of therapy was important, with overall survival better in those who waited more than eight weeks (HR 0.92, 95% CI 0.86–0.97, $P = 0.004$). These findings suggest that completion of a full course of treatment is more important than early initiation, and that allowing patients to fully recover from surgery may lead to better tolerability of therapy and an increased likelihood of completing treatment [29].

Second-line Chemotherapy

By definition, second-line chemotherapy is treatment of recurrent pancreatic cancer after surgery and adjuvant chemotherapy. There are no specific trials reviewing recurrent disease but there are a number of phase III randomized controlled trials in advanced pancreatic cancer focusing upon second-line agents. These are summarized in Table 148.3.

In the palliative setting, up to 86% may undergo second-line therapy, and in the PRODIGE 4 trial of advanced cancer, 165 of 342 patients proceeded along this strategy [30,31]. The CONKO-003 trials randomized

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Table 148.3 Summary of phase III randomized trials of second-line chemotherapy for advanced pancreatic cancer.

Trial	Year	Regimen	N	Median survival (m)	*P*
CONKO-003 [32]	2014	Oxaliplatin, 5-FU FA	76	5.9	0.01
		5-FU FA	84	3.3	
PANCREOX [33]	2014	FOLFOX6	54	6.1	0.02
		5-FU FA	54	9.9	
NAPOLI-1 [34]	2016	Liposomal irinotecan, 5-FU FA	117	6.2	0.009
		5-FU FA	149	4.2	

160 gemcitabine-refractory patients to 5-FU and folinic acid (FA) or 5-FU and FA combined with oxaliplatin. They found a significant increase in survival of 2.6 months, without clinically relevant toxicity [32]. The PANCREOX study randomized 108 similar patients into treatment arms of 5-FU leucovorin (LV) and FOLFOX6 which includes 5-FU, LV, and oxaliplatin. They found overall survival was significantly worse with FOLFOX6 by 2.8 months and 63% had grade 3/4 adverse events [33]. Nanoliposomal irinotecan is an irinotecan base encapsulated in a liposome and maintains a higher level of the drug intratumorally. The NAPOLI-1 trial used this drug in combination with 5-FU FA against 5-FU FA alone in gemcitabine-refractory advanced pancreatic cancer patients. They found an increase in survival of two months with nanoliposomal irinotecan [34].

Given these trials, the evidence base for patients tolerating second-line chemotherapy is increasing, especially when maintaining good performance status. FOLFIRINOX is a clear agent of choice in a palliative setting but no trials exist with its use as a second-line agent. There are phase II trials that have reviewed capecitabine and monoclonal antibody but not progressed to phase III [35]. The current options with second-line agents in recurrent pancreatic cancer, refractory to gemcitabine treatment, are nanoliposomal irinotecan and 5-FU FA. There is a need for studies reviewing second-line agents post FOLFIRINOX, potentially exploring the use of gemcitabine with nab-paclitaxel.

Future Directions in Adjuvant Therapy

As well as attempting to use increasingly active regimens, targeted adjuvant therapies offer great appeal. Whole-genome sequencing of large numbers of tumors has led to the identification of frequently mutated genes in pancreatic cancer, as well as identifying distinct molecular subtypes [36,37]. Unfortunately, the four most commonly mutated genes (*KRAS*, *CDKN3A*, *TP53*, and *SMAD4*) are not currently actionable, with druggable mutations occurring with much lower frequencies. Although the reducing cost of whole-genome sequencing means that precision therapy based on identifiable and actionable mutations on a case-by-case basis is a possibility, its mainstream use remains some way in the future.

To overcome some of these limitations, targeted agents with wider mechanisms of action have been investigated. Erlotinib is an oral tyrosine kinase inhibitor that has demonstrated improvements in overall survival when added to gemcitabine in the palliative setting [38]. CONKO-005 therefore randomized 436 resected patients to receive gemcitabine or gemcitabine/erlotinib. However, there was no difference in disease-free survival (11.6 months for both) or overall survival (24.6 months for combination therapy vs 26.5 months for gemcitabine alone) [39].

Immunotherapy has shown great promise in other cancer types. Around 90% of pancreatic cancers contain an activating mutation in *KRAS*. A small phase II trial therefore assessed the use of a novel *KRAS* vaccine in the adjuvant treatment of 23 patients with resected pancreatic cancer. The researchers found an immune response in 85% of patients, with a median survival of 28 months [40]. However, these results have not been replicated by other groups [41].

During repeated rounds of DNA replication, the telomeric ends of DNA become progressively shortened, leading to eventual cell death. Reactivation of telomerase, the telomere repair enzyme, is a crucial event in oncogenic transformation and occurs in nearly all pancreatic cancers. The TELOVAC trial therefore compared gemcitabine/capecitabine with or without a novel telomerase peptide vaccine (GV1001) in the palliative setting, but demonstrated no significant survival benefit, suggesting that further ways to enhance the immune response are required for clinical efficacy [42].

As well as trialing novel agents, there are increasing efforts to improve patient stratification for existing treatments. Penetration of gemcitabine into dense pancreatic stroma appears to be highly variable. Koay et al.

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demonstrated widely variable incorporation of gemcitabine into tumor DNA despite consistent serum pharmacokinetics. They also identified and validated a series of novel radiomic markers that would allow preoperative assessment of gemcitabine efficacy. This issue was further confused by the demonstration of widely varying incorporation of gemcitabine even within individual tumors, suggesting intratumoral heterogeneity may pose a problem not only for novel targeted agents but also for existing cytotoxic regimens [43,44].

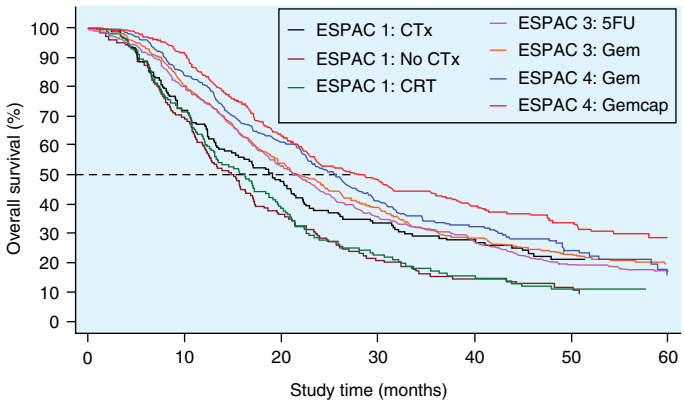
Biomarkers to predict response to treatment also offer significant potential to improve the stratification of treatment. Human equilibrative nucleoside transporter 1 (hENT1) is a cell surface protein that bidirectionally transports gemcitabine across pancreatic cell membranes. Greenhalf et al. assessed hENT1 expression in 434 patients from the ESPAC-3 trial, of whom 176 received gemcitabine. Median survival for patients treated with gemcitabine was 17.1 months for those with low hENT1 expression compared to 26.2 months for those with high hENT1 expression (P = 0.002), suggesting hENT1 may predict response to gemcitabine chemotherapy [45]. This finding was not confirmed in the prospective LEAP (Low hENT1 Adenocarcinoma of the Pancreas) trial in patients with metastatic disease where there was no difference in overall survival following treatment with gemcitabine in the hENT1 high and low groups [46].

Further publications from the Greenhalf group have elicited that hENT1 alone may not select patients who benefit from gemcitabine; further markers from the metabolism process can combine with hENT1 to personalize chemotherapy regimens. High levels of dihydropyrimidine dehydrogenase (DPD) have been found to be a negative prognostic marker in combination with low hENT1 expression in the ESPAC-3 patients who received 5-FU but not gemcitabine [47]. Similar findings were found using cytidine deaminase (CDA) transcript levels in the same group of patients, where low mRNA levels were associated with improved survival overall with either gemcitabine or 5-FU. Patients with low levels of hENT1 had better outcomes with 5-FU if the CDA levels were low compared to high (29.3 vs 14.2); the differences were less pronounced with gemcitabine (18.3 vs 14.6) [48].

The use of a single biomarker has not proved successful in the management of pancreatic cancer, though using a combination may personalize patients into effective chemotherapy arms. The ESPAC group has developed a specific stratification signature in order to randomize patients into oxaliplatin- or gemcitabine-based chemotherapy arms. The phase III trial aims to recruit 394 patients, with the primary outcome measure being disease-free survival [49].

Conclusion

The last 20 years have seen a paradigm shift in the management of pancreatic cancer. The routine use of adjuvant treatment has led to significant increases in median and five-year overall survival. The results of ESPAC-4 and PRODIGE trials define standard of care, with growing recognition of the importance of patients receiving the full planned treatment course (Fig. 148.4). Future directions for adjuvant therapy include the use of more active regimens, as well as better stratification of patients to existing therapies.



No. at Risk							
E1–CTx	149	105	68	46	34	19	16
E1–No CTx	143	99	50	28	17	10	8
E1–CRT	145	103	54	30	19	10	8
E3–Gem	539	422	283	187	126	93	64
E3–5FU	551	430	283	180	131	81	56
E4–Gem	366	302	207	109	61	27	9
E4–GemCap	364	328	219	139	83	50	19

Figure 148.4 Kaplan–Meier plots for overall survival in the ESPAC-1 (E1), ESPAC-3 (E3), and ESPAC-4 (E4) trials.

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Role of Radiation Therapy for Pancreatic Cancer

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Introduction

The role of radiation therapy (RT) for pancreatic cancer (PCA) remains highly controversial amid recent technologic advances in radiation oncology and systemic therapy improvements. The origins of this debate arise from key landmark trials with conflicting results regarding the relative merits of radiation. However, the manner in which this data should be applied to RT as delivered in the modern day using contemporary techniques is unclear. Nevertheless, fluency in the clinical literature exploring the role of RT for PCA across the disease stage is critical. Equally important is an understanding of the way in which conformal radiation techniques and charged particle therapy can be used to improve the therapeutic window. Knowledge of these topics will yield both an appreciation of the value of modern RT for patients with PCA and an ability to better customize treatment regimens to individual patients in a multidisciplinary discussion.

In the context of improving systemic control with advances in chemotherapy, there is an evolving role for RT in providing durable locoregional control. Herein, we review the role of RT in the adjuvant and neoadjuvant settings and discuss advanced modalities including stereotactic body radiation therapy (SBRT), intraoperative radiation therapy (IORT), MRI-guided radiation therapy, and proton beam therapy (PBT).

Radiation in the Adjuvant Setting

The optimal management of patients with resectable PCA continues to evolve. Appreciation of the potential that modern RT may have for resected PCA requires an understanding of clinical trials that have explored the value of adjuvant chemoradiation (CRT). Early institutional reports demonstrated high rates of local failure (>50%) after surgical resection of PCA [1]. Therefore, the Gastrointestinal Tumor Study Group (GITSG) compared adjuvant 5-fluorouracil (5-FU)-based chemoradiation (CRT) with observation and found that CRT improved two-year overall survival (OS) (42% vs 15%, $P = 0.03$), sparking adoption of adjuvant CRT in the United States [2]. However, this survival benefit could not be replicated in subsequent trials by the European Organisation for Research and Treatment of Cancer (EORTC) and European Study Group for Pancreatic Cancer (ESPAC), with the latter trial suggesting improved survival with chemotherapy alone [3,4].

Importantly, key pitfalls of all these trials must be acknowledged, including slow accrual and poor trial adherence. Perhaps most importantly, the radiation techniques employed in all these trials were antiquated by modern standards, including suboptimal doses, nonconformal techniques, and split-course schedules. As a result, the latter two trials failed to demonstrate improved rates of local control (LC) in the CRT arms [3,4].

Since the early trials results, European trials for patients with resected PCA have focused on defining the optimal adjuvant chemotherapy-alone regimen. The Partenariat de Recherche en Oncologie Digestive Intergroup (PRODIGE) trial showed that adjuvant mFOLFIRINOX significantly improves median disease-free survival (DFS), distant metastasis-free survival (DMFS) and OS (median OS, 54.4 vs 35.0 months, $P = 0.003$) compared to gemcitabine alone [5]. Locoregional recurrence was 29.0% in the whole cohort and 23.1% in the adjuvant mFOLFIRINOX arm, highlighting a potential role for radiation even in the setting of improving chemotherapy.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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In the United States, outcomes with more conformal radiation techniques using higher doses without split-course schedules have been explored. The Radiation Therapy Oncology Group (RTOG) 9704 trial randomized patients to initial chemotherapy with either 5-FU or gemcitabine, followed by 5-FU-based chemoradiation to 50.4 Gy, followed by additional chemotherapy with 5-FU or gemcitabine and resulted in fewer local recurrences in both arms (25–30%) [6]. This local failure rate compared favorably with historical controls despite a predominance of patients with risk factors for local recurrence, including 35% with positive margins, 66% with positive lymph nodes, and 75% with advanced T-stage. Despite the high R1 rate and LN positivity, an analysis by Berger et al. comparing per protocol RTOG 9704 outcomes to chemotherapy-alone outcomes in a subset of CA 19-9 <90 U/mL showed median OS at 24 months vs 22 months and five-year OS of 34% vs 21% in favor of inclusion of RT [7].

These results highlight the potential benefits of radiation in the setting of high locoregional recurrence risk factors and improving OS benefit in a cohort of long-term survivors. Importantly, RTOG 9704 was the first trial to evaluate whether radiation field design influenced outcomes [8]. Failure to adhere to specified RT guidelines was associated with reduced survival. In fact, nearly 50% of the RT plans deviated from protocol guidelines. Consensus panel guidelines are now available for clinical target volume design, but the subset analysis of RTOG 9704 underscores the importance of appreciating the quality of radiation delivered when interpreting results from clinical trials [9]. Despite improved results seen in RTOG 9704, reported acute toxicity was still substantial, with 70.5% patients experiencing any grade ≥3 toxicity and 59% experiencing grade ≥3 nonhematologic toxicity [6]. To this end, technologic advances have allowed a more focused form of RT, termed "intensity-modulated RT" (IMRT), that may be helpful in sparing organs at risk (OAR) and minimizing toxicity. Less toxicity associated with IMRT allows for incorporation of more aggressive concurrent chemotherapy or targeted therapies.

Given the potential merits of IMRT, it was incorporated into the NRG/RTOG 0848 two-step randomization trial, which was examining gemcitabine plus erlotinib compared to gemcitabine alone and is still evaluating whether radiation to 50.4 Gy with 5-FU improves outcomes beyond gemcitabine chemotherapy alone. In the phase II setting, the addition of erlotinib to gemcitabine did not provide an OS benefit [10]. We await the maturation and results of the radiotherapy research question from RTOG 0848. Initial publication regarding quality assurance from the trial reported 86% IMRT usage [11]. Of note, quality assurance from the trial reported 33% resubmission rates for RT treatment plans prior to starting radiation therapy, again confirming the importance of the quality of radiation delivered. IMRT with volumetric arc therapy (VMAT) allows for more rapid treatment of therapy and further sparing of adjacent normal tissues including bowel, stomach, and kidneys.

Whether these advances translate into clinically meaningfully outcomes remains to be seen, especially as mFOLFIRINOX has changed the adjuvant therapy landscape per PRODIGE trial. Given the relatively high positive R1 resection rate of 40.1% and high rate of local and regional failure at 23.1% [5] in the PRODIGE study, pending results of RTOG 0848 is sure to add controversies surrounding the use of adjuvant radiation therapy in the setting of resected pancreatic adenocarcinoma.

Stereotactic body radiation therapy is another technique being evaluated in the adjuvant setting given recent technologic advances and early data demonstrating its safety. Adjuvant SBRT would allow for early initiation of systemic therapy after radiation and has been explored in patients with close or positive margins [12]. Local failure was only observed in six patients (12.5%) and local progression-free survival at one and two years was 85% and 77% respectively. The median OS was 20.0 months and one- and two-year OS was 68% and 50% respectively. Additionally, adjuvant SBRT is being explored in combination with other novel agents such as anti-programmed cell death agents and GVAX pancreas vaccine. In a pilot feasibility study, 19 patients were treated with adjuvant SBRT, GVAX pancreas vaccine, and FOLFIRINOX [13]. While preliminary, the study suggests that SBRT can be safely utilized in the adjuvant setting with a combination of different therapies with minimal acute or chronic side-effects.

Currently, there are no consensus guidelines on the appropriate SBRT volumes in the adjuvant setting. However, postoperative patterns of failure offer insight into potential SBRT volumes for treatment that would include a dose painted approach targeting high-risk areas with higher doses (33 Gy) with elective nodal areas covered in lower doses (25 Gy) in five fractions. Additionally, post-SBRT patterns of failure note that most failures occurred outside targeted PTV volumes of SBRT but within traditional conventional RT volumes described in RTOG 0848 [14].

The use of SBRT in the adjuvant setting remains an open question. The results of RTOG 0848 using IMRT in the context of growing use of SBRT and new standards in mFOLFIRINOX are sure to add further debate on best-use practices in the adjuvant radiation setting.

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Radiation in Resectable, Borderline Resectable, and Locally Advanced Disease

The role of neoadjuvant therapy is rapidly evolving in the setting of growing multidisciplinary approaches to pancreatic cancer (Fig. 149.1). There is a growing role for neoadjuvant chemotherapy with or without RT in PCA as neoadjuvant approaches offer several benefits, including early treatment of micrometastases and appropriate patient selection for surgery. Further, early chemotherapy avoids unnecessary surgical morbidity in patients whose cancer biology is unfavorable and rapidly progresses despite neoadjuvant therapy. In the context of neoadjuvant therapy, the use of neoadjuvant radiation is increasing, in part due to improvements in radiation technique and delivery. Neoadjuvant radiation is predominantly used for margin sterilization and local recurrence risk reduction in the resectable/borderline resectable setting and for improved LC in the locally advanced, unresectable setting [15–17].

Early data on neoadjuvant chemoradiation in resectable PCA and borderline resectable pancreatic cancer (BRPC) were limited to small phase II and single-institution data prior to the publication of the PREOPANC-1 study. The PREOPANC-1 trial is the first large phase III randomized trial to evaluate the use of neoadjuvant chemoradiation in resectable and borderline resectable PCA. A total of 246 (133 resectable and 113 BRPC) patients were randomized to preoperative chemoradiation consisting of three cycles of gemcitabine with concurrent radiation to 36 Gy in 15 fractions followed by surgery and four cycles of adjuvant gemcitabine vs immediate surgery followed by six cycles of adjuvant gemcitabine [15]. In the preoperative chemoradiation group, median OS was 15.7 months and five-year OS was 20.5% compared to 14.3 months and 6.5% in the immediate surgery group (P = 0.025) [15,16]. Additional secondary endpoints including DFS, local failure-free survival (LFFS), and pathologic findings were significantly improved with neoadjuvant chemoradiation. Of significance, the R0 resection rate by intent to treat was 41% (49/119) in patients who received preoperative chemoradiotherapy and 28% (35/127) in patients assigned to immediate surgery (P <0.001). Among patients who underwent surgery, the R0 resection rate was 71% (51 of 72) in patients who received preoperative chemoradiotherapy and 40% (37 of 92) in patients assigned to immediate surgery (P <0.001). On prespecified subgroup analysis of patients who underwent surgery and started adjuvant chemotherapy (N = 55 [46%] in neoadjuvant CRT vs N = 65 [51%] in immediate surgery arm), there was significantly higher OS with preoperative chemoradiotherapy (35.2 vs 19.8 months; P = 0.029). Additionally, in the subset of BRPC patients, preoperative CRT compared to immediate surgery showed a significantly improved OS and DFS with median OS of 17.6 vs 13.2 (P = 0.029). Given improvements in clinical outcomes with mFOLFIRNOX, the

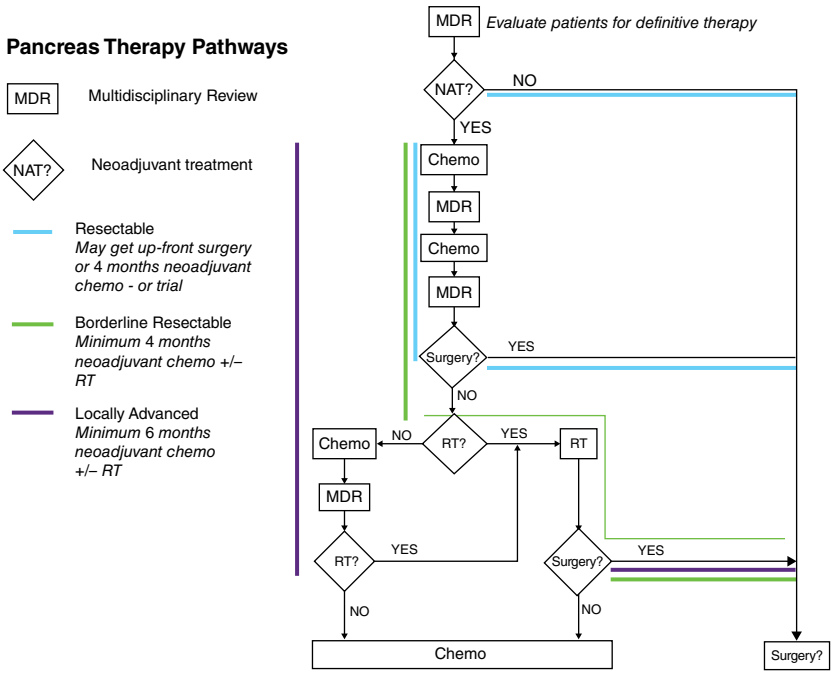


Figure 149.1 Definitive multidisciplinary therapy pathways across the different stages of pancreatic cancer with incorporation of neoadjuvant chemotherapy +/– radiation prior to surgery.

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PREOPANC-2 trial is comparing neoadjuvant FOLFIRINOX vs CRT as outlined in PREOPANC-1 (NTR7292). The NorPACT 1 and PANACHE01-PRODIGE48 trials (NCT02919787, NCT02959879) meanwhile are exploring chemotherapy-alone arms in comparison to initial surgery.

In the context of BRPC, a multicenter South Korean study randomized patients with BRPC to receive neoadjuvant CRT to 54 Gy with concurrent gemcitabine followed by surgery versus upfront resection followed by radiation [17]. The trial was terminated early on the basis of statistically significant neoadjuvant treatment efficacy on interim analysis after 50 out of planned 110 patients were enrolled. The two-year OS (40.7% vs 26.1%) and median survival (21 vs 12 months; $P = 0.028$) were both in favor of chemoradiation and a significant benefit in R0 resection rate was seen in the neoadjuvant CRT arm (51.8% vs 26.0%; $P = 0.004$). These data are in line with findings of PREOPANC-1 trial showing the benefit of neoadjuvant RT for localized pancreatic cancer.

Stereotactic body radiation therapy in the neoadjuvant setting is an area of active investigation given its safety and ability to shorten overall treatment duration, by allowing early resumption of systemic therapy or for early surgical resection. Early phase I/II studies using single-fraction SBRT (25 Gy) demonstrated excellent freedom from local progression (FFLP) at one year (>90%) and minimal acute toxicity, but high rates of late grade 2–4 gastrointestinal toxicity [18]. Subsequently, a single-arm phase II multiinstitutional study evaluated the safety of gemcitabine followed by SBRT to 33 Gy in five fractions in LAPC [19]. Forty-nine LAPC patients received gemcitabine followed by SBRT and continued gemcitabine until progression or toxicity. Rates of acute and late grade ≥2 gastritis, fistula, enteritis, or ulcer toxicities were 2% and 11%, respectively. Global quality of life scores remained stable from baseline to after SBRT and patients reported a significant improvement in pain (P <0.001) at four weeks after SBRT. Median serum cancer antigen CA-19-9 was reduced following SBRT (post-SBRT 4.2 weeks, 220 vs 62 U/mL; P <0.001) and median OS was 13.9 months. FFLP at one year was 78% and five patients with LAPC at diagnosis were deemed resectable, with four patients undergoing margin- and node-negative resections, with the fifth patient declining surgery.

Early work from the Moffitt Cancer Center and Johns Hopkins reported on the safety and efficacy of neoadjuvant SBRT after chemotherapy. A retrospective study of 159 patients (110 BRPC, 49 LAPC) [20] at Moffitt reported that amongst BRPC patients, 51% underwent surgery with 97% achieving a R0 resection and 7% had a pathologic complete response. Acute grade ≥3 toxicity was 2%, late grade ≥3 toxicity was 5% and median OS in the resected BRPC patients was 34 months. In a larger LAPC population, Johns Hopkins reported outcomes on 88 patients (14 BRPC, 74 LAPC) who received induction chemotherapy followed by 25–33 Gy SBRT [21]. Of the 19 patients (22%) who underwent surgery (including 17 LAPC) following SBRT, 84% had a R0 resection and 16% had a pathologic complete response. Median OS of resected patients was 20.2 months versus 12.3 months in unresected patients ($P = 0.07$).

The promising results of early studies on SBRT in the treatment of localized pancreatic cancer prompted its evaluation in a multicenter phase II Alliance A021501 that evaluated neoadjuvant mFOLFIRINOX with or without SBRT in BRPC. Patients were randomized to receive eight cycles of mFOLFIRINOX (Arm A) or seven cycles of mFOLFIRINOX followed by SBRT (33–40 Gy/5 fractions or 25 Gy/5 fractions) (Arm B). The study used a standardized intergroup definition of BRPC and centrally reviewed imaging prior to randomization to ensure quality of diagnosis. The goal of the study was to define the standard of care regimen for future phase III trials, and outcomes were compared to historical controls of OS of 50% at 18 months. Though not yet published, preplanned interim analysis resulted in early termination of the SBRT arm as it did not meet the prespecified R0 resection rate to be >11 out of first 30 patients who were enrolled.

Early results from the trial were presented at the ASCO 2021 GI Symposium [22] and provided early insights and considerable discussion on the challenges of PCA trial design and use of SBRT for BRPC. After enrolling 30 patients in each arm, interim analysis showed Arm A had a 57% R0 resection rate vs 33% in Arm B, which prompted the arm closure. When evaluating the SBRT arm, about half the patients did not make it to surgery due to development of progression or metastasis and only 35% of patients at final analysis underwent surgery in comparison to 49% in the chemotherapy-alone arm. One proposed explanation for the higher rates of progression of disease or metastasis prior to surgery in Arm B (14/155, 25.5%) compared to Arm A (8/65, 12.3%) could be the higher median CA 19-9 levels noted (median 248 U/mL vs 171 U/mL) respectively. Among patients who underwent pancreatectomy, 18-month OS rates were similar at 93.1% and 78.9% in Arm A and B, respectively. Surgical pathologic outcomes reported pathologic complete response of 11% vs 0% favoring RT and near complete response (defined as <5% viable cells) of 26% vs 13% favoring the RT arm. The 18-month OS rate by intention to treat was 66% vs 47% in favor of the chemotherapy-alone arm, and the SBRT arm did not meet the final efficacy rule of >50% OS at 18 months.

Given the conflicting findings of the PREOPANC and South Korean studies, and recent ALLIANCE trial, further studies are warranted to better elucidate how to

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select which patients are more likely to benefit from neoadjuvant RT and subsequent surgery. In addition, a large proportion of patients still succumb to both local and systemic recurrence, suggesting a need to enhance both local and systemic therapies.

The role of RT in LAPC remains controversial, similar to BRPC, but new techniques allowing for the safe delivery of ablative doses of radiation have provided hope to improve outcomes. The LAP-07 phase III trial showed no OS benefit in adding CRT (54 Gy with concurrent gemcitabine) compared to chemotherapy alone (median OS 15.2 vs 16.5 months; $P = 0.83$) [23]. CRT was well tolerated with no increase in toxicity and notably did improve local progression with 32% vs 46% ($P = 0.03$) and time off chemotherapy (6.1 vs 3.7 months; $P = 0.02$).

Given the suboptimal outcomes with older radiation techniques used in LAP-07, SBRT and SBRT-like techniques are being investigated. A pooled analysis of 19 total SBRT trials with unresectable PCA showed a median OS of 17 months with LC of 72%, offering a potential avenue for improvement in outcomes [24]. In another meta-analysis comparing SBRT to conventional fractionated RT, SBRT was statistically favored with two-year OS at 26.9% for SBRT vs 13.7% for conventionally fractionated radiation therapy and decreased rates of toxicity [25]. Further, with the consideration that patients originally deemed unresectable may be taken to the operating room, neoadjuvant SBRT in LAPC may improve margin-negative resection rates, with 10–20% resection rates reported retrospectively at Moffitt and Hopkins with 100% and 80% R0 rates [20,21]. In LAPC or high-risk patients, the recently opened MASTERPLAN (NCT04089150) trial is evaluating the safety of SBRT with multiple chemotherapy regimens in a multicenter phase II trial.

Similar to SBRT volumes in the adjuvant setting, treatment volumes in the neoadjuvant and definitive settings are an area of increasing debate. Although historically SBRT or high-dose volumes were limited to gross tumor (Fig. 149.2), growing data on the safety and tolerability of elective nodal irradiation (ENI) [26], and early closure of the Alliance trial with success of PREOPANC with larger target volumes have ignited controversy on best practice [27]. In a propensity-matched cohort study, Miller et al. reported that SBRT to 40 Gy to gross tumor with ENI to 25 Gy per RTOG guidelines improved locoregional progression at the expense of increased (60% vs 20%; $P < 0.001$) acute grade 1–2 nausea, with control rates of 22.6% vs 44.6% ($P = 0.21$) in favor of ENI vs SBRT to tumor alone. A recent patterns of failure study of 510 patients who received SBRT for LAPC offers insight on location and distance of common failures including the celiac and super mesenteric axis commonly covered as part of ENI [28]. Such information may guide selection

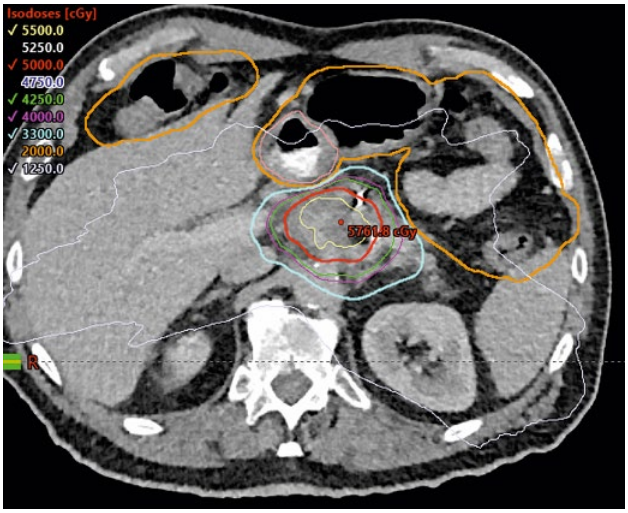


Figure 149.2 Pancreas SBRT plan demonstrating a highly conformal plan with a dose painted approach, 50 Gy to PTV (minus bowel PRV) and 35 Gy to PTV to meet strict dose constraints of nearby OAR including duodenum, small bowel, and stomach.

of appropriate SBRT volumes. Though current SBRT guidelines from the European Society of Radiation Oncology (ESTRO) currently advise against ENI due to lack of prospective evidence [29], there is growing consideration of and debate on the need of ENI.

Outside treatment volumes, there is considerable discussion regarding dose escalation in pancreatic cancer with the goal of reaching ablative doses (biologically effective dose $[BED]_{10} \geq 100$) [30]. However, dose escalation is limited by radiosensitivity of nearby gastrointestinal organs. Stereotactic magnetic resonance (MR)-guided adaptive radiation therapy (SMART) uses recent technologic advancements in MR-guided radiation therapy (Fig. 149.3) that allow for improved soft tissue contrast and ability to use real-time intrafraction assessment of tumor and OAR structures with on-table replanning and automatic beam gating. SMART to a dose to 50 Gy produced a 4.6% grade 3 GI toxicity with one-year LC of 84.3% [31] though OS was 68.2% and 37.9% at one and two years respectively, with 93% of radiation plans reoptimized during the course of treatment. Choung et al. reported on their outcomes of 35 patients treated with SMART showing 2.6% late grade 3 toxicity with one-year LC of 87.8%. Of note, ENI to 50 Gy was also completed in 57.1% of patients, highlighting the safety of MR guidance for both gross and regional nodal disease outside of OARs [32].

The use of MR-guided radiation therapy brings promise for the future of radiation therapy, including daily adaptive therapy. It is currently undergoing prospective evaluation for LAPC in a multiinstitutional phase II trial—SMART (NCT03621644).

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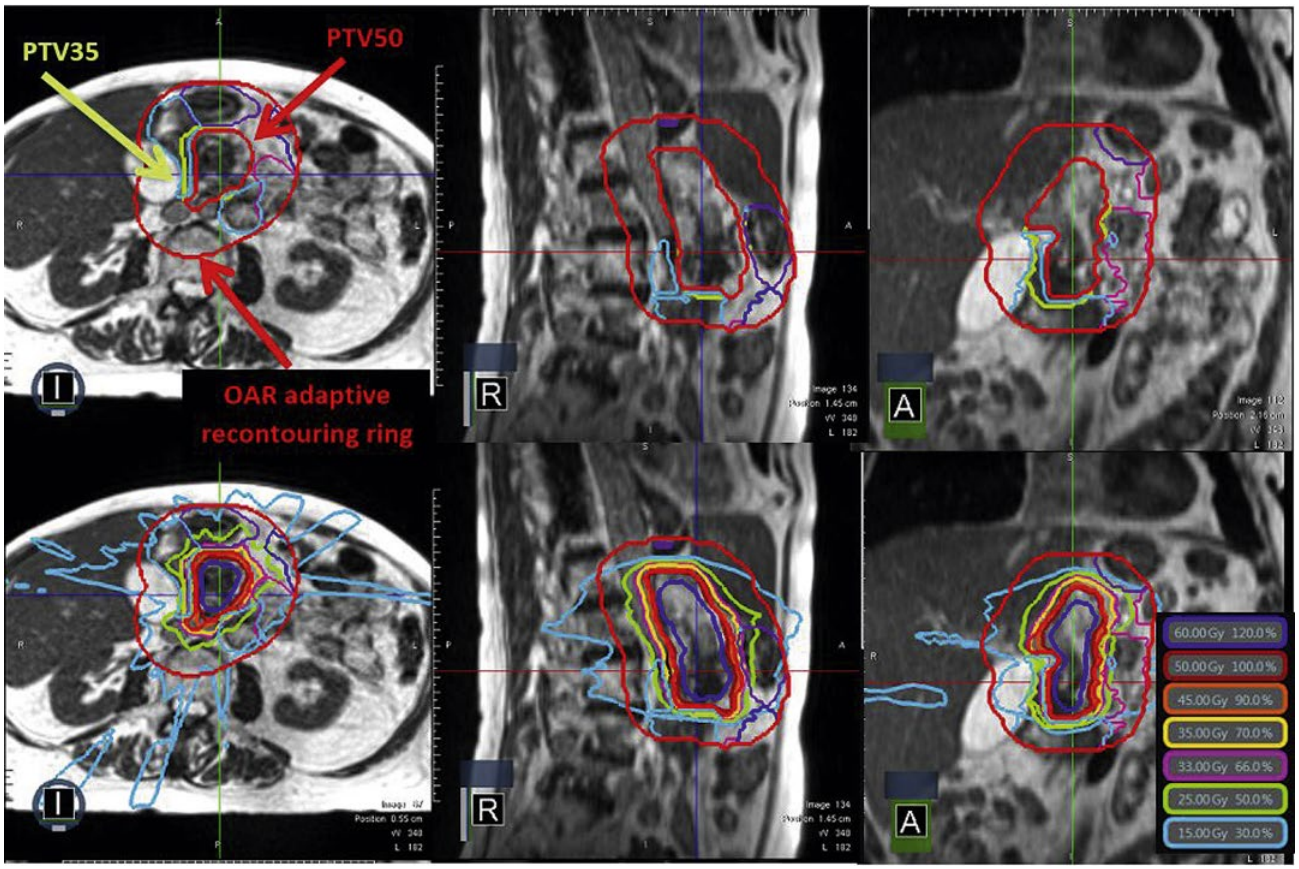


Figure 149.3 Target volumes (top row) and isodose lines (bottom row) for pancreas patient treated with SMART radiation using daily MRI and on-table adaptive replanning.

Dose-escalated intensity-modulated radiation therapy (DE-IMRT) using standard or moderate hypofractionation has also shown promise in the treatment of LAPC/unresectable pancreatic cancer. Retrospective single-institution work by Memorial Sloan Kettering demonstrated that a dose painted ablative radiation therapy approach with 75 Gy in 25 fractions (BED_{10} = 97.5 Gy) for tumors less than 1 cm from critical dose-limiting structures or 67.5 Gy in 15 fractions (BED_{10} = 97.88 Gy) for tumors >1 cm away from critical structures can be safe and effective [33]. In 119 patients with inoperable tumors, median OS was 26.8 months with 12- and 24-month OS rates of 74% and 38%, respectively. Locoregional failure rates at 12 and 24 months were 17.6% and 32.8%, respectively. Ablative radiation therapy using dose painted approaches allows high-dose ablative doses favored in SBRT with coverage of ENI volumes and is another growing area of interest in LAPC that are unlikely to undergo surgery. The use of dose-escalated radiation is currently undergoing prospective evaluation in a single-institution phase II trial—MAIBE (NCT03523312) at Memorial Sloan Kettering with a goal of completion in 2023.

Intraoperative Radiation Therapy

One method of delivering ablative doses of radiation involves intraoperative radiation therapy (IORT). Advantages of IORT include the ability to directly visualize the site of interest and shield normal OARs. Delivery methods of IORT include linear accelerator-based electron therapy, low-dose rate brachytherapy, high-dose rate (HDR) brachytherapy, or low-energy photons. Although there are no consensus guidelines on the indications for IORT, growing literature supports its use for close or positive margins at time of surgical resection and unresectable disease at time of surgical exploration with no to limited increase in the risk of perioperative or postoperative toxicity. Typical IORT doses range from 10 to 15 Gy in a single fraction.

Initial reports of IORT use in pancreatic cancer first came from Japan where doses of 20–40 Gy in one fraction were associated with improved outcomes and pain relief [34]. More recently, IORT has been used and investigated at Massachusetts General Hospital (MGH) where multiple large retrospectively publications highlight its benefit. Sekigami et al. reported IORT use for resectable

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disease in 201 patients treated with neoadjuvant FOLFIRINOX and chemoradiation (50.4 Gy in 28 fractions) followed by surgical resection with or without IORT to 10 Gy in one fraction [35]. In the no-IORT group, patients with R1 resection had significantly worse DFS and OS. However, in the IORT group, there was no difference in DFS or OS between patients who had R0 and R1 resections, suggesting that IORT may mitigate the negative effect of an R1 resection. Just as important, there was no difference in 30-day Clavien-Dindo III/IV toxicity (IORT 17% vs no-IORT 22%; $P = 0.477$) and 90-day mortality (IORT 3.4% vs no-IORT 2.7%; $P = 0.999$) between the two groups. The use of IORT is undergoing prospective evaluation in a single-institution phase II trial—PACER (NCT03716531) at MGH.

Proton Beam Therapy

While IMRT and SBRT can minimize the high doses received by OARs and therefore decrease the likelihood of adverse effects compared to 3D-CRT, pancreatic RT doses remain compromised by the proximity of these normal tissues. Therefore, some have looked to proton beam therapy (PBT) to improve the therapeutic ratio for PCA patients as well as to dose escalate doses, with encouraging early results. Protons have an inherent advantage over photons in that they deliver much of their dose at a specified depth beyond which there is no dose to normal tissues. Because proton beams have no exit dose, as few as two beams are needed to create highly conformal dose distributions (Fig. 149.4). Therefore, PBT can significantly minimize radiation dose from large volumes of normal tissue.

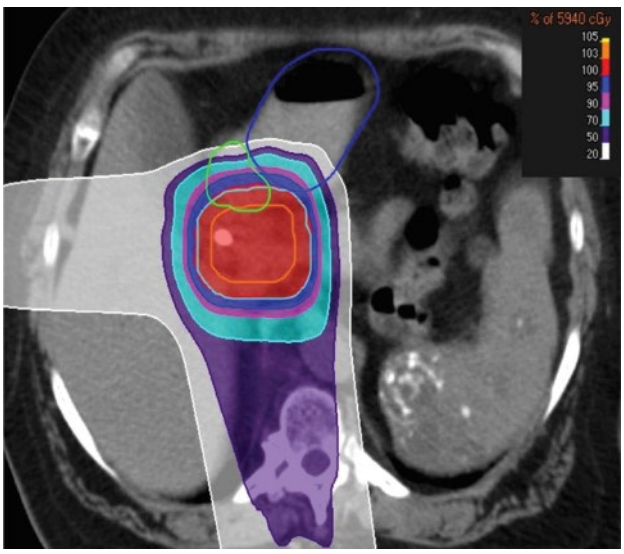


Figure 149.4 PBT treatment plan illustrating the delivery of a highly conformal dose (to 59.4 Gy) to the tumor while minimizing dose to surrounding normal tissue.

Multiple dosimetric studies have illustrated that PBT for PCA can significantly reduce dose to normal tissues compared to photon therapy, importantly without sacrificing target volume coverage. Nichols et al. compared IMRT and passive scattering PBT prescribed to 50.4 Gy for eight patients with resected pancreatic head tumors [36]. PBT plans had significantly lower doses to adjacent structures such as the right kidney V18 Gy (27.3 vs 50.5%; $P = 0.0156$), small bowel V20 Gy (15.4 vs 47%; $P = 0.0156$), and stomach V20 Gy (2.3 vs 20%; $P = 0.0313$). In a similar analysis, Ding et al. evaluated 3D-CRT, IMRT, passive scattering PBT, and a more conformal proton delivery technique called modulated scanning or pencil beam scanning for 11 resected PCA patients and found PBT (specifically the pencil beam scanning plans) had the lowest right kidney V18 Gy, stomach V20 Gy, and small bowel V15 Gy [37].

Another area of interest is the combination of PBT with SBRT, which would theoretically allow for deposition of therapeutic dose at a specified depth and steep dose fall-off. A recent study by Liu et al. compared photon SBRT plans with proton SBRT plans for 19 patients with localized disease [38]. The prescribed dose was 30 GyE in five fractions to the target and 45 GyE in five fractions to the boost area. Two-field proton SBRT led to lower maximum duodenum dose and lower maximum stomach dose when compared to photon SBRT in patients with pancreatic head lesions while photon SBRT led to lower maximum stomach dose when compared to the proton SBRT. These findings highlight the need for further investigation into the relationship between tumor location and selection of optimal treatment modality/technique.

While the published clinical experiences using PBT for PCA are limited, the outcomes from these studies are encouraging (Table 149.1). Investigators from MGH published outcomes of a phase I trial that evaluated neoadjuvant hypofractionated PBT with concurrent capecitabine for resectable PC [39]. A total dose of 25 Gy delivered in five consecutive fractions was well tolerated; no dose-limiting toxicities occurred. A subsequent MGH phase I/II trial of neoadjuvant PBT (25 Gy in five fractions) with capecitabine for resectable PCA enrolled 50 patients, with 35 being treated in the phase II portion [40]. Grade 3 toxicity occurred in only two patients (4.1%). With median follow-up of 38 months for all patients, median progression-free survival was 10 months and median survival was 17 months.

The initial results of a Japanese phase I/II trial of PBT with concurrent gemcitabine for LAPC were reported in 2012 [41]. Fifty patients were enrolled and were prescribed an aggressive regimen of gemcitabine for three

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Table 149.1 Summary of prospective studies evaluating the role of proton beam therapy in pancreatic cancer.

Author	Study type	N	Resectability	Prescribed Dose	Elective Nodal Irradiation	Concurrent chemotherapy	Median Follow up (mos)	LRC	PFS	OS	Grade ≥3 Toxicity
Hong et al.[39]	Phase 1	15	Resectable	**Level 1**: 3Gy(RBE) x 10 **Levels 2-4***: 5Gy(RBE)x 5	Yes	Capecitabine 825mg/m^2 BID	12	93%	Median 10 months	Median not reached	Level 4: biliary obstruction (n=1)
Hong et al.[40]	Phase 1/2	50	Resectable	5Gy(RBE) x 5	Yes	Capecitabine 825 mg/m^2 BID	38	84%	Median 10.4 months	Median 17.3 months	Colitis (n=1), chest wall pain (n=1)
Terashima et al.[41]	Phase 1/2	50	Unresectable	**P-1**:2Gy(RBE) x 25(5 patients) **P-2**: 2.7Gy(RBE) x 26 (5 patients) **P-3**: 2.7Gy(RBE) x 25 (40 patients)	Yes	Gemcitabine 800 mg/m^2	12.5	1-year 81.7%	1-year 64.3%	1-year 76.8%	**P-3**: gastric ulcer/ hemorrhage (n=4)
Sachsman et al.[46]	Phase 2	11	Unresectable	1.8Gy(RBE) x 33	No	Capecitabine 500 mg/m^2	14	1-year 86%	1-year 55%	Median 18.4 1-year 61%	None

LRC = locoregional control, PFS= progression free survival, OS = overall survival, RBE = relative biological effectiveness.
* Levels 2 and 3 treated on nonconsecutive days; level 4 treated on consecutive days.

weeks concurrent with PBT and 80% of patients were prescribed 67.5 Gy in 25 fractions. With median follow-up of 12.5 months, outcomes were encouraging and included a grade 3 toxicity rate of ~10%. However, a subsequent publication that included 91 patients had a nearly 50% incidence of radiation-induced ulceration in the stomach and duodenum [42]. While margin expansions up to 5 mm were permitted during treatment planning to account for respiratory motion, no specific description of motion management usage was given in the manuscript. Therefore, the aggressive nature of the treatment regimen, and not PBT itself, is likely responsible for this high complication rate. This should serve as a reminder that despite the dosimetric advantages of PBT, we must remain vigilant about limiting dose to normal tissues and that motion management should always be considered.

While there is much potential to improve the therapeutic ratio for PCA patients with PBT, some practical proton planning and delivery considerations should not be overlooked. Proton dose deposition is strongly influenced by tissue densities within the beam path and changes in these densities, such as from respiratory motion, setup errors, and even bowel peristalsis, can potentially lead to underdosing of target and overdosing of normal tissues. As such, motion management strategies like respiratory gating, breath hold, or abdominal compression for targets in the upper abdomen should be used.

Finally, image guidance for PBT is currently limited to only kV imaging and this is not ideal for soft tissue assessment in PCA patients. Cone beam CT (CBCT) for PBT has only recently become available at a few select proton centers and is expected to become more widely available over the next several years. CBCT will enable more selective margins to be used, thereby further reducing normal tissue dose.

Future Directions

Perhaps most critical to the appropriate use of radiation in patients with PCA is appropriate patient selection. Identifying those patients at greatest risk for local versus distant progression can help determine selective administration of RT and/or surgery. Development of predictive biomarkers that can identify those patients at greater risk for local failure is needed. One autopsy series of

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consecutive patients who succumbed to PCA demonstrated that roughly 30% of patients most likely died from locally destructive disease, highlighting the importance of achieving better LC [43]. In these patients, expression of Smad4 was highly associated with a locally destructive phenotype, findings which have also been replicated in a phase II study of chemoradiation for LAPC [44].

As we await identification of more biomarkers, clinical investigation into identifying optimal treatment dose, fractionation, and volumes may allow the benefit of time to understanding an individual patient's biology and risk of local failure. Recent reports highlight the benefit of dose escalation, and as a result, techniques to optimize radiation delivery (SBRT, SMART, DE-IMRT) are being actively investigated [31,32,45]. Furthermore, the ideal radiation treatment approach and volumes in the preoperative/definitive and adjuvant setting require consensus.

Finally, we eagerly await the results of combination therapy trials involving radiation and other novel immunologic and radiosensitizing agents such as GRECO2 (NCT04698915). These results may help guide clinicians in selecting more personalized therapy as improvements in systemic control and the promise of immunotherapy create an evolving role for RT in providing improved LC that results in OS benefits to select patients. Future studies are needed to determine how to optimally integrate these novel therapeutic advances in multidisciplinary clinical trials with meaningful endpoints that improve outcomes (OS and quality of life) of patients with pancreas cancer.

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Immunotherapy for Pancreatic Cancer: Checkpoint Blockade and Vaccine Therapy

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Introduction

Pancreatic ductal adenocarcinoma (PDA) is not one of the most common types of cancers diagnosed, yet it is the third-leading cause of cancer-related deaths in men and women [1]. The only current chance of cure remains surgical resection but <30% of patients who present with PDA are candidates for curative resection. In patients with locally advanced unresectable PDA, the role of radiation therapy is still questionable so for the majority of patients, palliative chemotherapy is the only known option that can prolong survival [2–6]. Although neoadjuvant chemotherapy has converted more patients into candidates for curative resection, adjuvant chemotherapy in the combination format following surgical resection is required to significantly prolong disease-free survival and overall survival. Despite the broad application of adjuvant chemotherapy, the majority of those who undergo surgical resection will ultimately relapse and die from their disease [1]. As a result of all these efforts, the five-year survival of all-stage PDA patients is rising, but slowly, and has only risen to 9%.

More recently, metastatic PDA patients who carry a germline mutation in *BRCA1* or *BRCA2*, who constitute a small subgroup of PDA patients, were found to benefit from poly-ADP-ribose polymerase inhibitors (PARPi) in the maintenance setting [7]. Otherwise, there has not been any significant progress in the development of targeted therapies for PDA patients because the most common genetic alterations in PDA, such as *KRAS*, *SMAD4*, and *TP53*, are not currently targetable.

Since 2014, the emergence of immunotherapy has changed the treatment landscape of many aggressive malignant diseases, but PDA remains one of most challenging tumors to treat. Although there have been positive advances created by harnessing the immune system to help combat PDA, the current immunotherapeutic strategy is still not effective for PDA. Nevertheless, in the last five years, our understanding of the immunotherapy resistance mechanism in PDA has advanced owing to a more in-depth analysis of the tumor microenvironment (TME) of pancreatic cancer.

Immunology of Pancreatic Cancer

The TME of pancreatic tumors is renowned for its stromal density and heterogeneity, containing numerous cellular components including fibroblasts, pancreatic stellate cells, blood vessels, and immune cells [8].

The immune system is classically activated in response to foreign antigens, whereas cancer cells can express tumor-associated antigens as well as neo-antigens that occur in response to the tumor's continuously changing molecular composition. In both cases, the immune system can be activated to recognize these tumor antigens. However, tumor cells are more likely to interact with the immune system and lose antigen recognition through the process of immunoediting [9]. This dynamic process consists of three phases: elimination, where the immune system successfully destroys the tumor cell; equilibrium, where the system controls tumor growth but does not destroy the tumor cell; and escape, where the tumor cell overcomes the immune system and progresses to a clinically detectable disease state.

The innate immune system consists of immune cells (e.g., macrophages, granulocytes, dendritic cells) that serve as "first responders" of the immune response and

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are attracted to regions of inflammation or infection within minutes or hours. The adaptive immune system comprises B- and T-cell lymphocytes which respond to foreign invasion of cells, typically by infectious agents. Professional antigen-presenting cells (APCs) (dendritic cells and macrophages) are alerted and take up foreign proteins for processing and presentation, subsequently triggering B- and T-cell responses. B lymphocytes are responsible for mounting a long-term response to foreign antigens by producing antibody-secreting effector cells. T lymphocytes, categorized according to cell surface markers, and cytokines, as well as the chemokines they produce, have many distinct effector functions. Cytotoxic T-lymphocytes (CTLs) express CD8 and eradicate cells by secreting molecules that induce apoptosis.

When an APC expresses an antigen on major histocompatibility class II (MHCII), a CD4+ T cell (helper T cell, Th) becomes activated and differentiates into distinct effector subtypes, mediating the immune response through the secretion of specific cytokines (Fig. 150.1). A specific subtype of CD4+ T cell, Treg, suppresses T-cell activation, thereby protecting the body from autoimmune reactions. CD4+ T cells make up the majority of T cells in PDA and are associated with metastasis and negatively associated with survival [10,11].

The protective role of the immune system in cancer is demonstrated by the observation that increased amounts of tumor-infiltrating lymphocytes (TILs) correlate favorably with survival in many tumor types, including melanoma and PDA [12,13]. The complexity of the immune system results in certain immune components promoting immune suppression, such as myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), and tumor-associated neutrophils (TAN) [14,15]. Preclinical models which faithfully recapitulate the progression of precursor pancreatic lesions in their development from preinvasive pancreatic intraepithelial neoplasia (PanIN) to invasive PDA show that immunosuppressive cells dominate the TME, even during the early stages of tumor development [16]. These cells, which include MDSC, Treg and TAM, result in reduced T-cell development and infiltration (specifically effector T cells) which indirectly drives tumor promotion. This has led to efforts to directly target these immunosuppressive cells, e.g., targeting colony-stimulating factor 1 (CSF-1R) which regulates the differentiation and survival of TAM [17].

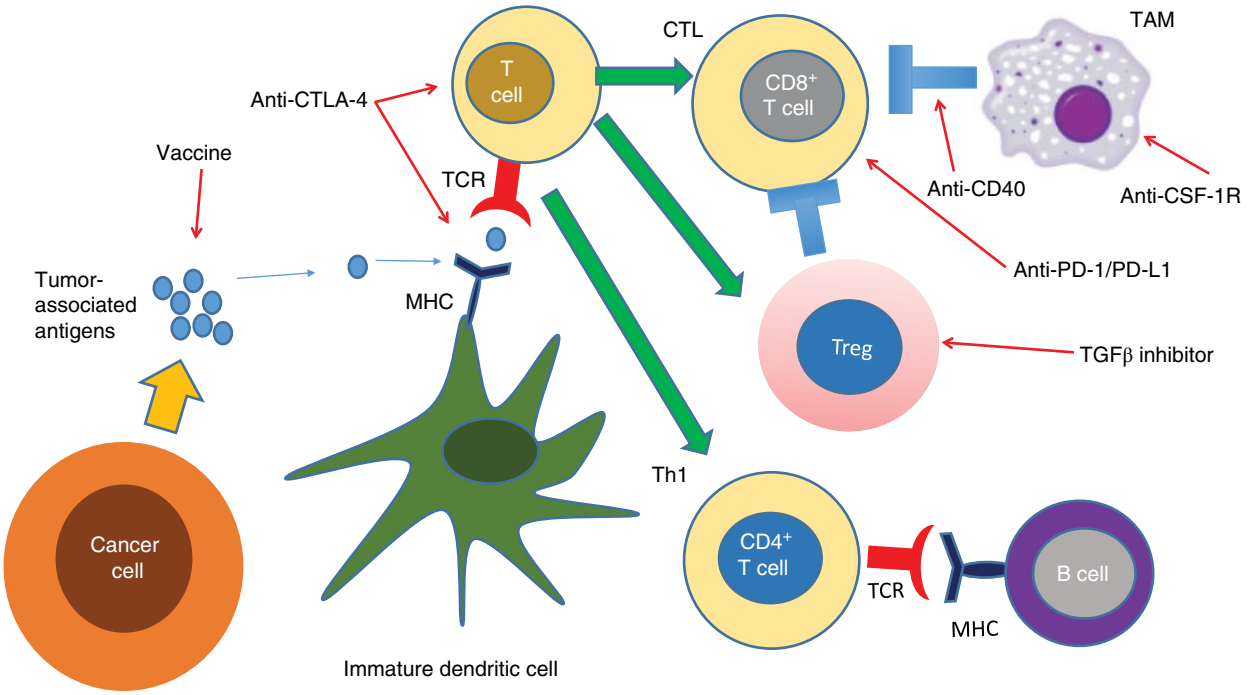


Figure 150.1 Components of immunotherapy in pancreatic cancer. Tumor cells express specific antigens which can activate antigen-presenting cells by binding to MHC molecules on their cell surface which in turn bind to T-cell receptors (TCR) on T cells. Anti-CTLA-4 therapy directly targets this interaction. This results in T-cell activation and differentiation into various T-cell subtypes including CD8+ cytotoxic T lymphocytes (CTL), regulatory T cells (Treg), and Th1 (T helper cells). CTL activity can be eliminated by tumor-associated macrophages (TAM) resulting in tumor progression. Pharmacologic inhibition of CSF-1R (colony-stimulating factor-1 receptor) and CD40 can reduce this effect. Tregs can also suppress CTLs, an effect which can be negated by targeting TGF (transforming growth factor) β. Th1 cells induce B-cell activation which results in antibody production and activation of humoral immunity.

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The procarcinogenic inflammatory response found in most tumors is highly regulated by the progressive genetic alterations that occur with cancer development and progression. For example, the *KRAS* proto-oncogene is mutationally activated in 90% of PDA and results in constitutive activation of *KRAS* and its downstream signaling pathways. *KRAS* activation drives cancer cell migration and metastasis [18]. Preclinical models have shown that *KRAS* inactivation results in the high expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) [19,20]. GM-CSF has been shown to result in the accumulation of MDSC by inducing the proliferation and differentiation of precursor c-kit$^+$ stem cells which leads to the suppression of CD8+ T-cell mediated antitumor immune responses, thereby permitting tumor growth.

T cells express a number of stimulatory and inhibitory signals depending on the type of inflammation they encounter. Whether a T cell becomes activated or deactivated depends on the net sum of the signals that are engaged. Two T-cell inhibitory signals, cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death-1 (PD-1) have been shown to have significant clinical relevance in cancer. CTLA-4 acts as an immune checkpoint striving to maintain immune homeostasis by downregulating T-cell function once CD28 binds to its ligand B7, therefore inducing T-cell cycle arrest (Fig. 150.2) [21]. Due to its role as a negative regulator of immunity, it was the first checkpoint to be clinically targeted after preclinical models showed that antibody blockade of CTLA-4 lead to antitumor immunity [22,23]. PD-1 is also an immune checkpoint which negatively regulates T-cell activity when it interacts with its ligands, PD-L1 and PD-L2 [24]. PD-1 is expressed on many immune cells and inhibits effector T-cell function [25]. Antagonist antibodies that inhibit these molecules, also called immune checkpoint inhibitors (ICIs), have recently become standard of care for cancers that naturally attract effector T cells into their tumor.

Despite the paragidm shifting implications of ICIs in many tumors, PDA has been ICI treatment refractory. The TME of PDAs is considered an immune "desert" because of the paucity of natural infiltration of effector T cells, the very cells that respond to ICIs [26,27]. Thus, PDAs are considered to be immunogenically "cold" tumors [28–30]. To convert PDAs into ICI-responsive tumors, effective immunotherapy strategies are required at a minimum to increase antigenicity, enhance effector T-cell infiltration and function, and overcome immunosuppressive signals in TMEs [31–33]. Emerging data from our group and others provide strong evidence that PDAs require all three to respond to ICI therapy.

We have been testing the hypothesis that cancer vaccines are effective in inducing effector T cells that can infiltrate PDAs. We have reported that our GM-CSF-secreting allogeneic PDA cell vaccine (GVAX) can induce the formation of tertiary lymphoid aggregates in PDAs just two weeks following single vaccination and that these aggregates serve as sites of T-cell education to PDA antigens [34]. Furthermore, PD-L1 expression is induced on both the tumor epithelium cells and myeloid cells within these lymphoid aggregates, suggesting that vaccine therapy may prime PDAs to respond to ICIs [34,35]. However, the current challenge is to identify the additional immune suppressive signals within the complex PDA TME that require further modification to effectively enhance effector T-cell function. Additionally, it is still not clear how best to activate the most potent effector T cells. Further studies are required to identify the best T-cell activating vaccines and combination ICIs for durable anticancer responses in the majority of PDA patients.

In an effort to seek an effective immunotherapy strategy for PDA, essentially all types of immunotherapy have been investigated in PDA patients. Consequently, PDA has been more and more recognized as a typical "cold" tumor model and thus an appropriate tumor platform

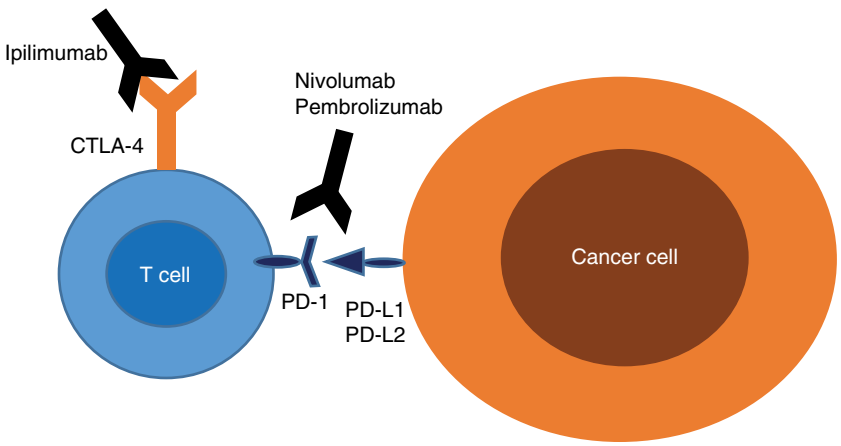


Figure 150.2 Checkpoint inhibitors in pancreatic cancer. T cells express CTLA-4 (cytotoxic T-lymphocyte associated-4) antigens on their cell surfaces which downregulate T-cell function. Anti-CTLA-4 antibodies (e.g., ipilimumab) can bind to CTLA-4 receptors on T cells and reverse immunosuppressive T-cell functions. PD-1 (programmed death-1) receptors on T cells bind to PD-L1 and PD-L2 ligands on cancer cell surfaces. Anti-PD-1 antibodies bind to PD-1 receptors preventing interactions with its ligands.

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for developing immunotherapeutic treatment strategies for "cold" tumors in general. Although presently there has not been a breakthrough in developing clinically successful immunotherapy for PDA, many different approaches have been attempted and are currently being further developed in treating PDA, as outlined below. Together, these efforts offer a rational approach that will ultimately lead to a breakthrough immunotherapy strategy for PDA, which would turn scientific hope into reality.

T-cell Priming in Pancreatic Cancer: From Therapeutic Vaccines to Adoptive T-cell Therapy

Cancer vaccines are used to generate a humoral/cellular immune response to stimulate the immune system as a defense mechanism against tumor cells. Therapeutic vaccines deliver specific pancreatic tumor antigens systemically with the aim of further stimulating the patient's immune system to recognize minor differences in the antigen that exists between normal and tumor cells. These vaccines are generally well tolerated because of their antigen specificity. Therapeutic vaccines can be broadly categorized into whole-cell vaccines and antigen-specific vaccines. ×

Whole-cell Vaccines

Polyvalent vaccines are derived from whole cells or cell lysates and have the capacity to allow the targeting of multiple antigens.

The allogeneic whole-cell pancreatic tumor vaccine GVAX developed by Jaffee et al. [36] was derived from two human pancreatic cancer cell lines stably transfected to produce the human cytokine GM-CSF. GM-CSF has the capacity to overcome tumor-induced suppression and promote the recruitment and maturation of APCs, resulting in upregulation of MHC class II costimulatory molecules and cytokine production. GM-CSF-producing tumor cells are subsequently irradiated and administered to patients intradermally. The phase I study comprised 14 patients with stages I–III pancreatic cancer who received multiple administrations of vaccine with concentrations ranging from 1–50 × 10^7 cells after surgical resection and standard adjuvant therapy. This study found that three patients who received ≥10 × 10^7 vaccine cells developed increased delayed-type hypersensitivity (DTH) responses and that these patients remained disease free for over 10 years [36]. GVAX was well tolerated without any local or systemic dose-limiting toxicities observed. The most common adverse effects were self-limiting skin reactions (erythema, induration, pain) at the sites of immunization.

The phase II study involved administering 5 × 10^8 GM-CSF-secreting cells to 60 patients with resected PDA [37]. Patients received five doses of vaccine in addition to 5-fluorouracil (5FU)-based chemotherapy. The median disease-free survival was 17.3 months (95% confidence interval [CI] 14.6–22.8) and the median survival was 24.8 months (95% CI 21.1–31.6). The addition of immunotherapy to chemotherapy did not result in additional toxicities and the development of mesothelin-specific CD8+ T cells in HLA-A1+ and HLA-A2+ patients was correlated with improved disease-free survival.

Based on preclinical data that giving cyclophosphamide (Cy) prior to immunotherapy could enhance the intended immune responses by inhibiting CD4+/CD25+ Treg cells [38–41], Laheru et al. designed a clinical study comparing the effects of administering Cy prior to GVAX vaccine in patients with advanced PDA. Fifty patients received Cy one day prior to the vaccine or the vaccine alone and minimal toxicities were observed in both arms. Survival data from this nonrandomized study suggested that adding Cy prolonged median survival (130 vs 69 days). This study also found that mesothelin-specific immune responses were detected in this cohort of patients with advanced disease.

Pancreatic ductal adenocarcinoma has traditionally been regarded as a nonimmunogenic cancer compared to melanoma or lung cancer. A neoadjuvant and adjuvant clinical trial was designed to test whether GVAX ± Cy could convert the relatively nonimmunogenic TME of PDA into an immunogenic tumor with infiltrating effector lymphocytes [42]. Two weeks prior to surgical resection, 39 patients were randomized to receive GVAX alone, GVAX preceded by a single intravenous Cy dose, or GVAX with daily Cy on alternate weeks. Examination of the resected PDAs showed that vaccines induced intratumoral tertiary lymphoid structures (TLS) in 85% of patients. Further analysis of these TLS aggregates showed that they consisted of organized T- and B-cell zones with a germinal center-like structure, indicating that they represented adaptive immunity. Specific gene expression signatures were found in these intratumoral aggregates, including those showing that a suppressed Treg pathway and enhanced Th17 pathway were associated with improved survival. Consistent with prior studies, there was an association between those who developed an immune response/lymphoid aggregates and improved survival. This study also showed that the expression of immune checkpoint signaling, such as PD-1 and PD-L1, was induced by vaccination, suggesting that GVAX therapy could play a role in priming patients to combat the lack of response

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to anti-PD-1 therapies seen in PDA. The final publication after the clinical trial completed the enrollment of 87 patients has confirmed the safety and feasibility of conducting a window-of-opportunity neoadjuvant clinical trial of examining the effect of an experimental immunotherapy on the TME and also confirmed that the density of vaccine-induced intratumoral TLS is associated with improved survival following the surgery and the neoadjuvant/adjuvant treatment of the vaccine [43].

Antigen-specific Vaccines

Antigen-specific vaccines take advantage of inherent defects in the genetics of PDA and translate these into functional targets for immunotherapy. As *KRAS* mutations are universal in PDA and are known for their role in driving the PDA development [44,45], they are an obvious target for immunotherapy.

Early studies which involved administering synthetic KRAS peptides to patients with unresectable PDA showed that it was safe and induced an immune response in two out of five patients [46]. Another phase I/II trial coadministered mutant KRAS peptides with GM-CSF in a study involving 48 patients with PDA [47]. Immune responses were elicited in 58% of patients and in those with advanced disease, a peptide-specific immune response was associated with improved survival. A further study evaluated the administration of patient-specific KRAS mutations (codon 12) with a 21-mer epitope containing the patient's mutation and GM-CSF in patients with resected PDA [45]. They demonstrated median recurrence-free survival and overall survival of 8.6 months and 20.3 months, respectively. However, there were low rates of immunogenicity, with a single patient developing a detectable mutation-specific immune response and 13% of patients developing a non-specific DTH.

Interest first arose in mesothelin, a tumor-associated antigen overexpressed in most PDAs, as a target for immunotherapy in PDA based on the observation that mesothelin-specific responses were associated with improved disease-free survival after GVAX therapy [48,49]. This led to the development of CRS-207, a recombinant live-attenuated, double-deleted strain of *Listeria monocytogenes* (LADD-Lm) which was engineered to secrete mesothelin into the cytosol of infected APCs which ultimately are processed and presented as major histocompatibility complex molecules. The phase I study involving CRS-207 demonstrated that multiple administrations were well tolerated and sufficient to induce mesothelin-specific T-cell responses [50]. Preclinical data suggested that a heterologous prime-boost strategy combining GVAX and LADD Lm-expressing mesothelin induced a synergistic T-cell induction and antitumor effect.

A subsequent phase II study randomized patients with previously treated metastatic PDA to receive Cy/GVAX followed by CRS-207 vs Cy/GVAX alone [42]. Overall survival for all patients was higher in the Cy/GVAX + CRS-207 group (6.1 vs 3.9 months). For those patients who received at least three doses, overall survival for the Cy/GVAX + CRS-207 group was 9.7 months compared to 4.6 months for the Cy/GVAX alone group. Enhanced mesothelin-specific CD8+ T-cell responses were associated with longer survival in both treatment groups. However, the clinical efficacy of this heterologous prime-boost vaccine therapy strategy was not substantiated in the follow-up randomized study in comparison with chemotherapy, suggesting that vaccine therapy by itself may not be sufficient to elicit an effective antitumor response.

Neoantigen-based Vaccines

Somatic gene mutations occurring in individual tumors can generate novel epitopes or "neoepitopes' which serve as targets for immune responses [51]. The technology to recognize individual neoepitopes now exists which can scan the entire cancer exome (coding regions). It is important to note that for neoepitopes to be functional, their mutant peptides must be processed by MHC molecules and T cells must recognize these peptide–MHC complexes. An added complexity lies in the fact that these epitopes must have been tolerated by the immune system to permit the tumor to grow. This tolerance appears to be mediated by immune checkpoints, e.g., PD-L1 [52]. It is unsurprising that these tumor types are typically sensitive to immune checkpoint inhibition since they induce effector T-cell infiltration that resembles untreated melanomas [53].

Unlike tumors typically associated with high rates of mutations, e.g., melanoma, PDA typically harbors fewer mutations, although neoepitopes do exist [54]. Notwithstanding the challenges of identifying tumor neoantigens suitable for immunization, determining the number of neoantigens required for targeting and the challenges of producing personalized vaccines, recent efforts have concentrated on developing shared neoantigen-based vaccines [55] such as mutant KRAS epitopes-based vaccines. Nevertheless, mutant KRAS peptide sequences are known to be weak CD8+ T-cell epitopes although T cells reacting to the mutant KRAS peptides do exist [56]. The key for the development of neoantigen-based vaccines for pancreatic cancers is unlocking how to activate the T cells that recognize the KRAS-mutation associated neoepitopes.

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In situ Vaccination

Although cancer vaccine can serve as an approach to T-cell priming in a cold tumor like PDA, it remains unknown whether sufficient tumor-specific T cells have infiltrated into PDA. On the other hand, evidence suggests that certain neoantigens in PDA are associated with long-term survival following surgical resection. Thus, PDA naturally has the potential to generate neoantigen-specific T cells. The question remains, however, how we can amplify these neoantigen-specific T cells and simultaneously unleash them to attack bulky diseases present at the metastasis stage.

Conventional chemotherapy and radiation have been studied as avenues to induce innate immune responses. The role of chemotherapy in antitumor immune response is controversial. Multiple preclinical and clinical studies have shown that chemotherapy decreases vaccine-induced T cells [37]. However, a preclinical study in a mouse syngeneic model of PDA found that gemcitabine enhances therapeutic efficacy of dendritic cell (DC) vaccination despite its negative influence on vaccine-induced T-cell proliferation [57]. This study also showed that the cytotoxicity function of T cells was preserved and that gemcitabine was able to further sensitize tumor cells to cytotoxic T-cell-mediated lysis in the *in vitro* assay. In addition, gemcitabine facilitated recruitment of CD8+ T cells into tumors.

In contrast, a more recently published preclinical study showed that chemotherapy induces an initial infiltration of proinflammatory macrophages and activation of cytotoxic T cells, leading only to a temporary restraining of PDA progression [58]. After stopping treatment, neutrophils were recruited to the tumors and enabled the regrowth of tumors by expressing growth arrest-specific 6 (Gas6) to activate the AXL receptor on tumor cells. The Vonderheide group thus showed that the addition of chemotherapy optimized myeloid activation and T-cell function following the CD40 agonist treatment [59]. Their studies further demonstrated that CD40 stimulation caused a clonal expansion of T cells in the tumor, demonstrating an *in situ* vaccination effect of the CD40 agonist. More importantly, such an effect is independent of the canonical innate immune response pathways, including toll-like receptors (TLRs), inflammasome, and stimulator of interferon genes (STING) [60,61].

Building upon this rationale, a clinical trial testing the combination of CD40 agonist with chemotherapy showed promising results. In this nonrandomized, open-label, multicenter, four-cohort, phase Ib study, untreated metastatic PDA with RECIST (response evaluation criteria in solid tumors criteria) measurable disease were treated with 1000 mg/m^2 intravenous gemcitabine and 125 mg/m^2 intravenous nab-paclitaxel. Patients received 0.1 mg/kg CD40 agonist antibody sotigalimab in cohorts B1 and C1 and 0.3 mg/kg in cohorts B2 and C2. In cohorts C1 and C2, patients also received 240 mg intravenous anti-PD-1 antibody nivolumab. Thirty patients were enrolled and received at least one dose of any study drug; 14 (47%) of 30 patients (four each in B1, B2, C1; two in C2) had a treatment-related serious adverse event. Objective response rate was 58% (14 of 24 dose limit toxicity-evaluable patients; four each in B1, C1, C2; two in B2), which is higher than what is anticipated for chemotherapy with gemcitabine and nab-paclitaxel [62]. Nevertheless, a challenge remains to tease out the contributive effect of each agent used in this study, in future follow-up studies.

Radiation has been shown to trigger the release of damage-associated molecular pattern (DAMP) signals and subsequently induce TLR2/4 and the receptor for advanced glycation endproducts (RAGE) pathways [63]. However, most studies with radiation or chemotherapy in either a preclinical setting or a clinical study have not found that radiation can induce effector T-cell infiltration as observed in the studies with innate immune agonists. However, our group's unpublished results from clinical studies suggest that radiation in combination with vaccine therapy can induce cytotoxic effector T-cell infiltration in PDA tumors, although radiation also induced immunosuppressive myeloid cells [64]. By combining radiation with myeloid cell-targeting agents, an *in situ* vaccination effect with intratumoral infiltration of cytotoxic effector T cells was achieved without the presence of vaccine therapy according to a preclinical study. In this preclinical study, such an *in situ* vaccination effect can similarly prime the tumors for ICI therapy (Wang et al. *Journal of Experimental Medicine* accepted).

Although chemotherapy agents have been shown to have immune-modulating effects, in the clinical setting, chemotherapy treatment is often associated with a decrease of effector T cells in the tumor. However, our recent unpublished preclinical study showed that chemotherapy in a sequential combination with innate agonists including STING and NLRP3 (NLR family pyrin domain containing 3) agonists and ICIs, but not chemotherapy alone or ICIs alone, led to a significantly enhanced infiltration of cytotoxic, activated, effector memory T cells, and such an enhancement is associated with improved antitumor activities. Therefore, combining innate immune agonists with conventional chemotherapy and/or radiation therapy as an *in situ* vaccination strategy and a T-cell priming mechanism for sensitizing the tumors for ICI therapies warrants further clinical testing.

Other *in situ* vaccination strategies include oncolytic viruses which are designed to be able to selectively replicate within and eradicate tumor cells, sparing healthy tissues. Beyond the oncolytic mechanism of direct

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tumor eradication, these specialized viruses are also able to induce and promote tumor-directed immune responses, leading to further tumor killing by a variety of mechanisms [65]. For example, through a CD8+ T-cell-mediated specific adaptive antitumor response, these oncolytic viruses are able to induce long-lasting tumor-specific inflammatory cascades and immunogenic cell death (ICD) [66]. The oncolytic activity of these viruses increases tumor-associated antigen availability, where immunogenic cell death and inflammation promote recruitment of dendritic cells, inducing activation of the adaptive immune response. Genetic engineering has specifically permitted the insertion of genes, such as GM-CSF and type I cytokines, which allow the viruses to have additional immune priming mechanisms [67].

The immunomodulatory transgene enhancement of oncolytic activity and immunogenicity leading to clinical activity in malignancies is best illustrated with the first FDA-approved oncolytic virus for the treatment of melanoma, talimogene laherparepvec (T-VEC) [68]. This genetically engineered vector utilizes an attenuated herpes simplex virus that also contains genetic instructions for GM-CSF production. A clinical trial of locally administrated TVEC for locally advanced PDA is ongoing (NCT03086642). New oncolytic viruses that can be administered systemically, but still maintain a tumor preferential delivery and/or carry tumor antigens, are particularly attractive for being developed as novel treatments for PDA, which nearly always presents as a systemic disease.

Cytokines

T-cell priming achieved by the *in situ* vaccination mechanism includes both an induction of antigen specific T cells and a proliferation of existing antigen-specific T cells. The former can be enhanced by cytokines that enhance antigen presentation and maturation of dendritic cells. The latter may be achieved in a more robust way by direct cytokine therapy. Despite its narrowed use and benefit in melanoma and renal cell carcinoma (RCC) [69], as well as its toxicity profile, interleukin (IL)-2 has led to ongoing investigations of IL-2 agents with a better safety profile or an intratumoral delivery as well as other cytokines in the treatment of a broader spectrum of cancers.

It has recently been reported that currently there are over 40 clinical trials looking at various recombinant cytokines, with a significant number involving GM-CSF [70]. However, the focus recently has shifted to cytokines that are selective in their cellular targets and more refined in their immune actions, such as IL-12, IL-15, and IL-21 [70]. IL-12 induces natural killer (NK) cells and activates CD4+ cells into Th1 type signaling [71,72]. IL-15 is another T-cell growth factor that promotes the growth of intestinal epithelium, T cells, and NK cells, and enhances CD8+ memory T-cell survival [73]. IL-21 is an inducer of Th2 signaling and induces proliferation of T cells, B cells, and NK cells [74].

All these cytokines present as viable targets for inhibition by which the TME can be modulated in favor of pro-immunotherapy and antitumor response. Nevertheless, the research on cytokine therapy has been primarily focused on ICI-sensitive malignant diseases whereas limited studies of cytokine therapy as a single agent in PDA have been disappointing [75]. The efficacy of cytokine therapy is impeded by the fact that cytokines have significant pleiotropism, redundant signaling, and dual functionality, which can both activate and suppress the immune system [76]. To overcome some of these challenges, novel strategies of incorporating cytokines as an *in situ* vaccination mechanism into other immunotherapies need to be investigated.

T-cell Therapy

At the core of vaccine therapy's capacity to eradicate cancer stands the ability to prime T cells with specific antigen responses. Similarly, adoptive transfer of T cells, particularly those genetically engineering T cells, is another T-cell priming venue. Chimeric antigen receptor (CAR) T-cell therapy, which binds to the tumor antigens in a non-HLA type restricted manner and is self-sustainable in both proliferation and activation, was thought to be an ideal therapy for PDA. However, CAR T cells often fail to traffic efficiently into solid tumors, particularly PDA which is more desmoplastic than most other malignancies.

The best studied target for CAR T therapy in PDA patients is mesothelin since more than 80% of PDA express mesothelin [77–79]. However, evidence supporting a clinical efficacy of mesothelin-targeting CAR T-cell therapy in PDA patients is still lacking. PD-1 and T-cell receptor (TCR)-deficient mesothelin-specific CAR T cells using CRISPR-Cas9 technology were evaluated in a dose escalation study of 15 PDA patients [80]; the best response was stable disease in only two patients. In a phase I study of HER2-targeting CAR T cells in 11 cases of advanced PDA [81], one patient has a partial response and five achieved stable disease. Other targets being evaluated in clinical studies include PSCA, CEA, Claudin18.2, MUC1, and CEACAM7 [82,83]. Thus, these studies focus on testing different tumor antigens for CAR T therapies in PDA. Indeed, more studies are needed in order to investigate how to overcome the barriers of CAR T-cell trafficking to solid tumors by using PDA as a study model.

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TCR T-cell therapy, which delivers T cells engineered with TCR that recognizes corresponding specific antigenic epitopes, is an alternative T-cell therapy option for PDA treatment. Although TCR-engineered T cells depend on *ex vivo* activation and do not proliferate *in vivo*, evidence suggests that they can infiltrate desmoplastic PDA tumors in genetically engineered mice. Thus, TCR T-cell therapy may potentially achieve T-cell priming in PDA. Bispecific antibody T-cell engagers such as BiTE may be another effective T-cell priming therapy for PDA.

T-cell Immunomodulators in Pancreatic Cancer: Reinvigorating and Activating T Cells

Whether a T cell becomes activated or deactivated depends on the sum of the signals that are engaged. Therefore, treating PDA with T-cell priming therapies alone would not be sufficient. T-cell immunomodulators are also needed. Two T-cell inhibitory signals have already been proved to have therapeutic relevance in cancer, CTLA-4 and PD-L1/PD-1, which are also among the most studied immunotherapeutic targets in PDA.

CTLA-4

Ipilimumab is a fully human IgG1κ antibody which recognizes CTLA-4 and blocks its interaction with B7-1 and B7-2 on APCs. This results in prolonged T-cell activation and amplification of T-cell-mediated immunity [84]. Ipilimumab has received FDA approval for use in stages III–IV melanoma due to improved recurrence-free survival (adjuvant setting) [85] and overall survival (metastatic setting) [86]. More recently, ipilimumab has received FDA approval for use in advanced non-small cell lung cancer, hepatocellular carcinoma, and squamous cell carcinoma of esophagus in a combination with nivolumab.

A phase II study evaluated single-agent ipilimumab for patients with locally advanced or metastatic PDA [87]. Twenty-seven patients received ipilimumab 3 mg/kg every three weeks for a maximum of eight doses. There were no responders by RECIST although one subject experienced a delayed response after initially being diagnosed with progressive disease. This study suggested that an immune checkpoint inhibitor as single agent is not effective in an immunogenically "cold" tumor such as PDA.

Le et al. thus conducted a phase Ib study of ipilimumab alone versus the combination of GVAX and ipilimumab for treatment of patients with chemotherapy-resistant advanced PDA [88]. Thirty patients with previously treated PDA were randomized 1:1 to ipilimumab at 10 mg/kg alone or in combination with GVAX. CA 19-9 declines were seen for 7/15 patients in the combination arm whereas 0/15 patients who received ipilimumab alone had CA 19-9 declines. Median overall survival was 3.7 months for the single-agent arm and 5.7 months for the combination arm (P = 0.072). The percentage of patients alive after one year also favored the combination arm (7% vs 27%) [88]. The best RECIST response was stable disease seen in both arms. The quality of the responses in the two arms, however, was different. Two patients with stable disease in the single-agent arm had continuous disease progression that did not reach the 20% growth cutoff at week 7 and 22. All three patients with stable disease in the combination arm maintained stable disease until week 31, 81, and 71, respectively, when they were taken off the study. One patient initially received GVAX as a participant in the above-mentioned neoadjuvant and adjuvant vaccine study in 2009. After he had recurrence, he received additional chemotherapy and radiation therapy, but continued to have disease progression. However, after he received the combination of ipilimumab and GVAX treatments, even after he had an early local progression and developed a new omental lesion at week 7 after beginning the combinatorial treatment, thereafter he had a delayed but durable disease stabilization starting at week 22 until week 71 when he received his last treatment. Although his CT scan still showed soft tissue density in the local pancreatic region and peritoneal nodularity, biopsy of these lesions failed to demonstrate malignant cells. He remains alive today.

These data, albeit anecdotal, suggest that the combination of checkpoint inhibitor and vaccine therapies may reverse an unfavorable TME that is dominated by immune suppressive signals and allow for the generation of a productive antitumor response.

PD-1/PD-L1

A number of FDA-approved antibodies disrupting the PD-1 axis have been developed. At the time of writing, there are seven US FDA, European EMA, and/or China NMPA-approved anti-PD-1 antibodies and four anti-PD-L1 antibodies for the treatment of over 10 malignancies [89]. These drugs target PD-1 by blocking its interaction with PD-L1 and PD-L2 or target the ligand, PD-L1. Initially, they demonstrated objective responses in advanced cancer patients who have progressed through one or multiple lines of chemotherapy. However, they demonstrated durable response rates in multiple types of cancer including melanoma, lung cancer, and renal cell cancer [90,91], thus changing the prognosis of several malignant diseases in their late stages. More recently, they have gradually replaced conventional treatments and become the first-line therapies or part of

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the first-line combination for advanced cancer patients. In the most contemporary studies, their indications have been advanced to the early-stage cancers either in the adjuvant setting following surgical resection or in the neoadjuvant setting prior to surgical resection [92–94]. Nevertheless, none of these anti-PD-1/PD-L1 antibodies, as single agents, have demonstrated a reproducible efficacy in treating PDA except the rare subtype with a high microsatellite instability. The results of combining anti-PD-1/PD-L1 with chemotherapy in PDA have also been disappointing [95].

Therefore, a number of clinical trials have been conducted to test the hypothesis that vaccine therapy can prime PDA for anti-PD-1 therapy. In a recently completed phase II clinical trial [96], PDA patients who received one prior therapy for metastatic disease and had RECIST measurable disease were randomized 1:1 to receive a heterogeneous prime/boost dual vaccine treatment including GVAX and CRS207, the above-described live, attenuated *Listeria monocytogenes*-expressing mesothelin, with or without nivolumab anti-PD-1 antibody. Ninety-three patients were treated (GVAX/CRS207+nivolumab arm, 51 patients; GVAX/CRS207 arm, 42 patients) and demonstrated median overall survival of 5.9 and 6.1 months, respectively, with a hazard ratio (HR) of 0.86 (95% CI 0.55–1.34). Objective responses were seen in three patients using immune-related response criteria (GVAX/CRS207+nivolumab, 4%, 2/51; GVAX/CRS207, 2%, 1/42). The high-grade adverse event rate was higher in the GVAX/CRS207+nivolumab arm than the GVAX/CRS207 arm (35.3% vs 11.9%) but these toxicities were manageable. Although the clinical efficacy was modest, the changes in the TME, including increase in CD8+ T cells and decrease in CD68+ myeloid cells, were observed only in long-term survivors who received the combination of GVAX/CRS207 and nivolumab. Therefore, additional studies are needed to identify the best T-cell activating strategy in combination with the anti-PD-1 antibody treatment for durable anticancer responses in the majority of PDA patients.

T-cell Exhaustion

The upregulation of T-cell coinhibitory receptors is a hallmark of T-cell exhaustion upon chronic infections and in cancer. Following the T-cell priming treatment, the presence of persistent tumor antigen stimulation is anticipated to induce prolonged and increased expression of cell surface inhibitory signals. In addition to CTLA-4 and PD-1, T-cell exhaustion signals such as mucin-3/T-cell immunoglobulin (TIM-3), T-cell activation gene (LAG-3), and T-cell immunoreceptor with Ig and ITIM domains (TIGIT) were all reported to have elevated expression in PDA [97,98]. However, targeting these T-cell exhaustion signals has not yet been supported by preclinical studies in PDA. Despite this, it is possible that a proper strategy of applying specific targeting agents to T-cell exhaustion signals in PDA treatment may lead to therapeutic efficacy. This successful approach in PDA remains to be identified.

T-cell Agonist

In contrast, many preclinical studies strongly support antitumor roles for agonists of T-cell costimulatory receptors [99,100]. Clinically, the combinations of ICIs and a T-cell agonist were tested on a limited scale in other malignancies, and the development of anti-CD137 antibody or anti-OX40 antibody was aborted due to toxicity concerns [101,102].

Recently, Muth et al. compared the triple combo of GVAX, anti-PD-1 antibody, and anti-CD137 agonist antibody to the double combo of either GVAX and anti-PD-1 or GVAX and anti-CD137 antibody for antitumor efficacy in a syngeneic liver metastasis model of mouse PDAC and found that the triple combinabtion significantly prolonged the survival of PDA-bearing mice compared to double combination treatments [103]. However, similar to anti-PD-1 antibody, the antitumor effect of anti-CD137 antibody was dependent on the presence of GVAX. Our group thus conducted a three-arm clinical trial of neoadjuvant and adjuvant immunotherapy in resectable PDA patients. Adults with clinically resectable, untreated PDA were enrolled in one of three study treatments: Arm A (GVAX alone), Arm B (GVAX + anti-PD-1 antibody nivolumab), or Arm C (GVAX, nivolumab, and anti-CD137 agonist antibody urelumab) [104]. At median follow-up of 23 months (Arm A), 26 months (Arm B), and 22 months (Arm C), median disease-free survival was 14.82 months and 16.23 months, for Arms A and B respectively and not reached for arm C. The combination of GVAX, nivolumab and urelumab was associated with nearly significant improved disease-free survival compared to GVAX alone (HR 0.38, 95% CI 0.12–1.19) and GVAX+nivolumab (HR 0.38, 95% CI 0.12–1.21).

Targeting Stroma in Pancreatic Cancer: Overcoming Immunosuppressive Signals

As described above, another strategy is to identify the additional immune suppressive signals within the PDA TME that require further modification to effectively enhance effector T-cell function. It has been determined in a number of preclinical and clinical studies that stroma and/or myeloid cell modulating agents can overcome the

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barrier of the effector immune cell infiltration in PDA. Inflammatory response mediated by stromal fibroblasts and myeloid cells is anticipated to restrain tumor initiation and inhibit growth. However, evidence also suggests that these innate immune response components are reprogrammed epigenetically by the tumor cells and subsequently acquire the capability of attenuating effective T-cell infiltration and function [105–108].

Fibrotic Stroma

Recently, a nonreceptor protein tyrosine kinase, focal adhesion kinase (FAK), which is implicated in the proliferation, differentiation, and signal transduction cascades of various tumors, has been investigated as a target for TME immunomodulation. Preclinical studies have revealed that tumor-intrinsic FAK signaling modulates the activity of MDSCs, TAMs, and Treg within the TME. In both squamous cell carcinoma and PDA mouse models, the small molecule FAK inhibitor VS4718 was shown to decrease immunosuppressive MDSCs, TAMs, and Treg cells and consequently led to increased CD8+ T cells within the tumor and enhancement of CD8+ T-cell-mediated suppression of cancerous cells [109,110]. Osipov et al. showed that another small molecule inhibitor of FAK sensitized PDA for radiation therapy in a CD8+ T-cell-dependent manner and in association with a decrease in myeloid cell infiltration in mouse PDA tumors [111].

More recently, our group explored whether the addition of VS4718 to hyaluronidase augments modulation of cancer-associated fibroblasts (CAFs) and myeloid cells leading to enhanced intratumoral infiltration of effector memory T cells and survival of PDA-bearing mice. We found that simultaneous modulation of both FAK signaling in the cellular compartment of the stroma and of extracellular matrix by using hyaluronidase to degrade hyaluronic acid had a synergistic effect on decreasing the infiltration of tumor-associated granulocytes, particularly those expressing a known immunosuppressive cell surface receptor, CXCR4 (unpublished data).

IL-1β emerges as another therapeutic target of CAFs in PDA. Multiple published studies suggest that tumor-derived IL-1β drives tumor fibrosis, chemoresistance, and poor prognosis in PDA [112,113]. These studies showed that tumor-derived IL-1β promotes immune suppression in PDA. Tumor cell expression of IL-1β *in vivo* was driven by microbial-dependent activation of TLR4 signaling and subsequent engagement of the NLRP3 inflammasome [112]. Anti-IL-1β antibody enhanced the antitumor activity of anti-PD-1 antibody in the preclinical model of PDA, which was accompanied by an increased tumor infiltration of CD8+ T cells [113]. Therefore, we hypothesize that the combination of anti-IL-1β antibody and anti-PD-1 antibody can overcome the resistance of PDA to anti-PD-1 antibody therapy. To test this hypothesis, our group has proposed a phase II study of the combination of anti-IL-1β and anti-PD-1 antibody as a neoadjuvant therapy for resectable PDA. A similar combination has recently been tested in metastatic PDA (NCT04581343).

Tumor-associated Macrophages

Tumor-associated macrophages (TAM) alter their functional subtypes based on signals in the TME in an attempt to maintain immune homeostasis [114]. Higher density of TAMs in pancreatic tumors is associated with worse survival due to their tumor-promoting effects [115]. In addition to CSF-1 and CSF-1R as described above, one of the best studied targets is the chemokine receptor CCR2 and its cognate ligand CCL2, which has been implicated in tumor infiltration by immunosuppressive cells, notably protumoral M2-like TAMs and MDSCs. PDA patients with tumors that exhibit high CCL2 expression and low CD8 T-cell infiltrate have significantly decreased survival [116]. In mice, CCR2 blockade depletes inflammatory resident monocytes and macrophages from the primary tumor and premetastatic liver, resulting in enhanced antitumor immunity, decreased tumor growth, and reduced metastasis [117]. Tumor-derived CCL2 was shown to mediate the resistance to radiation in a mouse model of PDA by recruiting CCR2+ monocytes [118].

More recently, it was found that CCR2 blockade synergizes with radiation for antitumor activity by targeting CCR2+ monocytic MDSCs [119]. Targeting TAM with a CCR2 inhibitor (PF-04136309) in combination with FOLFIRINOX chemotherapy in patients with stage III pancreatic cancer was tested in a phase Ib trial showing a promising, high objective tumor response rate [120]. Nevertheless, this is a small, nonrandomized study in which the CCR2 inhibitor was given in the absence of ICIs, and the role of CCR2 inhibitor in controlling systemic disease and conferring survival benefit has not been established. A randomized phase II clinical trial testing the combination of a small molecule dual antagonism of CCR2 and CCR5 with chemotherapy with and without nivolumab in metastatic PDA has recently completed enrollment (NCT03496662) but the results have not been reported yet.

In a prior study, anti-CSF-1R antibody failed to confirm its benefit in metastatic PDA in the phase II study (NCT03336216) of cabiralizumab administered in combination with nivolumab and chemotherapy in patients with metastatic PDA. However, the early phase Ib study (NCT02526017) of cabiralizumab and nivolumab in the absence of chemotherapy did demonstrate an objective response in three patients who had been heavily pretreated with chemotherapy. Taken together, how

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immunotherapy may be combined with chemotherapy in clinical trials appears to be a more crucial question for the field to address first before the combination of immunotherapy and chemotherapy can be tested in the future.

Tumor-associated Neutrophils

The granulocytic population of myeloid cells including PMN-MDSC is composed of eosinophils, basophils, and neutrophils. Neutrophils are the most abundant type of granulocytes, and form the first line of defense in our immune system against microbial infection and facilitate wound healing [121]. Studies in recent years have demonstrated that tumor-associated neutrophils (TANs) promote angiogenesis and immunosuppression in the TME which can support tumor initiation, growth, and metastasis [121–125]. In PDA, this has lead to more attention on TANs as a therapeutic target. IL-8 is a proinflammatory chemokine in the CXC family and has been demonstrated to be a potent chemoattractant, recruiting granulocytic myeloid cells into the TME in order to promote tumor progression and immune escape [126]. In cancer patients, the main sources of IL-8 include tumor cells, CAFs, and TAMs. Studies have shown that high IL-8 levels in the plasma correlate with poor prognosis in multiple cancer types [127–129] and poorer outcomes in patients who received PD-1 therapies [130,131]. Thus, IL-8 and its receptors are considered to be novel molecular targets on TANs in cancer treatment [132,133].

Monoclonal antibodies and small molecular inhibitors that block the IL-8–CXCR1/CXCR2 axis have been in clinical development [134,135]. Among them, BMS-986253 is a first-in-class, fully human IgG1 κ monoclonal antibody inhibitor of IL-8 [136]. A phase I trial of BMS-986253 in patients with advanced solid tumors was completed, and BMS-986253 is currently being tested in combination with nivolumab in a phase Ib/II "basket" clinical trial (NCT03400332) that is currently focused on non-small cell lung cancer.

Our group recently completed the first preclinical study of anti-IL-8 therapeutic antibodies in a mouse model of human PDA. In this humanized mouse model, reconstituted with human myeloid cells and *ex vivo* activated T cells, we demonstrated the antitumor activity of an anti-IL-8 and anti-PD-1 antibody combination *in vivo*. We also revealed that one potential mechanism of action of anti-IL-8 antibody is to reeducate granulocytic myeloid cells by activating their innate immune response and type I cytokine response. A clinical trial testing the combination of nivolumab and BMS-986253 as neoadjuvant and adjuvant therapies for resectable PDA is ongoing (NCT02451982).

Conclusion

Pancreatic cancer has notoriously poor survival rates which are not dramatically improved with the use of traditional cytotoxic chemotherapy. Immunotherapy has the potential to produce durable remissions which has been demonstrated in other tumor types. Cancer vaccines have shown the ability to reverse the relatively non-immunogenic phenotype associated with PDA and induce subsets of immune cells which can, in turn, be sensitized to immune checkpoint blockade [42,53]. The future success of treating PDA with immunotherapy likely lies in the use of combinatorial regimens to further activate and sustain the function of effector T cells and to overcome the immunosuppressive mechanisms in the TME. There is also potential for optimizing these regimens with alternative strategies including epigenetic modulation, T-cell transfer therapies, and *in situ* vaccination, which have the added advantage of targeting other cell types in the TME.

Given the marked heterogeneity in tumor genetics and phenotypes, there is also a need to discover novel biomarkers which can reliably predict which subsets of patients are likely to respond to immunotherapy. Further research and development of combinatorial treatment strategies, novel targeting agents, and unique predictive biomarkers will lead to the greatest changes in clinical outcomes in patients with PDA.

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Targeted Therapies for Pancreatic Cancer

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Introduction

Despite a continuously evolving understanding of the molecular underpinnings of pancreatic ductal adenocarcinoma (PDAC), current therapeutic strategies have only achieved modest improvements in patient outcomes. With FOLFIRINOX and gemcitabine-based therapies being the main weapons in our armamentarium, intrinsic and acquired chemoresistance has prevailed as the rule rather than the exception in this disease.

In the past two decades, the majority of phase III studies in this disease have failed, underscoring the challenges of drug development in PDAC [1]. Despite the setbacks, subsets of patients with PDAC now have the opportunity to receive several newly developed, molecularly targeted therapies. Recent large-scale efforts in next-generation sequencing (NGS) technologies have allowed us to interrogate the genomic landscape of PDAC and with this, the ability to tailor personalized therapeutic options that exploit tumor-specific molecular abnormalities [2]. Further, while immunotherapy has been largely ineffective in this recalcitrant disease, we are finally beginning to see the emergence of combinations that are showing promising activity [3].

In this chapter, we describe how insights from understanding the molecular pathogenesis of PDAC have translated into novel therapies with the hope of improving survival in this aggressive disease.

Genomic Landscape of PDAC

Significant efforts through the International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA) have allowed us to make meaningful progress in deciphering the genomic landscape of PDAC [4,5]. Among the earliest events in PDAC pathogenesis is the activating point mutation in the *KRAS* oncogene, which is present in more than 90% of these cancers. In the multistep progression model, there is progressive accumulation of additional genetic alterations, including loss of function mutations in *TP53*, *SMAD4*, and *CDKN2A*. Aside from these four key oncogenic drivers, it is important to note several low-frequency mutations that have been identified that converge on core signaling tumorigenic pathways, including regulation of apoptosis, DNA damage, cell cycle, *KRAS* signaling, invasion, and transforming growth factor (TGF)-β signaling (Fig. 151.1) [6]. By identifying and understanding how these altered genes and pathways can affect tumorigenesis, we begin to interrogate how targeting these key nodes can be exploited for therapeutic stratification.

Targeting the Previously "Undruggable" KRAS Oncogene

KRAS is among the most commonly mutated oncogenes in human cancers, making it the most obvious choice for targeted therapies. Activation of the Ras protein is the result of growth factor receptor signaling, which induces cycling between an active GTP-bound (ON) and an inactive GDP-bound (OFF) state, regulating multiple downstream effectors. Within the protein lies an intrinsic GTPase, which leads Ras proteins to hydrolyze GTP to GDP, thus allowing the cycling of GTP and GDP to continue [7]. Point mutations in *KRAS* effectively inhibit productive interactions of Ras with GTPase-activating proteins (GAPs), leading to the attenuated ability to

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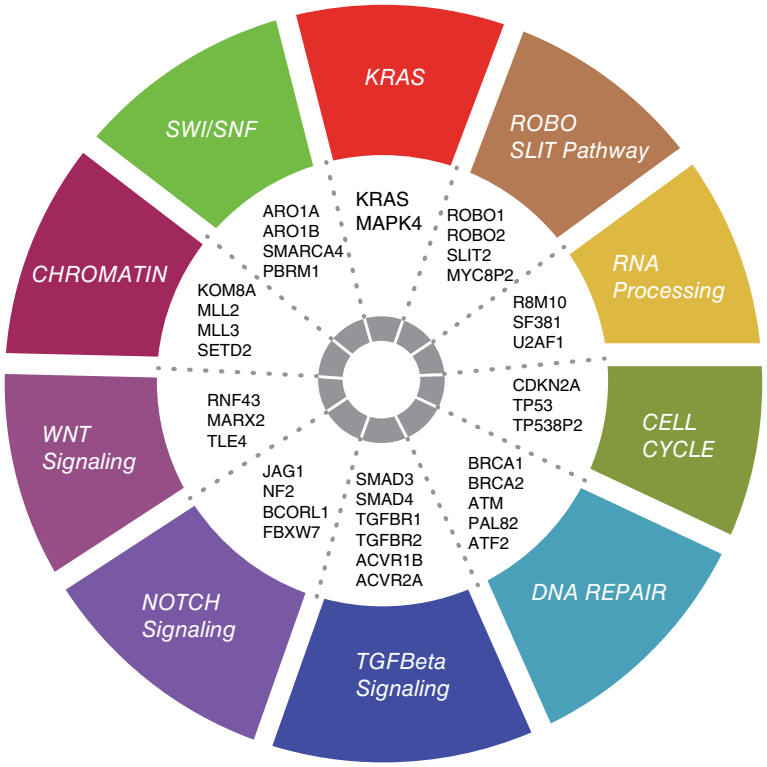


Figure 151.1 The genomic hallmarks of pancreatic ductal adenocarcinoma (PDAC), with key altered genes within each aberrant pathway highlighted. *Source:* Bailey et al. [4]. Reproduced with permission from Nature Publishing.

hydrolyze bound GTP to GDP, resulting in a constitutively active protein. For many decades, Ras was notorious as a "undruggable" target in cancer due to the inability to identify small molecules that bind with high affinity into the altered binding pocket of the mutant protein. As a result, clinically facile efforts to target Ras signaling in cancers were focused on downstream effectors, such as MAP kinase and Akt pathways, with mixed success [8,9].

One of the most welcome advances in oncologic drug development of the past five years has been the development of direct covalent inhibitors of mutant KRAS protein [10]. The initial class of agents that have advanced to the clinic binds to the cysteine protein encoded by the mutated *KRAS*^{G12C} allele, with the first two small molecule inhibitors – sotorasib (Lumakras) and adagrasib (Krazati) approved for use in non-small cell lung cancer by the US Food and Drug Administration [11–13]. Of note, the *G12C* allele only accounts for ~1.6% of all mutant *KRAS* cases in PDAC, and therefore there is considerable anticipation for the next series of inhibitors undergoing preclinical development that either target the more common mutant *KRAS*^{G12D} allele or bind to KRAS protein agnostic to the specific allelic variant [14–16]. Most of these inhibitors bind with the "off" state of KRAS (GDP-bound), although a few bind with the GTP-bound "on" state as well [17].

Despite the low frequency of *KRAS*^{G12C} alleles in PDAC, several patients have been accrued on early-phase clinical trials and treated with single agents, demonstrating objective responses, albeit transient in nature [18]. This suggests that inherent and/or adaptive mechanisms of resistance are likely to emerge on monotherapy, mandating the requirement for combinations. In fact, studies in lung and colorectal cancer patients have shown that the rapid emergence of genomic and nongenomic adaptive mechanisms is common in the face of targeted therapy against KRAS [19–22]. Such resistance mechanisms tend to be multiple in the same patient (for example, secondary mutations in *KRAS* itself or genes located within effector pathways) and heterogeneous across patients, underscoring both the immense selective pressure on cancer cells to sustain Ras signaling in the face of inhibition, and the challenges of targeting KRAS in the clinic for long-term benefit. With that said, combination therapies against these adaptive mechanisms are already under way [23–25] and for the first time in four decades, the concept of targeting this "undruggable" oncogene with small molecules has become a reality.

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While small molecule inhibitors against KRAS have emerged as one of the most exciting new developments in targeted therapies, it is important to note that several other strategies are being evaluated to target mutant KRAS directly in solid cancers, including PDAC. For example, genetic extinction of mutant $KRAS^{G12D}$ using siRNA loaded with inhibitory exosomes (iExosomes) is currently under way in early-phase trials in advanced pancreatic cancer [26,27]. Similarly, immunologic approaches to target mutant KRAS as a neoantigen, either using peptide or nucleic acid vaccines or engineered T cells expressing a mutant epitope specific T-cell receptor (TCR), are all under way [28,29].

Targeting of *KRAS* Wild-type Pancreatic Cancers

While *KRAS* mutations are by far the dominant oncogenic event in PDAC, approximately 8–10% of cases are *KRAS* wild type [4,5]. *KRAS* wild-type tumors tend to be more frequent in "young-onset" PDAC, defined as cases occurring prior to 50 years of age [30,31]. A number of alternative drivers are present in *KRAS* wild-type PDAC, including fusions of *ALK*, *RET*, *NTRK1*, *MET*, *FGFR2*, *BRAF*, and *NRG1*, amplifications of *EGFR* or *ERBB2*, and other driver events. From a targeted therapy standpoint, many of these alternative drivers are considered "actionable" due to the availability of small molecule inhibitors which are approved and used in other solid cancers where such drivers are more common (for example, *ALK* fusions in lung cancer) and can be used off-label in PDAC patients, or because of a "tissue agnostic" approval across multiple cancer types [32–36]. Of note, young-onset PDAC also tends to be enriched in patients harboring pathogenic germline mutations in cancer-predisposing genes and represents a subset that should be particularly encouraged to receive both somatic and germline sequencing [30,31].

Targeting DNA Damage Repair Defects in Pancreatic Cancer

Beyond KRAS and aforementioned alternative drivers, DNA damage repair defects have emerged as an important subset of PDAC cases for which therapies can be tailored based on a defined molecular alteration [37]. Approximately ~8–10% of tumors harbor germline and/or somatic pathogenic variants in genes that encode for proteins involved in repair of DNA damage, most commonly double-strand break repair, including *BRCA1*, *BRCA2*, *PALB2*, and *ATM* [38,39]. A minor subset (~1%) harbor germline and/or somatic mutations in genes encoding proteins that repair DNA mismatch repair (including *MLH1*, *MSH2*, *MSH6*, and *PMS2*). Both of these distinct DNA damage repair defects are actionable, albeit with somewhat different strategies. PDAC with biallelic loss of function defects in *BRCA1*, *BRCA2*, and *PALB2* is unable to deploy a mode of repair known as "homologous recombination repair" in response to DNA double-strand breaks, resulting in profound chromosomal instability and genome-wide structural defects (for example, unbalanced translocations) [40]. These tumors are exquisitely susceptible to platinum agents (cisplatin and oxaliplatin), which further exacerbate DNA double-strand breaks, and to inhibitors of PARP, an enzyme that provides an alternative avenue for DNA repair in the absence of homologous recombination repair.

This therapeutic approach of leveraging a tumor-specific molecular defect by shutting off the available "escape hatch" (in this case, PARP-enabled DNA repair when tumor cells already lack homologous recombination repair) is known as "synthetic lethality," a paradigm that was first described in unicellular yeast but has emerged as a well-established avenue for discovery of targeted therapies in oncology [41].

PARP inhibitors are now approved for use in patients with germline *BRCA1*, *BRCA2*, and *PALB2* mutations, in the so-called "maintenance setting" following a favorable initial response to platinum-based therapy [42]. While the pivotal phase III POLO trial that led to approval of the first PARP inhibitor as monotherapy in PDAC was focused on germline mutations in DNA repair genes and in an advanced disease setting [43], several PARP inhibitors are now being investigated in tumors with somatic mutations of these genes, in additional settings (such as adjuvant therapy following surgical resection), and in combination with immunomodulatory agents [44,45]. Of note, although ATM also encodes for a protein that is engaged in the response to double-strand breaks, the response of PDAC harboring these mutations to PARP inhibitor monotherapy is less obvious [46,47]. Instead, ATM-defective tumors appear to depend on sustained function of the related ATR protein, which has led to initiation of trials using ATR inhibitors, including trials combined with PARP inhibitors [42,48].

Finally, PDAC with mismatch repair defects typically manifests with microsatellite instability and significantly higher tumor mutational burden (TMB) compared to mismatch repair-proficient cancers [49,50]. These tumors respond favorably to immunotherapy with immune checkpoint inhibitors, and mismatch repair-defective PDAC are included in the "tumor agnostic" approval of the use of immunotherapy [51].

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Targeting the Altered Transcriptome in Pancreatic Cancer

While the genomic landscape of PDAC has been pivotal in the development of new and emerging targeted therapies, we have also come to recognize that there are transcriptomic subtypes in PDAC, which can correlate with responses to therapies [52]. The existence of transcriptomic subtypes based on RNA profiling of neoplastic epithelial cells in PDAC was first described in 2011 [53], and since then several distinct classification schemes have been proposed, which incorporate epithelial specific RNA profiles, stromal RNA profiles, or a combination of both [4,54–56].

Of the various RNA-based classification schemes proposed, the one most commonly adopted currently is a two-tier system that dichotomizes PDAC as "classical" and "basal-like" [52], phenocopying the four-tier Consensus Molecular Subgroups (CMS) classification used in colorectal cancers [57]. Retrospective data demonstrate that the "classical" and "basal-like" transcriptomic subtypes of PDAC are both predictive of response to cytotoxic chemotherapy, as well as prognostic in terms of outcomes [58,59]. Emerging data also suggest that the two transcriptomic subtypes are not static but display plasticity in response to ongoing therapy, tumor evolution, and *ex vivo* propagation [60,61]. Multiple clinical trials are now under way that take into consideration the transcriptomic subtype of PDAC at baseline to assign patients to various therapeutic regimens, including trials like PASS-01 and PREDICT-PACA, amongst others [62,63].

Targeting the Pancreatic Cancer Stroma

Pancreatic ductal adenocarcinoma is characterized by a profound host stromal response ("stromal desmoplasia") that is a *sine qua non* of this cancer. The PDAC stroma is composed of both cellular elements, most importantly fibroblasts, but also vascular and neural elements, as well as extracellular (acellular) matrix components [64]. The traditional viewpoint on the PDAC stroma has been that it is a barrier to the influx of both chemotherapeutic agents and a productive immune response, with the overarching premise being that depletion of the stroma will enable improvements in therapeutic responses and disease outcomes [65]. This simplistic premise of the stroma as a "monolith" has been intensely challenged in recent years, with several clinical trials targeting the PDAC stroma, both cellular elements (hedgehog inhibitors) and extracellular matrix components (hyaluronic acid), resulting in failure to improve overall survival compared to chemotherapy alone [64,66–68].

Over the past few years, and especially with the advent of single cell profiling approaches, we have come to appreciate the considerable heterogeneity and plasticity inherent in the PDAC stroma, particularly in terms of fibroblasts that form the pivotal stromal cellular component [69]. It is now widely accepted that the PDAC stroma is composed of both "tumor promoting" and "tumor restraining" fibroblast components, with prevalent identities such as "inflammatory cancer associated fibroblasts" (iCAFs) ascribed to former and "myofibroblastic cancer associated fibroblasts" (myCAFs) ascribed to the latter [70–72]. The existence of hybrid fibroblast transcriptomic features (based on single cell profiling approaches) suggests that the aforementioned dichotomy in fibroblast identity is not stable, and likely to be influenced by both tumor intrinsic factors, like the genetic makeup, and extrinsic factors, such as administration of chemotherapy and targeted agents [72,73]. In autochthonous preclinical models, genetic or pharmacologic depletion of tumor-restraining myCAFs (or myCAF-generated collagen 1 [74]) leads to more aggressive disease and shortened survival [75,76], mimicking the findings observed in the clinic with indiscriminate stromal targeting.

An improved understanding of stromal fibroblast heterogeneity and diversity in function has led to more recent trials being geared towards reprogramming of activated tumor fibroblasts towards a normal or resting state, such as with vitamin D receptor agonists, or all-trans retinoid acid, amongst others [77,78]. Ultimately, targeting the PDAC stroma will require strong pairing of underlying biology with translation, in order to prevent the missteps of the prior decade in this arena.

Targeting the Immune Microenvironment in Pancreatic Cancer

Amongst solid cancers, the resistance of PDAC to immunotherapy is notorious [79]. In contrast to melanoma or lung cancers, the administration of immune checkpoint inhibitors targeted against PD-1 and CTLA-4 has produced minimal response [80,81], with the exception of PDAC cases harboring DNA mismatch repair defects (see above). Similarly, adoptive cellular therapies like infusion of chimeric antigen receptor (CAR)-expressing T cells targeted against PDAC tumor antigens such as mesothelin have thus far been largely ineffective [82,83]. While whole-cell vaccines targeted against PDAC (with or without attenuated *Listeria*-expressing mesothelin as an added immunogen) have undergone extensive clinical trials, these too have demonstrated at most modest effect in advanced cases [84,85], with more sustained responses demonstrated in subsets of patients in the adjuvant setting [86].

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The reasons for these failures of various immunotherapy modalities in PDAC are manifold and include the profound immune suppressive tumor microenvironment, composed of both cellular elements like tumor-associated macrophages, regulatory T cells and neutrophils, as well as cytokines like TGF-β and interleukins IL-6 and IL-1β, which attract immune suppressive cells to the peritumoral milieu and dampen effector T-cell function [3,87]. Further, the relatively modest tumor mutation burden and neoantigen load in most microsatellite stable PDAC [50], paired with defects in antigen presentation [88,89], underscore the challenges of generating a productive immune response in this disease.

The principal lesson learned from the clinical failures of immunotherapy has been the understanding that any immunotherapy modality cannot be deployed in isolation but needs to target multiple aspects of the cancer immunity cycle [90], such as pairing activation of effector T cells with disruption of immune suppressive myeloid cells, preferably in conjunction with chemotherapy to reduce tumor volume and release tumor antigens within the tumor milieu. In fact, some of the recent encouraging signals that have emerged in PDAC immunotherapy trials have been those that embraced this concept of combining multiple modalities (chemotherapy, immune checkpoint inhibitor, and myeloid/macrophage targeting agent) to overcome the profound barriers to immune rejection that exist in this disease [91–93].

Conclusion and Future Directions

Despite the considerable therapeutic nihilism and reluctance to conduct somatic molecular profiling in PDAC, several studies have now shown that a substantial minority of cases (~15–20%) harbor mutations that would be considered clinically actionable, even prior to the widespread availability of agents targeting mutant *KRAS* [30,94]. Biospecimens used to generate molecular profiles include not only tissues, which can sometimes be challenging to procure in advanced PDAC, but also noninvasive liquid biopsy approaches that can serve as a reliable surrogate for identifying actionable mutations in a clinically meaningful time frame [95]. Further, germline mutation profiling can identify patients who might benefit from PARP inhibitor or immune checkpoint-based immunotherapy. Moreover, in patients who harbor a germline pathogenic variant, cascade genetic testing can be extended to asymptomatic family members who might benefit from surveillance for PDAC [96]. Based on these mounting lines of evidence, guidelines bodies like the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) in the USA have recommended that all PDAC patients undergo targeted somatic profiling of their tumors and receive universal germline testing using a multigene panel [97,98].

Increasingly, clinical trials in PDAC are incorporating biomarkers as an inclusion criterion, whether these be genomic alterations, transcriptomic subtype, or aberrantly expressed proteins or epitopes. The benefits of established and emerging targeted therapies in PDAC (be it with small molecule inhibitors, antibodies or antibody–drug conjugates, vaccines or engineered adoptively transferred T cells) can only be leveraged if the molecular landscape of the tumor is accurately known. Further, the benefits of these emerging and exciting therapeutic approaches should not be restricted to the "ivory towers" of specialized cancer centers, but need to be extended to the community at large, including diverse populations that are often at the epicenter of health disparities in PDAC [99,100]. Only through such extrapolation will we make *bona fide* progress in this recalcitrant disease.

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Precision Cancer Medicine

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Introduction

In the 20 years since the human genome was first sequenced, genomics has developed into the more refined, patient-centered approach of precision medicine. Tumor sequencing has become the standard of care for many cancers as using genetic alterations and a patient's unique tumor biology guides diagnosis and treatment, resulting in the adoption of trastuzumab for *HER2*-positive breast cancer and vemurafenib and dabrafenib for $BRAF^{V600E}$ mutated melanomas as examples. More recently, precision medicine is being applied to pancreatic ductal adenocarcinoma (PDAC), a cancer that is difficult to treat. Over the past several years, molecular analyses have identified patients with PDAC harboring *BRCA1/2* mutations or microsatellite instability that benefit from novel therapeutics [1,2]. However, the vast majority of patients with PDAC do not exhibit these "actionable" mutations. With most PDAC patients presenting with advanced disease and a overall survival rate of 11% [3], improved therapies for PDAC patients are needed, and the molecular features of a patient's tumor should be leveraged in this approach.

Pancreatic ductal adenocarcinoma sequencing efforts have uncovered key mutations in aberrant molecular programs driving pancreatic carcinogenesis along with distinct molecular subtypes and epigenetic plasticity, which may contribute to therapeutic resistance [4–10]. Research has also revealed therapeutic vulnerabilities conferred by disrupted DNA repair mechanisms, and several large-scale studies demonstrated real-time feasibility and clinical benefit of genomic sequencing to guide targeted therapy [1,11–14]. In this chapter, we outline how the current understanding of PDAC's mutational landscape directs the clinical practice of precision cancer medicine while reviewing targeted therapies currently under investigation.

Mutational Landscape of Pancreatic Adenocarcinoma

In 2008, the genome-wide mutational landscape of PDAC was characterized for the first time by Sanger sequencing [15]. As next-generation sequencing (NGS) technologies evolved, additional whole-exome (WES) and whole-genome sequencing (WGS) studies emerged, including those from the multicenter consortiums the Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC). Today, our resolution of PDAC's genomic landscape has sharpened as each study has augmented our knowledge of tumorigenesis and disease progression while defining a rationale for more personalized treatment.

Four key driver genes (the oncogene *KRAS* and tumor suppressors *TP53*, *CDKN2A*, and *SMAD4*) largely shape the molecular events underlying tumorigenesis [4,16]. *KRAS* is the most commonly mutated gene in PDAC, with more than 90% of tumors harboring a pathogenic mutation [4]. In the stage-wise progression model of PDAC development, early premalignant lesions (pancreatic intraepithelial neoplasia or PanIN) harbor *KRAS* mutations, thus representing an early event in pancreatic carcinogenesis. A small percentage of cases present with multiple *KRAS* mutations, indicating convergent evolution of tumor clones [17].

Mutations in the tumor suppressor genes *TP53*, *CDKN2A*, and *SMAD4* occur in 50–75% of patients [4].

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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During PDAC tumorigenesis, these alterations accumulate in a stepwise fashion with *CDKN2A* inactivation occurring after *KRAS* activation and *TP53/SMAD4* lost in advanced PanIN stages [7]. Moreover, a large number of additional recurrent mutations are present at a low frequency (<5–10%). Mutational combinations vary widely between tumors, making PDAC a highly heterogeneous disease. Not surprisingly, therapeutic strategies utilizing an unselective approach may limit the opportunity to identify effective avenues of treatment for individual patients.

Next, we highlight the genetic alterations and accompanying aberrant signaling pathways that are beginning to be exploited clinically.

DNA Damage Repair Pathways

DNA damage accumulates in cells due to endogenous factors (e.g., errors in replication, oxidative stress) and exogenous factors (e.g., chemotherapy, ionizing radiation). The ability to reliably repair DNA breaks is essential to genomic integrity, with multiple overlapping pathways dedicated to lesion repair [18]. Altogether, over 400 genes make up the DNA damage repair (DDR) signaling pathways, with each component susceptible to genomic and functional alterations. Thus, DDR deficiency poses a therapeutic vulnerability in malignant cells, and recent studies demonstrate that loss of function in one or more of these genes sensitizes PDAC to certain DNA-damaging chemotherapies, including platinum-containing agents [1,16].

To leverage the vulnerability DDR deficiency confers, drugs targeting DDR have been developed based on the concept of synthetic lethality. Specifically, a PDAC-associated DDR mutation forms a synthetic lethal pair with another DDR gene targeted by a therapeutic drug. One classic example is poly-ADP-ribose polymerase (PARP) inhibitors which treat tumors defective in homologous recombination (HR) repair [18]. Upon DNA damage, PARP1 binds to unrepaired single-strand breaks (SSBs) and double-strand breaks (DSBs) to recruit downstream effectors [19]. PARP inhibitors thereby "trap" PARP1 on DNA strands, leading to unrepaired damage that promotes genomic instability and cell death in the absence of functional HR [19].

Recent molecular analyses reveal that approximately 25% of PDAC patients harbor mutations in DDR pathway genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, *ATM*). In one study, Waddell et al. examined genomic data from 100 PDAC tumors and identified four subtypes: stable, locally rearranged, scattered, and unstable [16]. Notably, tumors with unstable genomes harbored mutations in DDR genes. Among this cohort of patients, the BRCA mutational signature predicted response to platinum-based chemotherapy.

Several small retrospective studies demonstrated survival benefit when patients with PDAC and germline *BRCA1/2* mutations were treated with platinum-based chemotherapies [1,13,20]. Clinical trials utilizing PARP inhibitors in HR-deficient (HRD) breast and ovarian cancer also significantly improved outcomes, leading to a randomized phase II trial in which the combination of the PARP inhibitor veliparib with gemcitabine and cisplatin therapy was compared to gemcitabine and cisplatin only in patients with PDAC and a germline *BRCA1/2* or *PALB2* mutation [13]. Concurrent veliparib did not improve outcomes compared to gemcitabine and cisplatin alone, and increased hematologic toxicities were noted in the group that received triple therapy.

In an alternate approach, the Pancreas Cancer Olaparib Ongoing (POLO) trial evaluated the efficacy of PARP inhibition when used sequentially with chemotherapy [1]. This randomized, double-blind, phase III trial investigated olaparib as maintenance therapy among patients with metastatic PDAC and germline *BRCA1/2* mutation without disease progression on first-line platinum-based chemotherapy. The study's primary endpoint of progression-free survival (PFS) was significantly prolonged with olaparib compared to the placebo (7.4 vs 3.8 months; $P = 0.004$). This led to the US Food and Drug Administration's (FDA) approval of olaparib as maintenance therapy in this disease setting, and the POLO trial notably became the first successful phase III trial targeting a specific biomarker in PDAC.

Unfortunately, not all patients with *BRCA1/2* mutation respond to PARP inhibition or platinum-containing regimens, and some who initially respond eventually progress on treatment. Biallelic inactivation of DDR genes occupies a crucial role in PDAC's therapeutic response [21]. BRCA-mutated tumors may also acquire therapeutic resistance through reversion mutations or secondary mutations restoring the BRCA reading frame and thereby functional HR repair [21]. As such, the need for improved biomarkers to predict who will respond to DNA damage agents is apparent.

Current markers to identify patients who may benefit from these therapies are defined by genomic hallmarks such as an unstable genome, single-base signature 3, and HRDetect score [16,22,23]. However, emerging data suggest that these modalities testing germline alterations do not wholly capture patients with an elevated HRD score. Parallel somatic profiling identified an additional 10% of patients who exhibit a BRCA-like phenotype with an elevated HRD score, expanding those who may benefit from DNA damage agents [21]. Improved predictive biomarkers may also

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help define patients beyond those with germline *BRCA1/2* mutations who may respond to other DDR inhibitors, including *ATM*, *ATR*, *WEEI*, and *CHK2* inhibitors, which are currently under clinical evaluation [24].

Recent evidence suggests that accumulated DNA damage from DDR deficiency also induces changes in the tumor microenvironment (TME) that may affect therapeutic response. The PD-1/PD-L1 axis, a target for immune checkpoint blockade, is upregulated by DSBs or PARP inhibition in cancer cells [25,26]. DNA damage also activates immune signaling by introducing genomic double-stranded DNA (dsDNA) into the cytosol and inducing the cGAS/STING signaling pathway [27]. Cytosolic cGAS activates STING along with downstream effectors interferon regulatory factor 3, nuclear factor κB, and STAT6 signaling to induce a type I interferon inflammatory response. In a *BRCA1*-deficient breast cancer model, treatment with PARP inhibition *in vivo* augmented DNA damage and the cGAS/STING pathway, increasing intratumoral CD8+ T-cell infiltration [28]. This led to the combination of DDR inhibitors with immunotherapy in multiple clinical trials [29,30].

A small but significant group of patients with PDAC (1–2%) exhibit defects in mismatch repair (MMR), another pathway for DNA repair. Defects in one of four MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) leads to dysfunctional identification and repair of mismatched DNA base pairs. Unrepaired replicative errors in repetitive DNA sequences, called microsatellites, increase levels of microsatellite instability (MSI-H) among patients with biallelic inactivation of DDR genes, as in Lynch syndrome, and in MSI-H tumors [2]. Elevated tumor mutational burden in MSI-H tumors results in higher neoantigen expression, enhancing tumor immunogenicity and rendering tumors susceptible to immune checkpoint blockade (ICB). As a result, inhibiting PD-1 in tumors with MMR deficiency (dMMR)/MSI-h significantly improved outcomes.

In 2017, the FDA approved pembrolizumab for dMMR/MSI-H PDAC following the phase II KEYNOTE-158 study, which demonstrated a PFS of 4.1 months and OS of 23.5 months [2].

Oncogenic *KRAS* Mutations

Given its mutational frequency and role in tumorigenesis, *KRAS* is a promising therapeutic avenue in PDAC. Until recently, targeting oncogenic *KRAS* directly has proven particularly challenging due to the RAS protein's lack of druggable pockets to which small molecule inhibitors can directly bind [31]. However, a shallow pocket within the $KRAS^{G12C}$ mutant allele has recently been identified, leading to the first selective $KRAS^{G12C}$ inhibitor [32]. Although most PDAC tumors harbor mutations at G12D (40%) or G12V (33%), the significant responses seen with non-small cell lung carcinoma and the $KRAS^{G12C}$inhibitor sotorasib demonstrate the gene's potential as a therapeutic target [32,33]. Early-phase clinical reports in the 1–2% of PDAC patients harboring $KRAS^{G12C}$ mutations are promising. Sotorasib's success depends on a stable covalent bond with the mutant cysteine component unique to $KRAS^{G12C}$ [32]. Efforts are under way to develop direct inhibitors against other *KRAS* variants [33].

Downstream of *KRAS*, activation of the RAF/MEK/ERK pathway contributes to PDAC proliferation, and previous efforts targeting this signaling have been largely unsuccessful due to pathway reactivation by a complex network of feedback loops [33,34]. However, several MEK inhibitors combined with novel inhibitors are currently delivering promising results. One exciting strategy targets the protein-tyrosine phosphatase SHP2, which is critical to KRAS activation by regulating SOS1-dependent RAS-GTP loading [35]. In preclinical studies, SHP2 and MEK inhibition prevented adaptive resistance in multiple cancer models expressing mutant *KRAS* [36]. Consequently, SHP2 inhibitors are under investigation in phase I clinical trials. The small molecule SOS1 inhibitor BI-3406 also decreases RAS-GTP loading, thereby attenuating feedback reactivation by MEK inhibition [35]. When combined, BI-3406 and trametinib caused tumor regression in *KRAS*-mutated mouse models, leading to testing in phase I clinical trials.

In addition to downstream effectors, KRAS-dependent metabolic targets such as autophagy present a therapeutic target. *KRAS*-mutant tumors with upregulated cellular proliferation meet increased nutritional demands with elevated levels of autophagy [33]. Preclinical models demonstrated that autophagy inhibition synergizes with MEK inhibition to suppress PDAC growth, and this combination is being studied in phase I clinical trials [37].

Transcriptional Subtypes and Epigenetic Heterogeneity

Parallel to deciphering genomic mutations driving PDAC, the transcriptomic landscape has also emerged as a key contributor to PDAC heterogeneity. In 2011, Collisson et al. analyzed differential expression of 62 genes to first report three transcriptomic subtypes with prognostic significance: classical, quasimesenchymal, and exocrine-like [6]. Later, Moffitt et al. recognized the

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complex nature of the TME, role of desmoplastic stroma, and variability in malignant epithelial cellularity [8]. They analyzed whole transcriptomes to describe two subtypes, basal and classical, where basal tumors resemble the quasimesenchymal subtype proposed by Collisson et al. Since then, multiple studies have validated the basal and classical subtypes in both primary and metastatic tumor samples [17]. Basal-like tumors are associated with worse prognosis, higher pathologic grade, and poorer chemotherapy response compared to classical tumors [5,10].

To analyze molecular subtype in the clinical setting, immunohistochemistry markers distinguish between transcriptional subtypes. Basal-like tumors display elevated nuclear GLI1 and KRT17 while GATA6 expression identifies classical tumors [10,38,39]. However, recent findings reveal that while bulk tumors classify as basal-like or classical, varying proportions of these cells at the single cell level place tumors along a continuum between the two subtypes [5].

Molecular subtype plasticity has been documented in response to chemotherapy, highlighting a dynamic transcriptional landscape regulated by epigenetic reprogramming [9]. Defining these subtypes identified master regulators of basal-like (e.g., ΔNp63, EZH2) and classical tumors (GATA6-centered regulatory network) [40–42]. Additionally, the epigenetic landscape holds potential as a therapeutic target in PDAC. Dhara et al. recently isolated malignant epithelial cells from 54 treatment-naïve, resected tumors to describe a tumor cell-intrinsic epigenetic signature [43]. This signature correlated with up to a seven-fold improvement in disease-free survival (DFS), and over 700 putative gene-regulatory elements were silenced in patients with poor prognosis after resection and adjuvant gemcitabine/abraxane. In light of these discoveries, efforts to define clinically relevant transcriptional and epigenetic subtypes seek to determine potential targets at these new levels of molecular profiling.

Precision Medicine for Pancreatic Cancer

The past decade's genomic and transcriptomic analyses identifying biologically significant PDAC subtypes have built the foundation for larger studies examining real-time feasibility and the clinical benefit of molecular profiling. These multidisciplinary studies (e.g., IMPaCT, COMPASS, PancSeq, Know Your Tumor) rapidly returned results to clinicians (<30 days) with feasibility >90% in most cases [11,12,14,44]. This suggests that prospective molecular profiling can produce therapeutically relevant results within the time frame to aid clinical decision making.

In these studies, actionable genetic alterations were identified in 26–48% of patients, although the number and criteria used to define these targets varied [11,12,14,44]. On a larger scale, the Know Your Tumor program examined 677 patients and uncovered actionable mutations in 189 [14]. Of these, 46 (24%) received matched therapy guided by genomic results while 488 patients (72%) did not. Although the number of patients who received matched therapy was small, they experienced significantly longer survival compared to those without actionable genetic alterations (2.58 years vs 1.32 years; $P < 0.0001$).

Executing molecular profiling, efficient turnaround of results, and application guiding therapeutic decisions require coordination across multiple disciplines. Several challenges facing the implementation of precision medicine in PDAC are discussed later in this chapter along with the role of platform trials, such as Precision Promise, in breaking down these barriers. Despite the challenges, these studies indicate that molecular analysis to target genomic alterations is both attainable and critical in improving outcomes among patients with PDAC (Fig. 152.1).

With increased genomic profiling and the development of therapeutic agents, molecularly targeted therapy for PDAC has grown over the last several years and established several exciting therapeutics in the clinical setting. As previously discussed, olaparib is approved for maintenance therapy for patients with *BRCA1/*2 mutation following the POLO trial, and the KEYNOTE-158 study proved pembrolizumab's benefit in MSI-H tumors [1,2]. Tumors harboring neurotrophin receptor kinase (NTRK) gene fusions are now targeted by the TRK inhibitors larotrectinib and entrectinib (FDA approved in 2018 and 2019, respectively) [45,46]. More recently, a phase I/II study demonstrated significant radiologic regression when *NRG1*+ tumors were treated with zenocutuzumab [47]. Although current opportunities for therapy benefit a fraction of patients with PDAC (Table 152.1), ongoing research continues to identify new targets against this disease.

Challenges to Precision Medicine

Despite numerous studies exemplifying their promise, precision oncology-driven programs face multiple challenges, from identifying actionable results to delivering targeted therapies. These hurdles emphasize that only through a multidisciplinary approach and collaboration can we improve survival among patients with PDAC.

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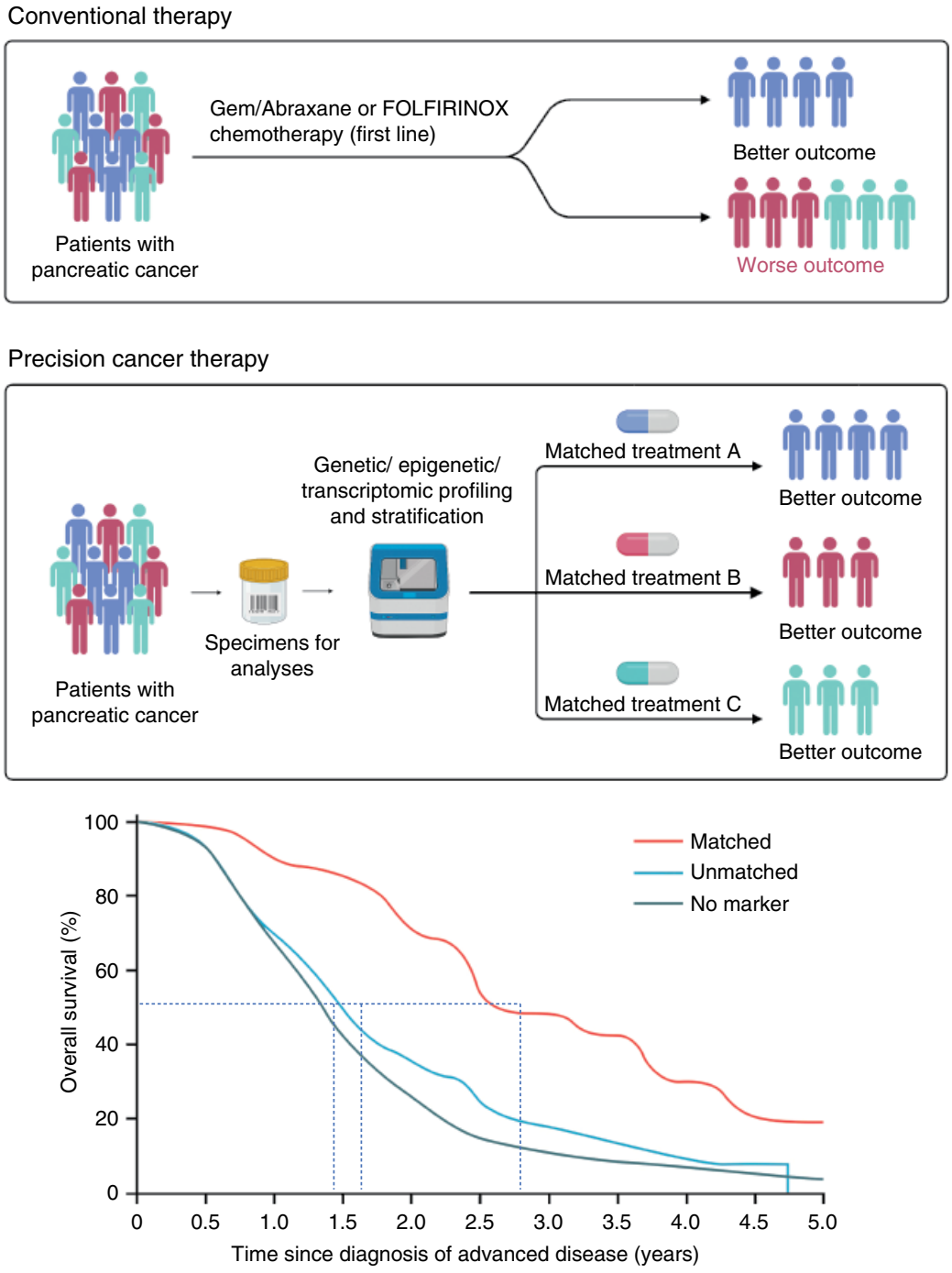


Figure 152.1 Precision medicine in pancreatic cancer. (Top) Schematic diagram comparing traditional and precision medicine in patients with PDAC. (Bottom) Improved survival among patients with PDAC who receive matched therapies via a precision medicine approach.

Tumor Biology

Molecular tests require adequate quantity and quality of tumor tissue to successfully identify tissue-specific markers for targeted therapies. Biopsy via endoscopic ultrasound fine-needle aspiration (EUS-FNA) may not obtain adequate tissue, as data suggest that core needle biopsy is more effective for molecular analysis [12]. Specimens may also not be optimal for genomic testing due to difficult anatomic location for acquisition, low cellularity, and abundant stroma [48]. Additionally, tumor biology challenges the clinical timeline as disease progression demands efficient turnaround for molecular analysis and application.

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Table 152.1 Actionable mutations in PDAC.

Genetic alteration (target)		FDA-approved agents: Agent	FDA-approved agents: Trial	Targeted therapies in clinical trial
DDR	*BRCA1/2*	PARP inhibitor (olaparib), platinum-based chemotherapy	2019, NEJM (POLO trial)	Yes; other PARP inhibitor agents, combination therapy (PARP inhibitor with ICB)
	PALB2	None	–	Yes; other PARP inhibitor agents, combination therapy (PARP inhibitor with ICB)
	ATM	None	–	Yes; novel ATR inhibitors, combination therapy (PARP inhibitor with ICB, PARP inhibitor with AKT inhibitor/WEE1 kinase inhibitor/ATR inhibitor, ATR inhibitor with chemotherapy)
	MMR-d/MSI-h (*MLH1, MSH2, MSH6, PMS2*)	PD-1 inhibitor (pembrolizumab)	2020, JCO (KEYNOTE-158)	Yes; novel ICB agents, combination therapy (ICB with radiation therapy)
KRAS	*G12C*	G12C inhibitor (sotorasib)	2020, NEJM	Yes; other novel G12C inhibitors, combination therapy (G12C inhibitor with ICB/SOS1 inhibitor/SHP2 inhibitor)
NTRK Fusion		TRK inhibitors (larotrectinib, entrectinib)	2020, Lancet Oncology; 2020, Lancet Oncology	No novel agents
NRG1 Fusion		HER2/HER3 inhibitor (zenocutuzumab)	2021, JCO	Yes; other HER2/HER3 inhibitors

ICB, immune checkpoint blockade; DDR, DNA damage repair; MMR-d, mismatch repair deficient; MSI-h, high microsatellite instability.

Access to Precision Medicine

Clinical providers must also be educated on molecular test options, the timing of testing, optimal tissue collection, and actionable results [49]. Molecular tumor boards, composed of clinical personnel and research coordinators, provide guidance in developing and implementing personalized treatment plans. Improving access to these multidisciplinary meetings may represent one strategy to reduce disparities in access to precision oncology. Patient education in precision medicine opportunities is also essential to its success. Access to genetic counseling, given evolving guidelines for germline genetic testing in all PDAC patients, may be challenging in the community setting, and how to optimize patient outreach is still under investigation [50].

Organizational Barriers and Next Steps

As effective precision medicine spans multiple clinical and research entities, program organization poses additional challenges. Precision oncology is implemented primarily at academic tertiary care centers. However, patients treated at these facilities represent only a small fraction as 80% of patients with cancer in the US are treated in the community setting. Additionally, enrollment into precision medicine trials depends on molecular criteria. These challenges have given rise to innovative platform trials, including Precision Promise (US) and PRECISION-Panc (UK), which integrate molecular data from clinical trials to identify therapeutic biomarkers and match an effective treatment plan. Increasing access to these types of clinical trial platforms across the pancreatic community may lead to significant advances in drug development in PDAC.

Conclusion

As its incidence rises, PDAC poses a significant and continued clinical challenge. Hope to improve survival among those affected resides in early detection and more effective treatment. Over the last decade, precision cancer medicine has emerged as a promising avenue, and its application is revolutionizing the approach to PDAC. Recent molecular studies highlight the challenges that PDAC tumor heterogeneity and biology pose. As our understanding grows, it becomes more apparent that PDAC cannot be treated with a single approach. Only through collaborative effort among scientists, clinicians, patients, and community organizations can we expand our understanding of the disease's biology and develop the novel, molecularly driven therapeutics that will be effective in the years to come.

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Palliative Chemotherapy for Advanced Pancreatic Cancer: Treatment Modalities, Side-effects, and Benefits of Survival

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) not only has the worst five-year survival of all common malignancies but also the smallest increase in overall survival during the last 40 years [1]. Surgery can cure some patients with early disease, but most patients are diagnosed with locally irresectable tumors or metastatic disease [2,3]. Current guidelines recommend chemotherapy for every PDAC patient if performance status and comorbidities permit it [4,5]: after curative resection, adjuvant therapy can improve recurrence rate and prolong survival (see Chapter 148). In patients with locally advanced disease, induction chemotherapy may convert the tumor to resectability and therefore still offer a chance for cure (see Chapter 147). In metastatic disease, chemotherapy can improve quality of live and prolong survival.

The unfavorable PDAC prognosis is caused by an aggressive tumor biology with early systemic spread and a relative resistance against systemic therapy. In contrast to some other cancers like seminoma, chemotherapy alone does not offer a chance for cure, and the gained survival benefit is short compared to other cancers like breast cancer or colon cancer. Even with the best currently available chemotherapy, stage IV patients have a median overall survival of less than a year [6]. Immunotherapy, although very successful in many other cancers, has so far been largely ineffective (reviewed in Chapter 150).

Targeted therapy, a very valuable option in many malignancies, has, with a few exceptions, not been successfully used in pancreatic cancer, mainly because about 95% of tumors harbor KRAS mutations that are usually not yet druggable. However, the approval of olaparib as maintenance therapy after platinum-based chemotherapy for patients with germline BRCA mutations [7], the occasional druggable alterations in patients with KRAS wild-type tumors [8], and the development of strategies to inhibit KRAS, e.g., with mutant-specific inhibitors for KRAS G12C [9], offer some hope that there will be further advances soon (reviewed in Chapters 151 and 152). For now, outside clinical trials, classic chemotherapy remains the mainstay of treatment for patients with advanced pancreatic cancer.

First-line Chemotherapy

The first chemotherapy with broader use in pancreatic cancer patients was 5-fluorouracil (5-FU) monotherapy in various dose regimens. Early trials testing combinations with drugs like carmustine, streptozocin, or mitomycin C did not show a consistent survival benefit [10,11]. In a landmark randomized phase III study published in 1997, Burris et al. showed that gemcitabine monotherapy (1000 mg/m^2 weekly for seven weeks, one week of rest, followed by weekly gemcitabine for every three out of four weeks) was superior to weekly 5-FU (600 mg/m^2) in patients with locally advanced or metastatic PDAC [12]. Patients in the gemcitabine arm had a median overall survival of 5.65 months compared to 4.41 months in the 5-FU arm. Gemcitabine treatment also resulted in better quality of life: 23.8% versus 4.8% of patients achieved a "clinical benefit response" that was a composite measurement of pain, Karnofsky performance status, and weight status.

Subsequently, several gemcitabine combinations with different chemotherapeutic partners, including cisplatin, oxaliplatin, and capecitabine, were tested but not found superior to gemcitabine monotherapy in randomized

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phase III trials [13]. Metaanalyses showed a small benefit for gemcitabine combinations with platinum analogues or fluoropyrimidines, especially in patients with good performance status [14–17]. Gemcitabine was also combined with the EGFR tyrosine kinase inhibitor erlotinib in a randomized phase III study with 569 patients with locally advanced, irresectable or metastatic PDAC [18]. Median overall survival (OS) in the gemcitabine plus erlotinib group was statistically significantly longer than in the gemcitabine group (6.24 months vs 5.91 months, $P = 0.38$). The effect of erlotinib was more pronounced in patients who developed the typical skin rash caused by EGFR inhibition. It has been controversially discussed whether the survival benefit is clinically meaningful, especially when quality-of life aspects are also considered, and erlotinib was not included in the control arm of the major subsequent phase III studies (Table 153.1).

Gemcitabine monotherapy remained the standard of care until 2011, when Conroy et al. reported the results of the pivotal randomized phase III ACCORD11/PRODIGE4 study [6]. In this study, 342 patients with stage IV PDAC received either FOLFIRINOX, a combination therapy of bi-weekly oxaliplatin (85 mg/m^2), irinotecan (180 mg/m^2), and 5-FU (400 mg^2 as bolus and 2400 mg/m^2 as continuous infusion) or gemcitabine monotherapy. Median OS was increased from 6.8 months in the gemcitabine group to 11.3 months in the FOLFIRINOX group (hazard ratio for death 0.57, P <0.001). Objective response rate (31.6% vs 9.4%) and one-year survival (48.4% vs 20.6%) also clearly favored the FOLFIRINOX group. The study had strict inclusion criteria and only admitted patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, younger than 76 years, without significant cardiac disease, and with near normal bilirubin. Combination therapy with FOLFIRINOX resulted in a higher rate of grade III/IV toxicities including neutropenia, diarrhea, and peripheral neuropathy. Quality of life was still better in the FOLFIRINOX group than in the gemcitabine group, because FOLFIRINOX better improved cancer-related symptoms and delayed quality of life impairment due to progression [19].

Several groups have reported small studies using modified versions of the FOLFIRINOX protocol, and a modified version of FOLFIRINOX (mFOLFIRINOX) with lower irinotecan dose and omission of the 5-FU bolus has also been used in an adjuvant study [20]. The case series suggest that mFOLFIRINOX is similarly effective as the original protocol [21], and although this has not been proven in a phase III study, mFOLFIRINOX can be considered when there are doubts if a patient is fit enough for the therapy.

Table 153.1 Selected randomized trials of palliative chemotherapy for pancreatic cancer.

Name	Line of treatment	Stage	n	Treatment regimen	Overall survival (months)	*P*-value	References
n.a.	First	II/III/IV	63	Gemcitabine	5.65	0.0025	[12]
			63	Bolus 5-FU	4.41		
NCIC CTC PA.3	First	III/IV	285	Gemcitabine + erlotinib	6.24	0.038	[18]
			284	Gemcitabine	5.91		
PRODIGE 4/ ACCORD 11	First	IV	171	5-FU + irinotecan + oxaliplatin	11.1	<0.001	[6]
			171	Gemcitabine	6.8		
MPACT	First	IV	431	Gemcitabine + nab-paclitaxel	8.5	<0.001	[22]
			430	Gemcitabine	6.7		
CONKO-003 (1)	Second	III/IV	23	Oxaliplatin + 5-FU (OFF)	4.82	0.008	[30]
			23	Best supportive care	2.30		
CONKO-003 (2)	Second	III/IV	76	Oxaliplatin + 5-FU (OFF)	5.9	0.010	[31]
			84	5-FU	3.3		
PANCREOX	Second	III/IV	54	Oxaliplatin + 5-FU (mFOLFOX6)	6.1	0.02	[32]
			54	5-FU	9.9		
NAPOLI-1	Second	IV	117	nal-irinotecan + 5-FU	6.1	0.012	[33]
			151	nal-irinotecan	4.9		
			149	5-FU	4.2		

5-FU, 5-fluorouracil.
Source: Modified from Springfeld et al. [4].

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Finally, in 2013, a positive randomized phase III study was published that demonstrated a superior overall survival with a gemcitabine-based combination chemotherapy versus gemcitabine alone. In the MPACT trial, 861 patients with stage IV PDAC were randomized to receive either gemcitabine (1000 mg/m^2 weekly for three out of four weeks) plus nab-paclitaxel (125 mg/m^2 weekly for three out of four weeks) or gemcitabine alone [22]. Nab-paclitaxel is an albumin-bound, solvent-free, and water-soluble formulation of paclitaxel that does not require antiallergic premedication like previous castor oil-based formulations [23]. Patients had to have a Karnofsky performance status of at least 70% and a normal serum bilirubin level. Combination treatment increased overall survival from 6.7 months to 8.5 months (P <0.001) and objective response rate from 8% to 23% (P <0.001). The addition of nab-paclitaxel increased the rate of grade III/IV neutropenia (38% vs 27%), fatigue (17% vs 7%), and peripheral neuropathy (17% vs 1%).

The choice of first-line chemotherapy depends on the patient's fitness, comorbidities, and preferences. In a recent retrospective European observational study, 35.6% of patients were treated with mFOLFIRINOX, 25.7% with gemcitabine/nab-paclitaxel, and 20.5% with gemcitabine monotherapy [24].

Currently, there is no biomarker used in routine clinical practice that will predict success of a certain chemotherapy in an individual patient, but there is increasing evidence that patients with BRCA mutations should be treated with platinum-based chemotherapy [25–27]. For these patients, very high response rates have also been reported for the combination of cisplatin/gemcitabine [28], but it is uncertain whether this combination should be preferred to FOLFIRINOX. Patients with germline BRCA mutations can also receive olaparib maintenance therapy if there is at least stable disease after four months of platinum-based first-line chemotherapy [7].

Apart from the BRCA mutations, it is now clear that subtypes of pancreatic cancer exist that respond differently to different chemotherapies, and it is likely that predictive biomarkers will be developed in the coming years [29] (see Chapter 152).

Second-line Chemotherapy

After progression under first-line chemotherapy, second-line therapy can be considered provided the patient's performance status is still sufficient. After gemcitabine-based first-line therapy, 5-FU in combination with either oxaliplatin or nanoliposomal irinotecan (nal-irinotecan) can be used.

The CONKO-003 multicenter phase III study first randomized patients with failure of gemcitabine-based therapy to best supportive care or therapy with oxaliplatin and 5-FU [30]. Oxaliplatin (85 mg/m^2) was administered on days 8 and 15 of a six-week cycle, 5-FU (2000 mg/m^2 intravenously over 24h) with leucovorin on days 1, 8, 15, and 22 (OFF protocol). The study had to be terminated early due to slow recruitment, but median OS was increased from 2.30 months to 4.82 months (P = 0.008). After an amendment, the control arm was changed to 5-FU monotherapy [31]. The OFF protocol was also superior to 5-FU with an overall survival of 5.9 vs 3.3 months (P = 0.010). Surprisingly, the combination of oxaliplatin and 5-FU was inferior to 5-FU alone in the Canadian PANCREOX trial that used a different regimen (mFOLFOX6), probably due to increased toxicity in the combination arm [32]. Therefore, if oxaliplatin and 5-FU are used as second-line therapy, the OFF protocol should be preferred.

In the phase III NAPOLI-1 trial, nal-irinotecan and 5-FU (N = 117) were compared to 5-FU alone (N = 149) in stage IV patients with progression under gemcitabine-based first-line therapy [33]. Patients in the nal-irinotecan/5-FU group had a survival of 6.1 months compared to 4.2 months in the 5-FU only group (P = 0.012). Since many patients now receive first-line therapy with gemcitabine plus nab-paclitaxel and therefore suffer from taxane-induced polyneuropathy, nal-irinotecan is often the preferred choice for second-line therapy. For patients not fit enough for second-line combination therapy, 5-FU monotherapy can be considered.

After first-line therapy with FOLFIRINOX, gemcitabine-based second-line chemotherapy is reasonable and most commonly used [24], although there are no randomized trials defining the optimal protocol. In a French prospective cohort with 57 patients receiving second-line gemcitabine plus nab-paclitaxel, a response rate of 17.5% and OS of 8.8 months have been reported [34].

Future Perspectives

Despite some advances in recent years, namely the success of combination chemotherapy regimens and the approval of nab-paclitaxel, nal-irinotecan, and olaparib, the outlook for patients with metastatic pancreatic cancer is still dire. It seems unlikely that significant further progress will be made by novel chemotherapy combinations, but molecular markers predicting the success of currently available chemotherapies might improve outcome and save patients from unnecessary toxicities.

Pancreatic cancer is one of the last cancer entities without approved immunotherapy drugs; novel drugs, combination treatments with chemotherapy or radiation, and insights into the molecular resistance mechanisms

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will hopefully also pave the way for this important treatment modality [35–37]. Targeted therapies that are already improving the prognosis of rare patients with druggable lesions might be extended to more and more subgroups; the early results of the KRAS G12C inhibitors are encouraging, and the development of inhibitors for other KRAS mutations and combination treatments, e.g., with EGFR inhibitors, is under way [38]. Taken together, these advances will hopefully make pancreatic cancer less fearsome in the future.

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Management of Pain in Pancreatic Cancer

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Anatomy and Physiology of Pancreatic Cancer Pain

The pancreas is divided into four main segments as it extends from the midline laterally: the head (including the uncinate process), neck, body, and tail. While pancreatic cancer pain varies by tumor location, extension, and stage, it is typically abdominal, with referral to the epigastric region, upper abdominal quadrants, and less frequently lower abdominal quadrants, or it can be diffuse in nature [1–3]. Back pain in the T10–12 region, often misattributed due to its prevalence in the age group most affected by pancreatic cancer, is not only very common but is also the presenting symptom in many cases [4,5].

Visceral nociceptive signals, generated by tissue damage, inflammation, ductal obstruction, and glandular infiltration associated with pancreatic cancer, are transmitted along afferent sympathetic fibers to the celiac plexus (T12–L2). Here, they synapse with the splanchnic nerves (greater, lesser, and least) on their way to the T5–T12 dorsal root ganglia. Metastatic disease reaching other upper abdominal solid organs shares these pathways. Tumor extension into nonorgan surrounding tissues such as the peritoneum, retroperitoneum, and bones results in localized somatic pain [6]. Neuropathic pain may also be present as the result of perineural invasion (PNI) of cancer cells into the lumbosacral nerve plexuses, intrapancreatic nerve fiber destruction, and epidural spinal cord compression [7,8].

A variety of physiologic factors contribute to the generation and continuation of pancreatic cancer pain. Histologically, pancreatic cancer is characterized by extensive infiltration of inflammatory cells [9]. This inflammatory state, particularly the increased presence of macrophages, is associated with upregulation of nerve growth factor (NGF), the overexpression of which is correlated with both the extent of PNI and pain intensity [10]. Additionally, in the early stages of pancreatic cancer, NGF induces sprouting of calcitonin gene-related peptide (CGRP)-expressing sensory fibers, which increase in density with disease progression [11]. In later stages of disease, the central pancreas, now densely innervated with new sensory fibers, gradually becomes necrotic [12]. This results in the destruction of the distal ends of the sensory and sympathetic nerve fibers that had innervated the now necrotic tissue, resulting in a significant neuropathic pain state.

Pharmacologic Management of Pancreatic Cancer Pain

The principal philosophy behind chronic cancer pain management focuses on maximizing analgesia while minimizing unnecessary risk and patient side-effects. In order to achieve this balance, a gradual, stepwise approach is recommended, beginning with escalating pharmacotherapeutic treatments before progressing to more invasive interventions. The succession is paused for as long as satisfactory pain control is achieved. As 70–80% of cancer patients can be successfully managed with pharmacotherapy alone, analgesic medications, predominantly nonsteroidal antiinflammatory drugs (NSAIDs) and opioids, are considered to be the first line of chronic cancer pain management [13,14].

In 1987, the World Health Organization (WHO) published guidelines for the pharmacologic treatment of cancer pain. These guidelines, updated in 1997 and validated by multiple prospective studies, have served as the foundation upon which cancer pain pharmacotherapy

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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has been based for nearly four decades [15,16]. The guidelines outline a treatment strategy that is based upon five principles.

1) By mouth: Oral (least invasive) administration of analgesic medications should be chosen whenever possible.
2) By the clock: Analgesics should be given at regular intervals, titrated against the patient's pain such that pain is relieved by a given dose and does not return before the next dose is due. Additional rescue dosing may be given for incident and breakthrough pain.
3) By the ladder: Analgesics should be prescribed according to pain intensity as evaluated by a standardized scale.
4) For the individual: While there are toxicity-limited doses for some medications, there are no standard doses for opioid class medications, and doses should be tailored to the individual needs of each patient.
5) Attention to detail: Each patient's medication regimen should be meticulously planned out over a 24-hour period and written out in full for the patient/family.

Principle three, "by the ladder," proposes that the first medication used in the treatment of cancer pain be a nonopioid (Fig. 154.1). Though not specified, "nonopioid" has been interpreted to mean acetaminophen, acetylsalicylic acid (ASA), or an NSAID. These medications have the advantage of being widely available, familiar to patients, efficacious for a wide variety of etiologies, and easy to administer. Disadvantages include adverse side-effects such as hepatotoxicity with acetaminophen and gastrointestinal bleeding and renal toxicity with NSAIDs. The latter two can largely be avoided with the use of selective cyclooxygenase (COX)-2 inhibitors.

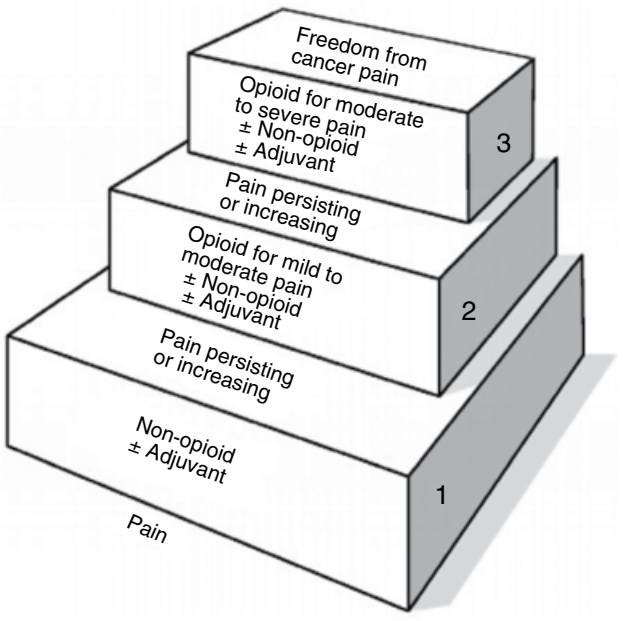


Figure 154.1 WHO pain ladder.

If pain is not adequately controlled with one of these medications, an opioid for mild to moderate pain should be added. This step has been controversial, as disagreement exists as to whether the addition of a "weak" opioid (with "ceiling" effects) to an NSAID decreases the necessary dose of either medication. The utility of this step seems to exist when either the ceiling effect or maximum safe dose of the nonopioid medication has been reached. If satisfactory pain control has not been achieved with the addition of a weak opioid, step three recommends the addition of a strong opioid (i.e, morphine, hydromorphone, oxycodone, etc.). The WHO guidelines state that only one drug from each group should be used at the same time.

Despite, or perhaps as a result of, its widespread use, the WHO analgesic ladder has been the source of much debate [17]. Multiple adaptations have been proposed, including elimination of the second step, accounting for acute and chronic noncancer pain, and including a fourth step representing interventional treatments (Fig. 154.2) [18–21]. Though imperfect, when combined with sound clinical judgment, such guidelines can serve as a foundation for the initial management of pancreatic cancer pain.

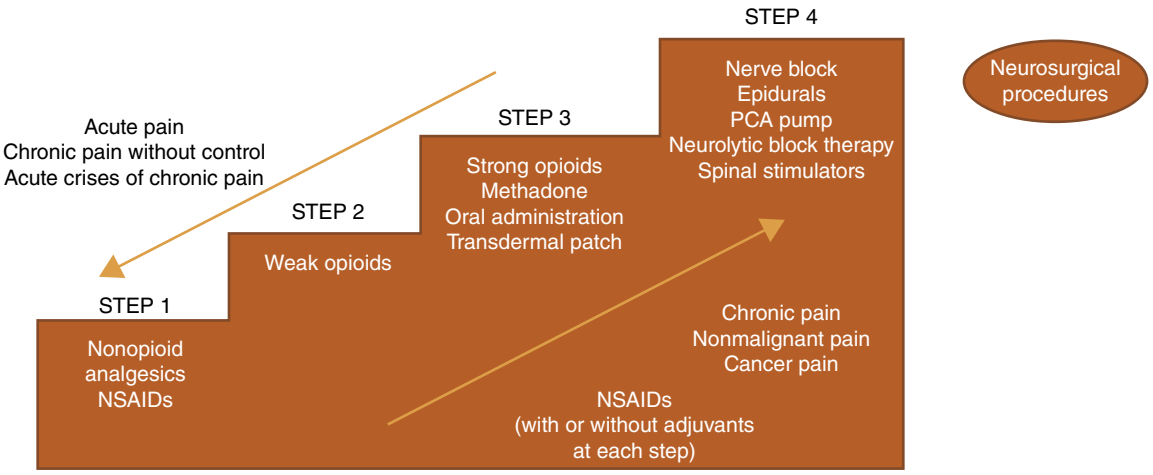
Interventional Management of Pancreatic Cancer Pain

Chemical Ablation of the Splanchnic Nerves or Celiac Plexus

Systemic analgesic therapy, per the WHO guidelines, is widely regarded as the standard of care for treating cancer pain. Unfortunately, not all cancer pain patients will achieve a satisfactory outcome by adhering to this algorithm, which has prompted some to challenge the clinical framework of the WHO guidelines for cancer pain [22]. A subset of patients with unresectable pancreatic cancer will suffer from medically refractory pain or develop intolerable side-effects from opioids, which preclude their continued use. For these patients, a variety of minimally invasive techniques have been developed since the early 20th century, the majority of which involve ablation of either the splanchnic nerves or celiac plexus, as these structures play a key role in the transmission of visceral pain from the pancreas.

A discussion of the various technical approaches to ablate either the splanchnic nerves or celiac plexus is beyond the scope of this chapter. Broadly, however, these

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NSAID, nonsteroidal antiinflammatory drug; PCA, patient-controlled analgesia.

Figure 154.2 New adaptation of the analgesic ladder.

procedures can be subdivided into endoscopic and percutaneous techniques, with the latter consisting of anterior and posterior approaches. A common theme in all of these approaches is image-guided placement of one or more needles in close proximity to the targeted nerves and the use of a neurolytic solution, either phenol or concentrated alcohol. The former destroys nerves via protein denaturation, whereas the latter induces Wallerian degeneration. In either case, the nerves will ultimately regenerate in a process that takes several months. In the interim, patients can experience profound pain relief with a reduced dose of systemic opioids and resultant side-effects.

Regardless of the technical approach, chemical ablation of these nerves tends to be quite effective in the setting of pancreatic malignancy. In the most recent systematic review of the literature by the Cochrane Group, the pooled experimental data on celiac plexus neurolysis reveal statistically significant reductions in reported pain scores, persisting for at least eight weeks post procedure, and markedly reduced overall opioid consumption, persisting until the day before death. As a corollary to the observed reduction in systemic opioid usage, patients randomized to celiac plexus neurolysis tended to experience far fewer opioid-induced side-effects such as constipation. Of note, the overall likelihood of successful neurolysis is variable, but the published success rates generally range from 70% to 90% [23,24].

Although on metaanalysis ablation of the celiac plexus is clearly effective regardless of technical approach, the approach with the highest efficacy and lowest risk of patient harm remains quite controversial, especially with the advent of newer, endoscopic approaches to celiac plexus neurolysis [25–27]. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) may be theoretically safer than posterior percutaneous approaches, as it allows more targeted deposition of neurolytic agent in the vicinity of the celiac ganglia, real-time visualization of arterial vasculature in the targeted areas via Doppler, and a potentially reduced risk of anterior spinal artery syndrome. However, these theoretical advantages have not been definitively established in the literature. Furthermore, an endoscopic approach may be limited in effectiveness if the tumor is encasing the celiac trunk, a situation where a percutaneous splanchnic approach might be preferred.

There are very limited data comparing endoscopic to percutaneous approaches for chronic pancreatitis pain, with available literature showing no difference in pain relief and complications between the two approaches [28]. And there are no experimental data thus far comparing the two approaches for treatment of pancreatic cancer pain. Randomized controlled trials are needed to determine the relative efficacy and safety of endoscopic versus percutaneous approaches in the treatment of severe pain due to pancreatic cancer [26,29].

The indications for chemical ablation of the celiac plexus (or splanchnic nerves) for pancreatic cancer pain are relatively straightforward. Given the palliative efficacy of surgical resection and the risks associated with chemical ablation of the splanchnic nerves or celiac plexus, these procedures have traditionally been reserved for a subset of pancreatic cancer patients with unresectable disease. More specifically, good candidates are patients with neoplasm-related pain that is either unresponsive to systemic analgesic medications or associated with intolerable opioid-induced side-effects [30,31]. Absolute contraindications include uncorrectable coagulopathy, lack of adequate resources for patient resuscitation, and local infection in the anticipated

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trajectory of the needle(s). Markedly impaired cardiac reserve or inability to lie in the prone position are relative contraindications, as these conditions could increase the risk of ischemic or direct chemical injury to the spinal cord, respectively. Another key consideration is anatomic distortion from the pancreatic malignancy. In some cases, the distortion is so pronounced that certain approaches are not feasible. In other cases, severe tumoral invasion or displacement of the celiac plexus may increase the risk of technical failure [32,33]. For this reason, cross-sectional imaging study is recommended prior to the procedure itself.

There are a variety of complications associated with neurolysis of the splanchnic nerves or celiac plexus, but major complications from these procedures are rare. Temporary back pain, abdominal pain, hypotension, and diarrhea are fairly common occurrences, but are generally self-limited and respond quite well to supportive measures. Injury to the kidneys or ureters may occur, which can result in hematuria. Given the close proximity of various approaches to the diaphragmatic crura, pneumothorax is a described complication. There are some case reports in the medical literature of rare complications from celiac plexus neurolysis, including hemorrhagic gastritis/duodenitis, gastroparesis, and aortic dissection. These reported complications are so rare that their actual incidence remains unknown [34–36].

The most feared complication from celiac plexus neurolysis is permanent neurologic injury, with the incidence of permanent paraplegia with posterior approaches being described as 0.15%. Bowel and bladder incontinence can also occur. Although one would expect inadvertent posterior migration of alcohol into the spinal canal to result in permanent neurologic injury, the advent of image guidance has minimized these mechanisms of neurologic injury. Some have posited that the mechanism of neurologic injury stems from alcohol-induced vasospasm of arteries feeding the spinal cord, resulting in infarction of the spinal cord, a theory supported in part by basic science research involving the direct effects of alcohol and local anesthetics on vasomotor tone. If, in fact, neurologic injury from celiac plexus neurolysis stems from a vasospasm phenomenon, this risk would be very difficult to prevent [37–40].

Radiofrequency Ablation of the Splanchnic Nerves or Celiac Plexus

Radiofrequency (RF) ablation of the splanchnic nerves and celiac plexus has been shown to be an effective treatment for chronic abdominal pain in patients with pancreatic cancer, liver cancer, and chronic pancreatitis. RF ablation uses a high-frequency, alternating current to heat tissue around an electrode, inducing focal thermal necrosis. Unlike conventional neurolytic methods with phenol and alcohol, it produces more predictable lesions, which may reduce the risk of inadvertent spread and tissue injury.

Radiofrequency ablation of the bilateral splanchnic nerves was first described by Raj et al, with lesioning performed at 80° C for 90 seconds [41]. Two small studies have since found that percutaneous RF ablation of the splanchnic nerves significantly reduces pain scores for pancreatic cancer pain and chronic pancreatitis for several months [42,43].

An endoscopic approach to RF ablation of the celiac ganglion has recently been described as well. A randomized controlled trial comparing EUS-guided celiac ganglion RF ablation to EUS-CPN showed significantly lower pain scores at four weeks post procedure in the RFA group compared to the CPN group. Mean scores for several quality-of-life measures were also significantly improved in the RFA group after adjusting for baseline pain scores, patient demographics, symptom duration, and chemoradiation therapy. However, there was no significant difference in opioid analgesic use between the two groups at the end of follow-up [44]. Further research is needed comparing RF ablation with traditional chemical ablation of the celiac plexus and splanchnic nerves in the management of pancreatic cancer pain.

Surgical Management of Pancreatic Cancer Pain

Thoracoscopic Splanchnicectomy

Thoracoscopic splanchnicectomy consists of the surgical interruption of the sympathetic chain via a thoracoscopic approach. Kang described 21 patients with unresectable upper abdominal malignancy and pain refractory to opioid analgesics who underwent bilateral thoracoscopic splanchnicectomy [45]. Baseline Karnofsky performance scale was greater than 60, and 71% of patients suffered from pancreatic cancer. Pain scores using a numerical rating scale decreased from an average of 8.5 preoperatively to 1.7 postoperatively, and patients required bilateral chest tubes for an average of three days postoperatively.

In another study, Johnson reported 65 patients (58 with pancreatic cancer) with unresectable upper abdominal malignancy who required opioid analgesia and were randomized to medical management, celiac plexus block, or thoracoscopic splanchnicectomy [46]. In this study, however, no significant differences were appreciated between the groups in pain scores or opioid consumption at two months. Potential limitations of this study

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include a failure to identify the presence of carcinomatosis in patients, use of only a drop in systemic blood pressure to identify successful celiac plexus block, and a change in sample size from a calculated 324 necessary for analysis to only 65 due to slow recruitment.

Intrathecal Drug Delivery Systems

Intrathecal drug delivery systems (IDDS, i.e, intrathecal pumps) are an option for the treatment of patients with moderate to severe, chronic, refractory pain. Their use has led to improved quality of life, reduced pain, and increased satisfaction in those who have failed other therapeutic options. IDDS have been shown to provide significant pain relief and statistically significant control of analgesic toxicity in cancer patients in a randomized study when compared with standard analgesic therapy, as well as a trend toward increased survival at six months [47].

The Polyanalgesic Consensus Conference (PACC) of the International Neuromodulation Society offers guidelines on intrathecal drug therapy. Since the initial publication in 2012, an updated best practices guideline on intrathecal drug delivery was published in 2017 [48]. Algorithms for nociceptive and neuropathic pain (cancer pain may involve both) were issued, as were recommendations for starting dose ranges, bolus trial ranges, and maximum daily dose and concentration ranges. Available intrathecal (IT) analgesic medications for infusion include opioids (morphine, hydromorphone, fentanyl, sufentanil), local anesthetics (bupivacaine), clonidine, and ziconotide. IT therapy at the end of life is best weighed against surgical and infectious risk, as well as nursing care of externalized systems for those with a very limited life expectancy. Concentration and daily dose limitations are important to help prevent the development of an intrathecal granuloma at the catheter tip, and these are included in the aforementioned guidelines. Additional potential complications of IT therapy include respiratory depression and peripheral edema.

A detailed discussion of intrathecal drug trialing, surgical implantation, and intrathecal pump programming is beyond the scope of this chapter. Broadly, trialing of IT analgesic medications has been described by both bolus dosing and continuous infusion, although some have argued a bolus trial is less representative of the long-term effects of IT therapy [49]. Decrease in pain score by greater than or equal to 50% is a commonly used criterion for success of the trial. There exists debate regarding whether to continue, decrease, or eliminate existing systemic opioids prior to and during IT trial. Typically, catheter trials may last between three and seven days, placed at a spinal level corresponding to the vicinity of the patient's pain. Trials may consist solely of an opioid, but there is also the practice of adding an adjuvant agent such as bupivacaine and/or clonidine to the trial. Some have advocated for the possibility of foregoing IT trials in cancer patients due to the reported high success rates of IT therapy among cancer patients.

Complications may occur with implantation, pump management, drug reactions, side-effects, device malfunction, and human error in programming or refilling the pump [50]. High concentrations of opioids and high daily doses predispose to the risk of intrathecal granuloma, while the addition of adjuvant agents may lessen the risk by an opioid-sparing effect (although some carry their own risk of granuloma at high doses). Additional risks include infection, respiratory depression, peripheral edema, pump failure, and catheter obstruction or migration.

Ultimately, the use of IDDS is based on an analysis of safety, efficacy, and appropriateness for the patient, with a goal of respect for economic neutrality.

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Management of Cancer Recurrence

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Introduction

Management of pancreatic ductal adenocarcinoma (PDAC) recurrence is a highly relevant topic, because even after complete tumor resection with curative intent and adjuvant therapy, the majority of patients will experience local or systemic tumor recurrence. Most patients eventually die from local, metastatic, or combined tumor recurrences, resulting in median survival and five-year survival rates of only 20–25 months and 20% after resection, respectively [1].

Several factors are thought to contribute to the high failure rate and poor prognosis. The most obvious reason for local recurrence is incomplete tumor resection with positive margins. The introduction of stringent margin assessment revealed substantially higher R1 resections than initially anticipated and published in earlier studies [2–5]. An even more relevant problem is systemic failure with metastatic recurrence, most frequently involving peritoneal carcinomatosis and liver metastases. Undetected micrometastatic disease at the time of resection is responsible for early systemic failure, providing a clear rationale for the administration of systemic neoadjuvant and/or adjuvant therapies. However, results from randomized controlled trials showed that systemic therapy can significantly delay, but not prevent, systemic recurrence (Table 155.1).

With significant improvements in surgical therapy and systemic treatment options, the long-lasting controversy on the role of surgery in resectable PDAC has been resolved [1]. High-volume centers have reported actuarial survival rates after resection and adjuvant therapy of approximately 20% overall and of up to 60% in patient subgroups with a favorable combination of prognostic factors [5–10]. Interestingly, although PDAC recurrence is a highly relevant problem affecting the majority of patients, its management remains poorly studied and highly controversial, and is far from being evidence based. Part of the underlying problem is a certain therapeutic nihilism towards PDAC recurrence that is reflected by the fact that current treatment guidelines do not even clearly endorse structured surveillance programs after resection due to a lack of evidence for effective treatment options or a survival benefit by regular follow-up examinations [11,12].

This chapter gives an overview of current treatment options for PDAC recurrence with a focus on isolated local recurrence. We also give an overview of several aspects that are relevant in this context, including incidence and pattern of recurrence after resection, and the potential value of structured surveillance after resection.

Incidence, Timing, and Pattern of Recurrence

Due to the lack of structured surveillance programs after resection for PDAC, our knowledge of the true incidence, timing, and pattern of PDAC recurrence is limited. The best information stems from randomized controlled trials on resection and adjuvant therapy (see Table 155.1) [13–20], from autopsy series [21,22], and from some observational studies dedicated to the topic of recurrence [23,24].

Data from randomized controlled trials (RCT) give the best reference with respect to the "clinical" pattern of recurrence that we would expect to see based on structured follow-up programs with assessment of patient history, physical examination, cross-sectional imaging (usually

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Table 155.1 Incidence, timing, and pattern of recurrence after potentially curative resection for pancreatic cancer in selected RCTs on adjuvant therapy.

Reference & name of study	Study arms	N	Overall survival (median & survival rates)	Disease-free survival (median & survival rates)	Incidence and pattern of recurrence	Follow-up (median)
Neoptolemos et al. 2004 [13] ESPAC-1	4 × 4 factorial design: • CRT (20 Gy + FU) • Chemotherapy: FU • Chemotherapy + CRT • Observation	73 75 72 69	13.9 months, 5YSR: 7% 21.6 months, 5YSR: 29% 19.9 months, 5YSR: 13% 16.9 months, 5YSR: 11%	Chemotherapy: 15.3 months No chemotherapy: 9.4 months	Local only: 35% Local and systemic: 27% Systemic only: 34%	Survivors: 47 months
Smeenk et al. 2007[a] [14] EORTC 40891 (long-term results)	CRT (40 Gy + FU)	110	21.6 months 5YSR: 25%, 10YSR: 17%	18 months 5YSR: 21%, 10YSR: 16%	Total: 68% Initially local only: 20% Local and systemic: 29% Initially systemic: 48%	Overall: 11.7 years Survivors: 9.8 years
	Observation	108	19.2 months 5YSR: 22%, 10YSR: 18%	14.4 months 5YSR: 20%, 10YSR: 17%	Total: 70% Initially local only: 21% Local and systemic: 30% Initially systemic: 46%	
Oettle et al. 2007 [15] CONKO-001	Gemcitabine	179	22.1 months 2YSR: 47.5%, 5YSR: 22.5%	13.4 months 2YSR: 30.5%, 5YSR: 16.5%	Total: 74.3% Local ± systemic: 34%, systemic only: 56%	53 months
	Observation	175	20.2 months 2YSR: 42%, 5YSR: 11.5%	6.9 months 2YSR: 14.5%, 5YSR: 5.5%	Total: 92.0%	
Ueno et al. 2009 [16] JSAP-02	Gemcitabine	58	22.3 months 2YSR: 48.3%, 5YSR: 23.9%	11.4 months 2YSR: 27.2%	Total: 76% Local: 23%, systemic: liver 30%, peritoneal 18%, other 27%)	60.4 months
	Observation	60	18.4 months 2YSR: 40.0%, 5YSR: 10.6%	5.0 months 2YSR: 16.7%	Total: 88% Local: 32%, systemic: liver 30%, peritoneal 13%, other 23%	
Regine et al. 2008 [17] RTOG 97-04	FU - CRT (FU, 50.4 Gy) - FU	230	16.9 months, 3YSR: 22%	NA	Total: 85.7% Local: 28%, regional: 8%, systemic: 71%	Overall: 1.5 years Survivors: 4.7 years
	Gemcitabine - CRT (FU, 50.4 Gy) - Gemcitabine	221	20.5 months, 3YSR: 31%	NA	Total: 83.3% Local: 23%, regional: 7%, systemic: 71%	
Neoptolemos et al. 2010 [18] ESPAC-3	FU + Folinic acid	551	23.0 months, 2YSR: 48.1%	14.1 months, 2YSR: 30.7%	Total: 63% (local, systemic, or both)	Survivors: 34.2 months
	Gemcitabine	537	23.6 months, 2YSR: 49.1%	14.3 months, 2YSR: 29.6%		
Van Laethem et al. 2010[b][19]EORTC-40013-22012/ FFCD-9203/ GERCOR	Gemcitabine (4 cycles)	45	24.4 months, 2YSR: 50.2%	10.9 months	Local only: 24%, local and systemic: 13%, systemic only: 40%	33.3 months 30.7 months
	Gemcitabine, (2 cycles) + Gem.-based CRT	45	24.3 months, 2YSR: 50.6%	11.8 months	Local only: 11%, local and systemic: 20%, systemic only: 42%	
Jones et al. 2019 [20] ESPAC-4	Gemcitabine	366	27.9 months, 5YSR: 17.1%	NA	Total: 65.6% Local: 49.7% Systemic: 40.3% Local and systemic: 10.0%	
	Gemcitabine + Capecitabine	364	30.2 months, 5YSR: 28.0%	NA		

[a] Only T1/2, N0-1a pancreatic or T1-3, N0-1a periampullary cancers included.
[b] Only R0 resections included.
ESPAC, European Study Group for Pancreatic Cancer; EORTC, European Organization for Research and Treatment of Cancer; CONKO, Charité Onkologie; RTOG, Radiation Therapy Oncology Group. YSR, Year survival rate; FU, fluorouracil; NA, data not available.

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contrast-enhanced computed tomography), and serum values of tumor markers, especially carbohydrate antigen (CA) 19-9. The follow-up results of selected clinical trials published since 2000 are summarized in Table 155.1.

Data on disease-free survival from previous RCTs comparing adjuvant therapy with observation show that without adjuvant therapy, more than 50% of patients develop clinically detectable cancer recurrence within 5–10 months [13,15,16], and chemotherapy with gemcitabine or 5-fluorouracil (5-FU) monotherapy can delay this to 11–15 months. The introduction of more aggressive multiagent chemotherapy regimens has been shown to substantially improve disease-free survival rates after curative-intent resections [25–27]. Data from the PRODIGE RCT comparing modified FOLFIRINOX and gemcitabine as adjuvant therapy in patients with resected PDAC show a median disease-free survival of 21.6 months and 12.8 months, respectively [28].

Although the pattern of recurrence of PDAC reported in the literature is somewhat heterogeneous, most studies reported isolated local recurrence rates of 20–35%, while the majority of patients present with systemic disease. The highest local-only recurrence rate of 50% was reported from a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. [20]. The reasons for the differing rates of local and systemic recurrences in the latter studies are unclear as well as the reasons why in patients with systemic disease progression, metastatic spread may be limited in some cases only to the liver, lung or peritoneum, and why other patients develop isolated local recurrences.

Neoadjuvant therapy has become the standard approach in patients with locally advanced PDAC and several RCTs are ongoing to assess its role in borderline and resectable PDAC. Whether neoadjuvant therapy affects the recurrence pattern after resection of PDAC has yet to be elucidated. A recent comprehensive metaanalysis of 26 studies, including 4986 patients, found neoadjuvant therapy to be associated with lower overall weighted locoregional recurrence of 12% compared to 27% after upfront surgery [29].

In summary, the data on recurrence from RCT show that even with modern aggressive adjuvant therapy, most patients develop recurrence within two years after resection. The data also suggest that based on structured surveillance programs, it may be possible to identify a subgroup of 20–50% of patients who first develop isolated local recurrence. While the RCTs and observational clinical studies give us a notion of the clinically detectable pattern of recurrence, the few available autopsy series demonstrate the "true" pathologic pattern of recurrence and the relevance of the sites of recurrence for death. In a Japanese autopsy study of 24 patients who died after resection of pancreatic cancer, 75% had local recurrence, 75% had distant metastases (50% hepatic), and local recurrence was the cause of death in 17% [21]. Another autopsy study in patients with PDAC included 22 patients after resection [22]. At autopsy, three patients (14%) had isolated local recurrence, four (18%) had only metastatic recurrence, and 13 (59%) had both local and systemic recurrence. These autopsy studies confirm that after resection and adjuvant therapy for pancreatic cancer, most patients die of systemic disease, but a subgroup of patients develop and die from isolated (or predominantly) local recurrence.

Surveillance After Resection for Pancreatic Cancer

Current evidence-based clinical guidelines on PDAC therapy do not clearly endorse structured surveillance programs after resection and completion of adjuvant treatment, mainly because there are no available data showing that earlier detection and treatment of recurrence lead to better patient outcomes [11,12]. Population-based or single high-volume center studies from the United States demonstrated no significant survival benefit but increased costs from regular surveillance computed tomography (CT) scans [30,31]. While the German guidelines do not recommend a structured follow-up at all [12], the American NCCN guidelines recommend history and physical examination every 3–6 months for two years, then annually and, as category 2B recommendations (lower-level evidence), CT scans and CA 19-9 measurements every 3–6 months for two years after surgical resection based on the consensus that earlier detection of recurrence may facilitate patient eligibility for investigational studies or other forms of treatment [11].

It has to be acknowledged that such clinical guidelines have to be based on current evidence and have to include socioeconomic considerations and that there is currently little evidence for any of the treatment options for pancreatic cancer recurrence discussed later (Table 155.2). But how should such evidence ever be generated if not based on structured surveillance for early detection of PDAC recurrence? Even with the limitations of cross-sectional imaging and serum levels of tumor markers in detecting metastatic disease known from the primary diagnosis of pancreatic cancer, the aforementioned data from RCTs suggest that a structured follow-up program based on these tools would allow for earlier detection of localized recurrence.

Heye et al. demonstrated that the comparison of sequential follow-up CT scans allows for early detection of local recurrences by observation of subtle but progressive changes at typical predilection sites for perivascular and lymphatic local recurrences (Fig. 155.1) [32]. In an analysis of 940 postoperative follow-up visits of 618

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Table 155.2 Treatment options for recurrent pancreatic cancer.

Treatment	Potential indications	Intention	Comments
Chemotherapy	Systemic recurrence	Palliation	Most frequently used for pancreatic cancer recurrence irrespective of pattern. No evidence based on randomized controlled trial (RCT) in the setting of recurrence. Choice for best regimen has to be based on previous chemotherapy, performance status, etc. (see Chapters 153 & 164). Similar rationale as for neoadjuvant and adjuvant therapy in primary pancreatic cancer. No evidence based on RCT.
In multimodal setting with re-resection	Isolated local recurrence	Medium- to long-term control Potential cure	Data from retrospective studies in selected patients with recurrence available (see Table 155.3b)
Chemoradiation	Isolated local recurrence	Palliation Local control Pain therapy	Preferred for isolated local recurrence in many centers, especially in a setting of unresectable perivascular recurrence. No evidence from RCT. Data from retrospective studies in selected patients with recurrence available (see Table 155.3a)
In multimodal setting with re-resection	Isolated local recurrence	Medium- to long-term control Potential "cure"	May be used in a "neoadjuvant" setting and in a multimodal concept involving external and intraoperative radiotherapy. Data from observational studies in selected patients with recurrence available (see Table 155.3b)
Surgery • *Local re-resection* In multimodal setting with chemotherapy or chemoradiation	Isolated local recurrence	Medium- to long-term control Potential "cure"	Performed by only a few specialized surgical centers. No evidence from RCT. Data from retrospective studies in selected patients with recurrence available (see Table 155.3b)
• *Metastasectomy* In combination with chemotherapy	Oligometastatic systemic recurrence	Medium- to long-term control	Literature restricted to case reports and small retrospective studies with mixed cohorts including synchronous metastases. Several small series with favorable survival after resection of isolated lung metastases.
Locally ablative therapies	Isolated local recurrence (in combination with chemotherapy)	Palliation Local control	Different modalities (radiofrequency ablation, irreversible electroporation, etc.) are currently evaluated in some centers. Literature restricted to case reports and retrospective studies with mixed cohorts of primarily unresectable tumors and local recurrences.

patients over a one-year period, recurrence was detected in 74 (40%) of 184 patients after PDAC resection, of whom only 26% had symptoms [33]. In all of these patients, cancer-directed therapy was initiated. Of 16 patients with isolated local recurrence, 12 (75%) were without symptoms and 11 were referred for re-resection.

These data have important implications, because they show that most recurrences are at first asymptomatic but will be detected earlier with regular surveillance including cross-sectional imaging, offering the opportunity for earlier initiation of oncologic therapy. In line with the latter data, Halle-Smith recently published a systematic review and metaanalysis on the clinical benefit of surveillance after PDAC resection [34]. Metaanalysis of five studies including 1596 patients showed that patients with active surveillance programs were more likely to have recurrence detected at an asymptomatic stage. These asymptomatic patients were more likely to receive treatment for

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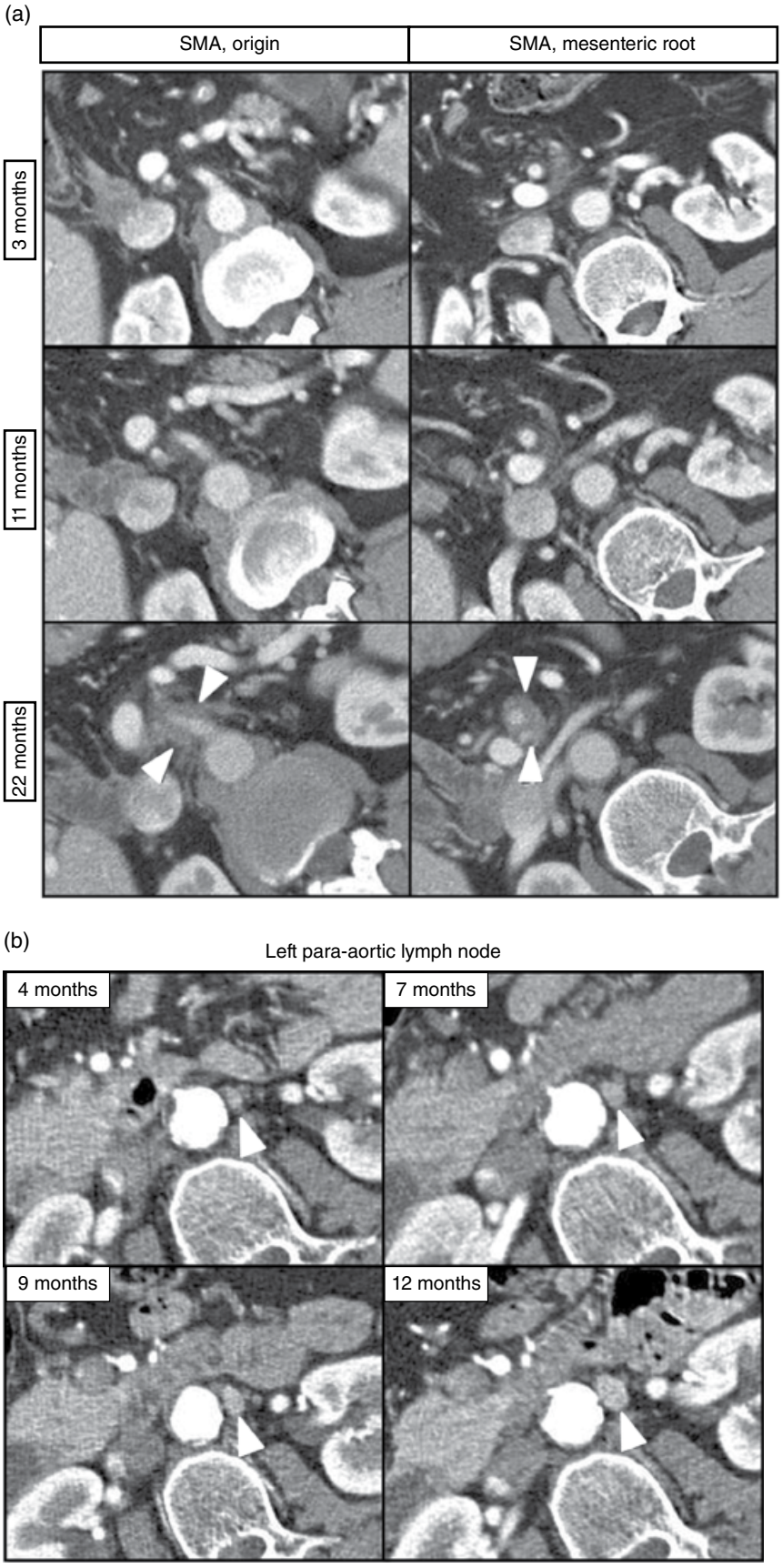


Figure 155.1 Typical findings of local recurrence during sequential CT scans for surveillance after pancreatic resection for cancer. (a) Perivascular recurrence around the superior mesenteric artery (SMA) at different time points after pancreatoduodenectomy for pT3pN1 adenocarcinoma in a 69-year-old patient. Unsuspicious findings after three months, gentle density around the SMA at 11 months, development of dense tissue encasing the SMA as evidence of recurrence after 22 months. (b) Lymph node recurrence in a left para-aorticlymph node at different time points after pancreatic left resection for cancer. Gradual increase in lymph node size from 9 mm at four months to 16 mm at 12 months. Source: Modified from Heye et al. 2011 [32]. Reproduced with permission of Baishideng Publishing Group.

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recurrence and had longer overall survival than those with symptoms at time of recurrence.

With advances in treatment options and diagnostic tools, the potential of structured surveillance programs will have to be reevaluated in the future. Novel analytic targets such as exosomal markers and cell-free DNA that are currently being evaluated in the early detection of PDAC may also be promising tools for postresection surveillance [35,36].

Treatment of Systemic Recurrence of Pancreatic Cancer

The treatment options for systemic recurrence of PDAC after resection are based on little evidence. The literature is restricted to mostly small retrospective studies in selected patients and multiple case reports, suggesting a considerable publication bias. Table 155.2 provides an overview of the available armamentarium for treatment of systemic PDAC recurrence. Based on common sense, the appropriate treatment options depend on multiple parameters, including the pattern and localization of recurrence, the clinical performance status and comorbidity of the patient, previous treatment, and timing (i.e., interval between resection and recurrence).

Clearly, systemic chemotherapy is the appropriate palliative therapy for the majority of patients with systemic PDAC recurrence, because they present with systemic disease. There is little evidence from the literature as to the best regimen in this situation. However, this is a palliative situation and depending on the time of recurrence (during or after adjuvant therapy), previous therapy, and performance status, the same principles as outlined for second-line adjuvant and palliative chemotherapy (Chapters 148 and 153) may be recommended. While metastastectomy for systemic PDAC recurrence is highly controversial, favorable survival has consistently been reported after resection of the rare cases of isolated lung metastases [37–39]. With respect to quality of life, adequate pain therapy and supportive care are very important aspects of palliative therapy in patients with PDAC recurrence (Chapter 154).

Treatment of Isolated Local Recurrence of Pancreatic Cancer

While the current NCCN guidelines recommend inclusion in a clinical trial (preferred), chemoradiation (if not previously performed), switch to an alternative systemic chemotherapy, or best supportive care for local recurrence [11], the German S3 guidelines recommend the evaluation of local therapy options for isolated local recurrence based on the retrospective studies available [12]. Available treatment options for local recurrences include chemoradiation, re-resection, and locally ablative therapies (see Table 155.2). In the following, we will focus on chemoradiation and re-resection. Data on feasibility, safety, efficacy, and long-term outcome of locally ablative therapies for local recurrence are limited and include mostly single-center series of small sample sizes [40].

Rationale for "Local" Therapy Options

Pancreatic ductal adenocarcinoma is a systemic disease and most patients will eventually die from metastatic disease. This notion has led to a long-lasting debate as to the value of resection even in resectable PDAC. Based on good evidence and with advances in both surgery and systemic therapy, resection in combination with systemic therapy has now been established as the only therapy with the potential for long-term survival or cure [1]. With further advances, the limits for surgery are today being pushed towards extended resections and resections after aggressive neoadjuvant therapies, with promising results for locally advanced PDAC [27,41,42]. Strategies of neoadjuvant treatment have the advantage that patients with early systemic progression who will have no benefit of surgical resection are selected out before surgery. Together with the pattern of recurrence and survival, data from molecular studies suggest that patients with isolated local recurrence may have biologically distinct PDAC subtypes of a less aggressive phenotype with slower systemic progression [22,43].

Groot et al. analyzed the pattern of disease recurrence after pancreatectomy in 877 patients from a single-center cohort. Six-hundred sixty-two (76%) of the 877 patients had disease recurrence [44]. Patients with multiple-site (4.7 months) or liver-only (7.2 months) recurrence had significantly worse median survival after recurrence compared to patients with lung- (15.4 months) or local-only (9.7 months) recurrence [44]. This notion provides a good rationale to test localized treatments such as re-resection and chemoradiation in this biologically selected subgroup of patients. However, the majority of patients presenting with suspected isolated local recurrence may also have micrometastatic disease and develop systemic progression later. Therefore, as for primary pancreatic cancer, local therapies for recurrence have to be embedded in multimodal treatment strategies that include systemic chemotherapy.

Chemoradiation for Isolated Local Recurrence

Chemoradiation is discussed by many as the main alternative to merely palliative chemotherapy for treatment of local recurrence. The evidence for chemoradiation is based on retrospective series of limited size (Table 155.3a). The actuarial overall median survival reported for chemoradiation is around 16–18 months,

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Table 155.3a Retrospective series of chemoradiation for local recurrence of pancreatic cancer.

Author	Year	N	Radiotherapy	Chemotherapy	Oncologic outcomes
Wilkowski [48]	2006	18	45 Gy	5-FU (N = 4) 5-FU, Gem (N = 6) Cis, Gem (N = 8)	OS: 17.5 months PFS: 14.7 months CR: N = 6 (33%)
Wild [47]	2013	18[a]	SBRT 25 (20–27) Gy	28% (N = 5)	OS: 8.8 months
Habermehl [45]	2013	41	39.6–54 Gy + IORT (15 Gy) in N = 15	Gem (90%) 5-FU or Cap (10%)	OS: 16.1 months PFS: 6.9 months CR: N = 6 (15%)
Nakamura [46]	2014	30	54 (39–60) Gy	Gem (N = 18) S-1 (N = 7)	OS: 15.9 months PFS: 6.9 months

Included are studies with >5 patients undergoing chemoradiation.
[a] Study includes N = 3 patients after definitive chemoradiation (no resection) for locally advanced disease.
SBRT, stereotactic body radiation therapy; OS, overall survival; PFS, progression-free survival; CR, complete remission (clinical).

Table 155.3b Retrospective series of re-resection for local recurrence of pancreatic cancer.

Author	Year	N operated	N resected	Resection rate	Mortality	Other cancer-directed therapy	Oncologic outcome
Lavu [40]	2011	NA	8	NA	0	NA	OS: 17.5 months
Thomas [39]	2012	NA	7	NA	0	NA[b]	OS: NA[b] DFS: 9 months
Strobel[a] [43]	2013	97	41	42.3%	1 (1.8%)	In cases with re-resection: Chemoradiation: N = 22 IORT: N = 22 Chemotherapy: N = 21 NA: N = 4	Re-resection: OS: 26.0 months Exploration (ILR): OS: 10.8 months Exploration (mets.): OS: 9.4 months
Boone[b] [51]	2014	NA	10	NA	0	NA	OS: 31.8 months
Miyazaki [52]	2014	NA	11	NA	0	Chemotherapy: N = 8 None: N = 3	Re-resection: OS: 25.0 months No re-resection: OS: 9.3 months
Shima [53]	2015	NA	6	NA	0	Chemotherapy: N = 1	OS: 27.5 months
Kim [49]	2019	197	48	24.4%	0	Chemotherapy: N = 35	OS: 14.7 months (all 197 patients) OS: 36.5 months (after resection of isolated lung mets.) OS: 28.0 months (after resection of isolated remnant pancreas recurrence)
Yamada [54]	2018	114	90	78.9%	1 (1.1%)	Chemotherapy: N = 15	OS: 26.0 months

Included are studies with >5 patients undergoing re-resection.
[a] The cohort by Kleeff et al. is from the same center and included in the follow-up study by Strobel et al.
[b] Mixed cohort of local and distant recurrence. Only data of patients with local recurrence included here.
OS, overall survival; DFS, disease-free survival; ILR, isolated local recurrence without evidence of systemic disease confirmed by surgical exploration.

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with median progression-free survival of 6.9 months in the two larger out of four studies [45–48]. A poorer median overall survival of only 8.8 months in the only series with a low reported rate of systemic therapy (28%) [47] supports the notion that any local therapy for recurrence has to be accompanied by systemic chemotherapy in order to achieve favorable survival results. Using stereotactic body radiation therapy in combination with chemotherapy, almost comparable outcomes have been reported with a median survival after stereotactic body radiation therapy of 12–16 months.

Re-resection for Isolated Local Recurrence

Although the evidence for re-resection for the treatment of local PDAC recurrence is mainly based on retrospective series of limited sample size (Table 155.3b) [39,43, 49–54], there is an increasing body of evidence suggesting that resection of isolated local PDAC recurrence can be safely performed and that re-resection may offer a survival benefit compared to palliative treatment in selected patients. The reported outcome with median overall survival rates of 25 to >30 months after re-resection in the most recent series [43,50–54] appears to be superior to the outcome reported after chemoradiation. It should be noted that these differences may in part be explained by selection bias due to the exclusion of patients with radiologically undetected metastatic disease prior to reoperation in the re-resection series. The summarized results demonstrate that re-resection was safe with 0–2% mortality and associated with very encouraging survival outcome at least in the selected patients who underwent re-resection. It should be emphasized that these results originate from specialized referral centers for pancreatic surgery and may not be commonly applicable.

We have reported our initial experience with re-resection of isolated local PDAC recurrence [43]. Analysis in this series allowed for several relevant observations. Of 97 patients with preoperatively suspected isolated local recurrence and histologic proof of recurrence, 57 (59%) had isolated local recurrence by surgical exploration, while distant metastases were identified in 40 (41%) patients. This again highlights the necessity of better diagnostic tools to detect small metastatic deposits, a problem known from primary PDAC staging. Of 57 isolated local recurrences, 41 (72%) were resected while 16 (28%) were locally unresectable. Median postoperative survival was 16.4 months in isolated local recurrence versus 9.4 months in metastatic recurrence, confirming the better prognosis of isolated recurrence that had been described previously [55]. Importantly, median survival in isolated local recurrence was significantly longer after resection (26.0 months) versus exploration for local unresectability (10.8 months). This observation in isolated local recurrence points to a potential survival benefit from re-resection. R0 re-resection was achieved in 18 patients and resulted in 30.5 months median survival. In accordance with our findings, a metaanalysis of surgical treatment for isolated local recurrence of PDAC showed an overall survival almost twice as long in patients with re-resection compared to patients with nonsurgical treatment. The median survival benefit for patients who underwent re-resection was 28.7 months [56].

Groot et al. recently performed a systematic review on the treatment of isolated local recurrence of PDAC after surgical resection and analyzed different treatment options including re-resection, chemotherapy, and stereotactic body radiation therapy (SBRT) [57]. The authors found 18 studies with a total of 313 patients. Comparison of the three different treatment options of isolated local recurrence showed median survival of 32, 19, and 16 months after re-resection, chemoradiotherapy, and SBRT, respectively.

While a true benefit of re-resection can only be demonstrated by RCT, these results suggest that selected patients with suspected isolated local PDAC recurrence may benefit from re-resection.

Conclusion

Pancreatic cancer recurrence is a pressing concern affecting the vast majority of patients even after complete tumor resection and completion of systemic therapy. While the majority of patients develop metastatic recurrence, a significant subgroup of patients (20–30%) first develop isolated local recurrence. These patients may have tumors of less aggressive subtypes with slower systemic progression and may therefore benefit from a multimodal treatment strategy that includes local therapy. As most recurrences are at first asymptomatic, structured follow-up programs are needed to identify these patients.

Although the literature provides little evidence with respect to the management of PDAC recurrence, both chemoradiation and surgical re-resection have been suggested to be safe and effective by several retrospective series. The best “standard” management for cancer recurrence can only be determined based on RCT, which will be difficult to conduct for this indication. More likely, the therapy for PDAC recurrence will remain a matter of interdisciplinary, personalized decision making. Novel effective treatments for PDAC therapy and novel biomarkers for early diagnosis will hopefully also advance the fields of surveillance after resection, and result in earlier detection and more effective management of isolated and systemic PDAC recurrence.

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Survival and Late Morbidity after Resection of Pancreatic Cancer

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Introduction

Pancreatic ductal adenocarcinoma (PDA) is the third leading cause of cancer mortality in the US, and is expected to become the second leading cause of cancer-related deaths in the US by 2030 [1]. Advances have been made in the treatment and management of pancreatic cancer. Enhanced diagnostic capabilities, improvements in surgical care, and new oncologic treatment regimens have been widely adopted. These have led to a near two-fold increase in overall five-year survival rates, from 6% to 12% [1,2], over the course of the last decade. A large proportion of this increase in survival can be attributed to the improvement in outcomes for patients following surgical resection, and to adjuvant therapy, which resulted in an increase in five-year postresection survival rates to almost 40%. However, despite these advances, pancreatic cancer remains a challenging disease, characterized by marked resistance to chemotherapy and radiotherapy, underscoring the urgent need for better therapies.

In this chapter, we will review the long-term survival of patients with resected PDA, and examine the oncologic outcome data from key clinical studies in PDA cancer care. We will summarize the literature on delayed post-operative complications of pancreatic resection, looking at pooled data from pancreatic resection for malignant and benign indications.

Survival after Resection for Pancreatic Cancer

Review of key studies involving adjuvant and neoadjuvant therapy in patients with PDA reveals the profound progress that was made during the past few decades in terms of a shift in treatment paradigms. Early large randomized, controlled studies such as ESPAC-1 [3] and CONKO-001 [4] proved the beneficial value of adjuvant therapy compared with observation only. Later studies such as ESPAC-3 [5] and RTOG 9704 [6] have reported postresection median survival of 23.2 months and 20.0 months, respectively. With the utilization of multidrug combination adjuvant therapies in studies such as ESPAC-4 [7], PRODIGE-24 [8], and APACT [9], the accumulating data tend to suggest an improved survival, reaching up to a median overall survival of 54.4 months in the modified FOLFIRINOX arm of the PRODIGE-24 trial. Similarly, early results from the ESPAC-5F [10] neoadjuvant study for borderline resectable tumors show a clear improved survival with neoadjuvant therapy (42% vs 77% one-year survival), with FOLFIRINOX-based treatment yielding the best survival outcomes (87% one-year survival rates).

It is important to note, however, that interpretation of these data needs to be done with caution, as possible confounding factors include strict selection criteria for participation in the study, often excluding patients with aggressive cancers, serious comorbidities, or extreme frailty. It is also important to consider that multidrug therapy is associated with greater toxicity and a higher study dropout rate, thereby possibly enriching the group with healthier participants.

Recurrences typically occur around 13 months after resection for patients who receive adjuvant monotherapy [7], compared to around seven months for patients without therapy [4]. The results of the APACT and PRODIGE-24 studies suggest a longer disease-free period with multidrug adjuvant therapy (16.6 months and 21.6 months, respectively). Unfortunately, these positive results are primarily encountered in patients who manage to complete the full treatment protocol.

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Retrospective single-institutional experiences provide real-world survival data compared to prospective clinical trials, in which study-specific selection biases may be mitigated in part. In a large, single-institution study of 1175 PDAs resected at the Johns Hopkins Hospital (JHH) over 25 years, the median survival was just 18 months; one-year, two-year, three-year, and five-year overall survival rates were 65%, 37%, 27%, and 18%, respectively [11]. More recent data published from the Moffitt Cancer Center, detailing 309 pancreatic cancer patients (2008–2015) [12], show that completion of adjuvant therapy resulted in a median survival of 28 months compared with only 14 months in patients who did not complete adjuvant therapy. Valuable real-world data can also be extracted from an analysis of Surveillance, Epidemiology and End Results (SEER) data. Shi et al. analyzed SEER data on 10 097 pancreatic cancer patients (2004–2016), showing that overall survival in patients receiving adjuvant chemotherapy was 22.0 months and very similarly, survival in patients who received adjuvant chemoradiotherapy was 23.0 months [13].

Neoadjuvant treatment of locally advanced or borderline resectable tumors prior to surgery has been shown to be an effective course of therapy over recent years. The advantages of neoadjuvant therapy include early systemic oncologic treatment, which addresses possible tumor dissemination and micrometastases at an earlier stage; potential tumor downsizing and increased resectability; and providing a functional biologic assessment of tumor response to oncologic therapy, which informs on tumor aggressiveness and helps to select out patients who would not benefit from surgical resection.

Several large randomized studies have assessed neoadjuvant and perioperative chemotherapy in pancreatic cancer. Preliminary results from the ESPAC-5F study [10], assessing neoadjuvant treatment of borderline resectable PDA, indicate that all neoadjuvant treatment arms (gemcitabine + capecitabine/FOLFIRINOX/chemoradiation) resulted in increased survival rates compared with immediate surgery (a surgery first approach). Interestingly, the data seemed to show that FOLFIRINOX neoadjuvant treatment yielded relatively higher survival rates. Data from the PREOPANC study [14], which assessed neoadjuvant gemcitabine and radiation therapy versus upfront surgery followed by gemcitabine-based adjuvant therapy for resectable and borderline tumors, show a small improvement in overall and disease-free survival, increased R0 resection rates and a significant improvement in locoregional control rates in the neoadjuvant arm. These results are concordant with previous, smaller scale studies in which neoadjuvant treatment resulted in R0 resection rates above 90% [15,16].

It is important to acknowledge potential confounding factors when interpreting data from prospective and retrospective neoadjuvant studies. A substantial portion of patients in the intent-to-treat neoadjuvant group fail to undergo resection, due to either disease progression or poor performance status. As a result, the neoadjuvant treatment paradigm enriches the study cohort (i.e., patients undergoing subsequent resection) with more favorable patients. For example, Kurahara et al. have published their results with S-1 or gemcitabine-based neoadjuvant treatment in 165 pancreatic cancer patients (2010–2014) [17]. Survival analysis of the patients who were successfully resected demonstrated a remarkable benefit of neoadjuvant therapy with median overall survival of 53.7 months, compared with just 17.8 months for upfront surgery followed by adjuvant therapy. However, an intention-to-treat analysis revealed no clear differences in overall survival.

In 2016, Christians et al. published results from their retrospective analysis of 69 patients with resectable PDA treated with neoadjuvant chemoradiotherapy from 2009 to 2013 at a single institution [18]. The reported median survival from this relatively small cohort was an impressive 44.9 months for patients who completed the neoadjuvant course and successfully recovered from pancreatic resection. However, the intention-to-treat analysis for the whole cohort was 13.5 months shorter (31.5 months), albeit still impressive. The survival of the nine patients (15%) who failed to advance to surgical resection was just 8.1 months, and on par with patients having advanced disease. Importantly, patients included in this study satisfied strict inclusion criteria of having 'resectable' PDA, which comprised a relatively favorable group compared to large institutional series of patients receiving adjuvant therapy. Similarly, in a prospective study from the Massachusetts General Hospital assessing total neoadjuvant FOLFIRINOX treatment for borderline pancreatic cancer [19], R0 resection rates were 97% among the patients taken to surgery. However, when accounting for the entire patient cohort, including patients who progressed or were found to be unresectable, the R0 resection rate decreased to 65%.

We eagerly await results from ongoing studies, such as the PANDAS-PRODIGE44 (NCT02676349) assessing neoadjuvant treatment with mFOLFIRINOX with or without concomitant chemoradiotherapy, the ALLIANCE A021806 study (NCT04340141) assessing perioperative FOLFIRINOX compared with immediate surgery and adjuvant chemotherapy, and the PREOPANC-2 study assessing total neoadjuvant FOLFIRINOX vs perioperative gemcitabine with chemoradiotherapy.

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How Common are Patients Cured of PDA by Resection?

The survival rates one year following pancreatic resection for PDA are estimated to be in the 75–82% range [11,13,20]. While this suggests surgical resection may not be beneficial for some proportion of cases, there is still no question that surgical intervention provides the best opportunity for long-term survival for many patients. Data from the latest adjuvant and neoadjuvant studies that show median survival durations of over 50 months [8,17] offer hope that biological cure of patients with PDA is realistic and achievable. Several studies shed light on this question with impressive survival outcomes reported out to 10 years and beyond (Table 156.1).

Generally, past studies assessing survival after pancreatic resection for PDA report five-year survival rates around 18–20%. However, more recent studies suggest that the rates are actually closer to 30%, and in some groups up to 40%. The data also indicate that overall survival 10 years after resection is roughly half the five-year survival rate, or 10–14%. The largest study to date on this subject was published by Seppänen et al., where the authors reported on the long-term survival of 853 patients with PDA [21].

While the 10-year survival rate presents a fairly good estimate of cure rate of PDA, the actual rate of true, biological cure (i.e., the permanent lack of imaging and biochemical findings suggestive of cancer) is hard to ascertain. This is mostly because metrics such as five-year survival rate fail to account for late recurrences, which have been shown to occur even after five years following surgery [22,23]. It is also important to note that there are varying interpretations of "cure" from PDA across different stakeholders. While many clinicians use the five-year survival benchmark as a definition for cure, patients and their caretakers prefer to interpret cure as renormalization of life expectancy or the persistent lack of any biological evidence of disease [24]. Therefore, in light of these differences in definitions and viewpoints, clinicians should be mindful when discussing long-term prognosis and PDA cure rates and remember that the meaning of cure may be neither fully understood nor consistent between patients and caretakers.

Prognostic Risk Factors

Prognostic factors are key aspects to any discussion of survival, mainly due to the information they provide regarding the natural history of the disease. When possible, prognostic information can be used to guide treatment decisions. Certain prognostic features have been consistently validated in patients with PDA. However, it is important to note and discuss with patients that these factors make only a partial contribution to estimating long-term survival, and that patients with unfavorable

Table 156.1 Five- and 10-year survival rates for patient with pancreatic cancer after surgical resection.

	Study period	N	Five-year Survival	Ten-year Survival
CONKO-001 (Adjuvant Group)	1998–2004	168	20.7%	12.2%
Shimada et al. [25]	1990–2013	229	17%	10%
Kimura et al. [26]	1988–2012	149	13.40%	3.60%
Ferrone et al. [22]	1985–2006	499	19%	10%
Dusch et al. [27]	1972–2004	360	19.20%	6.10%
Schnelldorfer et al. [28]	1981–2001	357	18%	13%
Adham et al. [23]	1983–2000	30	–	30% of 5 yr survivors had ≥10 yr survival
Riall et al. [29]	1970–1999	564	17%	9%
Paniccia et al. [30]	1998–2002	11 081	–	3.9%
Seppänen et al. [21]	2000–2013	853	22%	14%
Shi et al. [13]	2004–2016	10 097	~23%	
ESPAC-4 [7] (GemCAP Group)	2008–2014	732	28%	
APACT [9] (nab-Paclitaxel/Gem Group)	2014–2018	866	38%	

Gem, gemcitabine; GemCap, gemcitabine/capecitabine.

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features can achieve long survival after resection, just as patients with favorable features may suffer an unfortunate early recurrence and death.

Pathologic features that have been reproducibly found to be associated with worse long-term survival include increased tumor diameter, regional lymph node metastases (including alternative metrics of lymph node burden such as lymph node ratio) [31–37], poorly differentiated histology, positive resection margin, and perineural invasion [29,38–40]. In multivariate models, each of these features was shown to have only modest impact (with associated hazard ratios below 2.0), reflecting their weak prognostic capabilities and their limited utility for treatment-related decisions. Indeed, in a study that contrasted 137 patients with short survival (<12 months, N = 58) and long survival (>30 months, N = 79) after resection for PDA, no pathologic features proved to be significant predictors for the long-term survival group. Interestingly, 65% of the long-term survivors and 17% of the short-term survivors had regional lymph node metastases, respectively [41].

Aside from conventional pathologic features, the only other validated prognostic marker is the serum-based carbohydrate antigen (CA) 19-9. This protein is a secreted sialylated Lewis-A (sialyl Le^A) antigen that is produced in high amounts by pancreatic cancer cells. Elevated postresection levels are associated with early recurrence and worse overall survival [42–44]. In fact, an *ad hoc* analysis of patients enrolled in the RTOG 9704 adjuvant trial [6,42] revealed that a postresection CA 19-9 level >180 U/mL is associated with an adjusted hazard ratio of 3.6 (which is substantially more powerful than conventional pathologic features). This finding has also been replicated in multiple studies [43–46].

Other prognostic and predictive markers include several molecular features of tumors. *BRCA1* and *BRCA2* mutations (and associated mutations resulting in "BRCAness") are associated with improved response to platinum therapy and a sustained response to PARP inhibitor therapy [47–49]. The existence of *KRAS* mutation and its specific subtype has been shown in several studies to be an important predictor of overall survival. For example, wild-type *KRAS* status seems to confer a more favorable prognosis compared to G12D, G12C, and G12V mutants [50,51]. Furthermore, not all KRAS mutations share the same phenotype (e.g., G12R mutation is associated with PI3K pathway impairment [52]), suggesting a possible future role for mutation-specific treatment protocols.

While the clinical benefit of routine complete next-generation sequencing (NGS) of PDA tumors is still being evaluated, data from the Know Your Tumor (KYT) initiative of the Pancreatic Cancer Action Network (PanCAN) strongly suggest that identification of actionable mutations and tailored therapy based on these mutations can improve survival rates in PDA patients. In the KYT study, which assessed patients with metastatic, locally advanced or recurrent pancreatic tumors, researchers identified 189 patients with actionable mutations (i.e., mutations resulting in a unique therapeutic susceptibility). After randomization to standard care versus specific mutation-matched therapy, overall survival in the mutation-matched therapy group was substantially greater than for the control group (2.6 years, 95% confidence interval [CI] 2.4 to not reached, vs 1.5 years, 95% CI 1.3–1.9 years).

Many studies have attempted to identify molecular factors that impact long-term prognosis. However, very few molecular factors have been proven to offer greater accuracy or utility than the clinical, biochemical, and radiologic factors used today. Tatarian et al. [53] noted that cytoplasmic HuR expression was predictive of favorable response to 5-FU therapy based on data from the ESPAC-3 trial [5]. Smith et al. performed a metaanalysis of several immunohistochemical prognostic markers (P16, SMAD4, VEGF, EGFR, bax, and bcl-2) in resected pancreatic cancer patients (11 eligible studies) and found vascular endothelial growth factor (VEGF) to be the most informative prognostic marker [54]. In another multigene signature study, Chen et al. [55] described a prognostic 15-gene signature in early-stage PDA (hazard ratio 3.3) which was also validated in the Stratford cohort [56].

Currently, these findings have not been adopted into routine clinical practice and decision making. Newly emerging technologies, however, present greater hopes in terms of robustness of data, reproducibility, and external validation. A newly evolving potential biomarker is the existence of circulating tumor cells [57] and circulating cell-free tumor DNA [58]. Recent metaanalyses have shown circulating cell-free tumor DNA measurement (of high yield mutations such as KRAS [59,60]) to be a prognostic marker before and after therapy [59,61,62]. Repeated measurement of KRAS expression in circulating cell-free DNA has even been suggested to offer greater value than CA 19-9 in relation to long-term prognosis and response to therapy [63].

Long-term Morbidity

Pancreatic surgery is associated with a high rate of postoperative morbidity. Immense efforts and continuing research have gone into developing ways to minimize and mitigate these early complications (which are detailed elsewhere in this book).

Late morbidity after pancreatic surgery, however, is composed of a quite different set of complications. Naturally, since some of these complications develop as

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very late sequelae of pancreatic or duodenopancreatic resection, most of the data available are derived from patients who have undergone resection for benign or premalignant lesions. The most common late complications that have been observed include gastrectomy-associated complications (e.g., dumping syndrome, bile reflux gastritis, marginal ulcers, bleeding, gastric remnant cancer), biliary-related complications (bile duct strictures, recurrent cholangitis, pyogenic liver abscesses), pancreas-related complications (pancreatic duct strictures, pancreatogenic diabetes mellitus, pancreatic exocrine insufficiency), nonalcoholic fatty liver disease (NAFLD), and incisional hernias.

Gastrectomy-associated Complications

A classic pancreaticoduodenectomy (a Whipple operation which includes a distal gastrectomy) may carry a risk of delayed complications typically associated with a distal gastrectomy (Table 156.2). These include afferent limb syndrome, efferent limb syndrome, bile reflux gastritis, marginal ulcers (associated with bleeding, stricture, or perforation), dumping syndrome, delayed gastric emptying (discussed elsewhere in this book), and gastric remnant cancer.

Some early studies suggested that the rates of reflux gastritis, marginal ulcers, and dumping syndrome may be lower with a pylorus-preserving pancreaticoduodenectomy compared to those with the classic pancreaticoduodenectomy [69,70]. However, other studies have shown no clear difference in the risk for marginal ulcers or bile reflux gastritis [64]. The principle etiology of late afferent limb syndrome after pancreaticoduodenectomy is tumor recurrence, followed by radiation-induced stricture [68] and routine postsurgical adhesions.

The risk of gastric remnant cancer in patients undergoing a Whipple resection for pancreatic adenocarcinoma is extremely small. A recent case series and review of the literature published by the MD Anderson Cancer Center [71] reviewed 11 patients who underwent classic pancreaticoduodenectomy and subsequently developed gastric cancer. The median time to develop gastric cancer was 111.5 months and the overall survival post diagnosis of gastric remnant cancer was 61 months. Although this complication is very rare in patients with pancreatic cancer, data extracted from large cohort studies suggest that the incidence of gastric remnant cancer after gastrectomy for benign causes such as peptic ulcer disease is around 7% [72–74] and the average latency is about 20 years [74]. Most gastric remnant cancers occur at or near the gastroenterostomy, and the cause is believed to be related to the combined reflux of bile and pancreatic secretions. While this complication has been rarely documented after a classic pancreaticoduodenectomy, the purported mechanism of pancreatobiliary reflux is nonetheless exacerbated when the pylorus is resected. The relevance of this complication is likely low with the present survival rates for PDA (roughly 5% of patients, or less, will survive to 20 years), but may become an increasingly common issue for the current generation of hepatopancreaticobiliary surgical trainees as treatments and patient outcomes improve. Data from patients undergoing gastric resections for peptic ulcer disease suggest that endoscopic surveillance should be performed in appropriately selected patients starting five years after their distal gastrectomy [72].

As a case in point, Dr James J. Mezhir (1973–2016) suffered this very fate [75]. He was an accomplished pancreatic surgeon and scientist, and in fact reported the largest series of gastric remnant cancers as a surgical oncology fellow at the Memorial Sloan Kettering Cancer Center [72]. He underwent a pancreaticoduodenectomy as a teenager for the management of non-Hodgkin lymphoma causing bile duct obstruction [75,76]. Sadly, he developed an aggressive gastric remnant cancer 25 years after the index operation, and died after a two-year battle with the disease [75].

Table 156.2 Gastrectomy-associated complications for patients post pancreatoduodenectomy.

Complication	Prevalence
Bile reflux gastritis	11–25% [64,65]
Marginal ulcer	1–9% [64–66]
Perforated ulcer	2.3% [67]
Afferent limb syndrome	13% [68]
Dumping syndrome	10% [69]

Biliary Anastomotic Strictures

Biliary strictures occur in 3–8% of patients following pancreaticoduodenectomy [77-82], with the median time to stricture formation being just over one year. The occurrence of this complication is associated with an increased risk for cholangitis and it is best managed initially, when possible, by nonoperative interventions including endoscopic or percutaneous balloon dilation and deployment of plastic or metal biliary stents [83,84]. Surgical revision is appropriate in cases where these interventions fail (approximately 5–24% of the time). Reported risk factors for biliary strictures include small bile duct diameter at the time of the index resection (<5 mm) [82], preoperative biliary stenting, preoperative radiotherapy, continuous suturing of the anastomosis, postoperative occurrence biliary fistula, and postoperative biliary stenting [77,85,86].

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Pancreatic Anastomotic Strictures

Pancreatic duct strictures after pancreatic anastomosis occur in 2–7% of patients after pancreaticoduodenectomy [81,87,88]. The etiology of these strictures may be benign or neoplastic in nature (e.g., as part of a locoregional recurrence). This complication typically presents as abdominal pain in the setting of pancreatitis, and manifests within 1–4 years after the index operation [87]. Magnetic resonance cholangiopancreatography (MRCP) or computed tomography (CT) can provide visual clues to secure the diagnosis [88]. Pancreatic anastomotic strictures are best managed initially by endoscopic stenting (guided by endoscopic retrograde pancreatography [ERP] or endoscopic ultrasound [EUS]) in selected cases [89–91]. However, a definitive operative revision is at times required. Effective options include a revision of the pancreaticoenterostomy or, more commonly, a lateral pancreaticojejunostomy [88].

Pancreatogenic Diabetes Mellitus

Pancreatogenic diabetes mellitus (type 3c) refers to diabetes mellitus in which the etiologic cause was neither autoimmune nor peripheral insulin resistance, but rather damage or loss of pancreatic tissue. Notably, this form of diabetes is unique in that glucagon (α-cells), pancreatic polypeptide-producing cells, and exocrine acinar cells are also damaged or lost. The development of pancreatogenic diabetes mellitus (pDM) is dependent on many factors, most notably on pancreatic endocrine reserves in the islets of Langerhans. Greater resection volume, history of chronic pancreatitis, and hyperlipidemia appear to be important risk factors for the development of new-onset pDM after pancreatic resection [92,93]. Furthermore, the density of pancreatic β-cells in the islets increases from the pancreatic head towards the pancreatic tail [94,95], which underscores why distal (left-sided) resection is often associated with a greater impact on the pancreatic endocrine reserve. These notions are supported by clinical evidence which indicates that distal pancreatectomy is associated with greater rates of new-onset pDM [92,93,96–98].

Diabetes mellitus and PDA have a close "reverse causality" relationship [99]. While diabetes mellitus has been associated with increased risk for pancreatic cancer, PDA has also been associated with inciting new-onset diabetes mellitus both through pancreatic tissue destruction (type IIIc), as well as through a paraneoplastic phenomenon that results in the inhibition of insulin secretion and the exacerbation of peripheral insulin resistance [100] (type II-like DM).

Table 156.3 shows the reported prevalence of new-onset pDM after pancreatectomy across multiple studies. Exacerbation of existing diabetes is also observed in a large proportion of these patients. Paradoxically, resection of the pancreatic tumor occasionally leads to resolution of DM in a small number of patients (although the etiology is unclear, this may be related to the nearly universal weight loss of 10–15% after pancreatectomy) [101,102]. As the development of DM is very common following pancreatic resection, it is important to discuss it with patients prior to surgery and offer specific guidance and education.

Table 156.3 Prevalence of pancreatogenic diabetes mellitus after pancreatectomy.

	N	Pancreaticoduodenectomy	Distal pancreatectomy
Burkhart et al. [103]	267	New onset: 18% (N = 135) Exacerbation of DM: 48% (N = 44)	New onset: 31% (N = 55) Exacerbation of DM: 26% (N = 23)
Hirata et al. [104]	167	New onset: 22% (N = 58) Exacerbation of DM: 57% (N = 42)	New onset: 27% (N = 33) Exacerbation of DM: 77% (N = 34)
Wu et al. [101]	3914	New onset: 16% (N = 3914)	
Fang et al. [105]	42	New onset: 12% (N = 42)	
White et al. [106]	100	New onset: 11% (N = 79)	New onset: 9.5% (N = 21)
DiNorcia et al. [93]	49		New onset: 37% (N = 38) Exacerbation of DM: 82% (N = 11)
Wu et al. [92]	1410 without DM 570 with DM		New onset: 22% (N = 310) Exacerbation of DM: 60% (N = 173)
Kang et al. [107]	101		New onset: 25% (N = 25)

Percentage of patients with pancreatogenic diabetes mellitus (total study population size in parenthesis).
DM, diabetes mellitus.

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Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency (PEI) has been described as an immediate and long-term complication of pancreatic resection. Though described after any pancreatic resection, exocrine insufficiency is more frequently encountered after pancreaticoduodenectomy [96]. PEI occurs in roughly 30–70% [67,105,108–110] of patients undergoing pancreaticoduodenectomy.

The main mechanism is parenchymal loss of exocrine cells, which is similar to the mechanism of pDM, and in fact, exocrine insufficiency is one of the major criteria used to make the diagnosis of type IIIc DM [99]. Additionally, PEI can occur from failure of pancreatic enzymes to reach the jejunum. Symptoms may include abdominal distention; abdominal pain; pasty, floating and foul-smelling stools; and fat-soluble vitamin deficiency (vitamins A, D, E, and K).

Reported risk factors for postpancreaticoduodenectomy exocrine insufficiency include preoperative pancreatic endocrine impairment, history of chronic pancreatitis, preoperative decreased pancreatic parenchymal thickness, hard gland texture, postoperative imaging showing decreased pancreatic parenchymal thickness and postoperative dilation of the main pancreatic duct [109–112]. The type of pancreatic anastomosis performed has also been suggested in several studies to contribute to PEI occurrence, with pancreaticogastrostomy more commonly associated with PEI than pancreaticojejunostomy [113,114]. However, these findings were not reproduced in the RECOPANC study at 12 months follow-up (though the PEI endpoints were only assessed by questionnaire) [115]. A summary of reported rates and risk factors of pancreatic exocrine insufficiency is provided in Table 156.4. This complication, although not fatal or debilitating, is associated with a significant reduction in quality of life [116].

The treatment of PEI consists of oral pancreatic enzyme replacement with meals. Recommended doses are in the range of 18 000 to 30 000 USP units of lipase per meal. Of note, gastric pH should be maintained above 4.0 to prevent enzyme inactivation by acid [117].

Nonalcoholic Fatty Liver Disease

Increased hepatic fat deposition is a newly reported complication after pancreaticoduodenectomy [118]. In some cases, it can progress to nonalcoholic fatty liver disease (NAFLD). NAFLD attributable to pancreaticoduodenectomy is defined as hepatic steatosis (proven by imaging or histology) without other causes for secondary hepatic fat accumulation, such as significant alcohol intake, steatogenic medications or genetic disorders [119]. As this chronic condition progresses, the functional reserve of the liver diminishes and hepatic insufficiency may ensue [120]. This may assume increased relevance in patients with PDA who receive chemotherapy, which itself carries an independent risk of hepatotoxicity [121,122].

The prevalence of postpancreaticoduodenectomy NAFLD has been estimated at 8–40% [13–126], although the exact mechanism of this complication remains unknown. Sato et al. evaluated postoperative imaging studies in 110 patients who underwent a pancreaticoduodenectomy over a six-month period, and observed that decreased pancreatic volume was associated with NAFLD [125]. Tanaka et al. studied the physical and biochemical profiles in patients with NAFLD after pancreaticoduodenectomy [126]. They noted that unlike patients with conventional nonalcoholic steatohepatitis

Table 156.4 Prevalence of postpancreatectomy pancreatic exocrine insufficiency.

	N	PPPD-PG	PPPD-PJ	Risk factors identified
Lemaire et al. [112]	19	16/17 (94%)		Decreased postoperative pancreatic parenchymal thickness, postoperative dilation of the main pancreatic duct
Rault et al. [113]	33	12/23 (52%)	8/10 (80)%	Type of pancreatic reconstruction (PEI in PG more than PJ)
Fang et al. [105]	42	12/19 (63%)	10/23 (43%)	
Nakamura et al. [109]	61	38/61 (62%)		Preoperative endocrine impairment, hard gland texture, postoperative dilation of the main pancreatic duct
Nakamura et al. [111]	52	34/52 (65%)		Decreased pancreatic parenchymal thickness (preoperative and postoperative)
Hirono et al. [110]	199	59/90 (66%)	38/99 (38%)	Type of pancreatic reconstruction (PEI in PJ > PG), hard gland texture
Roeyen et al. [114]	186	51/68 (75%)	54/118 (46%)	Type of pancreatic reconstruction (PEI in PG more than PJ)

PPPD, pylorus-preserving pancreaticoduodenectomy; PEI, pancreatic exocrine insufficiency; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy.

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(NASH), patients with postpancreaticoduodenectomy, *de novo* NASH demonstrated significant decreases in body mass index and lower levels of serum albumin, cholesterol, and apolipoprotein B, and were noted to have decreased insulin resistance [127]. Since these findings are consistent with PEI, an increased dosage of oral pancreatic enzyme supplements was evaluated as a possible therapy, and the intervention indeed reversed these metabolic derangements in albumin, cholesterol, and lipoprotein levels in a number of patients. Additionally, treatment with increased oral dosing of pancreatic enzyme supplements improved the liver steatosis upon follow-up imaging.

These findings were reproduced by Nagai et al. in a separate study which prospectively treated 30 patients who developed NAFLD post pancreatic resection [128]. Treatment with oral pancreatic enzyme supplements resulted in improvement of liver function, near normalization of NAFLD imaging metrics, and laboratory improvement of total protein, albumin, and total cholesterol levels. Therefore, it may be advisable to initiate or augment oral pancreatic enzyme supplementation in patients with postpancreaticoduodenectomy NAFLD.

Future studies are needed to determine if enzyme supplementation should be recommended indefinitely in all patients (or in those at highest risk) in order to prevent this complication in the long term.

Incisional hernia

Available literature regarding the incidence of incisional hernia post pancreatic surgery is scarce, yet in our experience, the complication is not uncommonly encountered after open pancreatic surgery. In a recently published single-institution analysis of 678 long-term survivors after pancreaticoduodenectomy, the incisional hernia rate was reported to be 17.7% [79]. Similarly, a series of 205 pancreatic resection patients were reported to have an incisional hernia rate of 11.6% [129]. Risk factors for incisional hernia after abdominal surgery include obesity, history of smoking, previous abdominal surgery, and postoperative wound complications [130–132]. The incisional hernia rate following pancreatic resection is expected to improve when minimally invasive approaches like laparoscopic or robotic surgery are utilized [133,134].

Cholangitis and Pyogenic Liver Abscess

Biliary–enteric anastomoses result in chronic colonization of the biliary tract with enteric flora (bactibilia) due to the absence of the sphincter of Oddi. Though this bactibilia is generally of no clinical consequence because of continuous biliary drainage and decompression, there is a reported risk of cholangitis of 8–10% in the setting of biliary–enteric anastomosis [79,135]. Cholangitis, as well as colonized bile ducts, place patients with infarcted, injured, or necrotic liver parenchyma at risk for pyogenic liver abscesses. This can occur due to liver infarction from a retractor injury at the time of pancreaticoduodenectomy, or as a result of parenchymal injury related to liver-directed therapies used to treat hepatic metastases, such as hepatic arterial embolization or ablative procedures. Of note, these therapies are rarely performed for patients with conventional PDA at this time, and are more relevant for patients with metastatic neuroendocrine carcinoma.

In a large study from the Memorial Sloan Kettering Cancer Center, the liver abscess rate in patients undergoing hepatic arterial embolization was 33% for patients with prior biliary–enteric anastomosis, but just 0.05% in other patients [136]. The risk of a liver abscess with any liver directed therapy after pancreaticoduodenectomy was observed to be around 10% in a separate large multi-institution study (137). Patients found to have zones of infarct identified after pancreaticoduodenectomy, either from retractor injury or accessory hepatic arterial ligation, should be vigilantly monitored for potentially life-threatening liver abscesses that can develop with immunosuppression related to adjuvant chemotherapy. Extra caution is necessary for patients who developed liver abscesses in the early postoperative period. Most liver abscesses can be managed effectively with antibiotics and percutaneous drainage if diagnosed in a timely manner.

Conclusion

Long-term survival following pancreatic resection for cancer has slowly improved over the recent decade. However, this progress is most notable in patients with early-stage cancer, amenable to surgical resection that can also complete some form of chemotherapy. The possibility of tumor recurrence persists, even after many years. New treatments with multidrug combination regimens offer improved long-term survival. As more patients experience longer survival, the above-mentioned late complications will become increasingly important. Pancreatic surgeons should be mindful of the rates and risks of each of these complications and discuss them with their patients. Future studies aimed at reducing these risks are needed.

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Section 9

Periampullary Cancers and Tumors Other Than Pancreatic Cancer

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Periampullary Tumors: Clinical Presentation and Diagnostic Strategies

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Introduction

Periampullary tumors include several benign and malignant pathologies arising in proximity to or directly from the ampulla of Vater. Named for its bulbous appearance, the ampulla of Vater is 1–8 mm in length and originates at the confluence of the pancreatic duct of Wirsung and common bile duct before emptying into the second portion of the duodenum at the level of the major papilla [1,2]. The mechanism through which digestive fluids are secreted from the major papilla is regulated by the sphincter of Oddi, a muscular apparatus surrounding the ampulla. Importantly, substantial anatomic variability of these structures does exist and should be considered when evaluating pathology in this anatomic region [1].

Periampullary lesions comprise an important subset of hepatobiliary neoplasms, which often require pancreatoduodenectomy for treatment. From several large pancreatoduodenectomy series, the proximal pancreatic head represented the majority of periampullary tumors (56–66%) followed by the ampulla (16–25%). The distal common bile duct (12–15%) and duodenum (4–6%) were seen at lower frequency in resected specimens (Table 157.1) [3,4]. Relative to pancreatic ductal adenocarcinoma, nonpancreatic periampullary tumors tend to have more favorable prognosis, which is in part due to earlier detection and lower rates of nodal, perineural, and microvascular involvement [5,6].

Notably, ampullary adenocarcinoma has two dominant histologic subtypes: the more common intestinal and the more aggressive pancreatobiliary [7,8]. Important biohistochemical markers of the intestinal type include CDX2 and COX2 and cytokeratins (CK7 and C17) in pancreatobiliary tumors. Mucins (MUC1 and MUC2) are variably expressed in both histologic variants [9].

Inherited Syndromes

Inherited syndromes such as familial adenomatous polyposis syndrome (FAP), Gardner syndrome, Peutz–Jeghers disease, hereditary nonpolyposis colon cancer (HNPCC, formerly Lynch syndrome), and *MUTYH*-associated polyposis (MAP) are associated periampullary adenomas, which importantly can undergo malignant transformation. Periampullary adenocarcinoma is therefore a leading cause of morbidity and mortality in patients with these hereditary conditions [10–12]. Some common mutations and the rates of periampullary malignancy associated with each syndrome are listed in Table 157.2 [13,14]. Notably, only 33–37% of duodenal and ampullary adenocarcinomas harbor a *KRAS* mutation [15].

Upper endoscopic screening begins at a young age for patients with these hereditary syndromes. To prevent the risk of malignant transformation, duodenal and ampullary adenomas are removed if endoscopically feasible (Fig. 157.1) [16]. Larger, sessile, ulcerated, and dysplastic lesions, however, are surgically resected by way of ampullectomy, sleeve/segmental duodenectomy, or pancreatoduodenectomy [17,18].

In addition to the more common polyposis syndromes, patients with neurofibromatosis 1 (NF1) can develop small periampullary somatostatinomas, carcinoids, neural tumors, and GI stromal tumors (GISTs), which are less aggressive and more amenable to local resection than periampullary cancers [19].

Lastly, it is critical to rule out benign causes of obstructive jaundice such as choledocholithiasis, choledochocele, and pancreatic duct stricture from paraduodenal (groove) or autoimmune pancreatitis when evaluating patients for suspected periampullary neoplasms [20,21].

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Table 157.1 Location and relative frequency of periampullary tumors.

Location	Relative frequency
Pancreatic head	60%
Ampulla of Vater	20%
Distal common bile duct	15%
Duodenum	5%

Table 157.2 Hereditary syndromes associated with periampullary neoplasms.

Hereditary syndrome	Gene mutation	Lifetime risk of periampullary malignancy
FAP and Gardner	*APC* (tumor suppressor)	12%
Peutz–Jeghers	*STK11* (tumor suppressor)	13%
HNPCC	*MLH1, MSH2* (DNA mismatch repair)	6%
MAP	*MUTYH* (DNA repair)	5%

HNPCC, hereditary nonpolyposis colon cancer; MAP, *MUTYH*-associated polyposis.

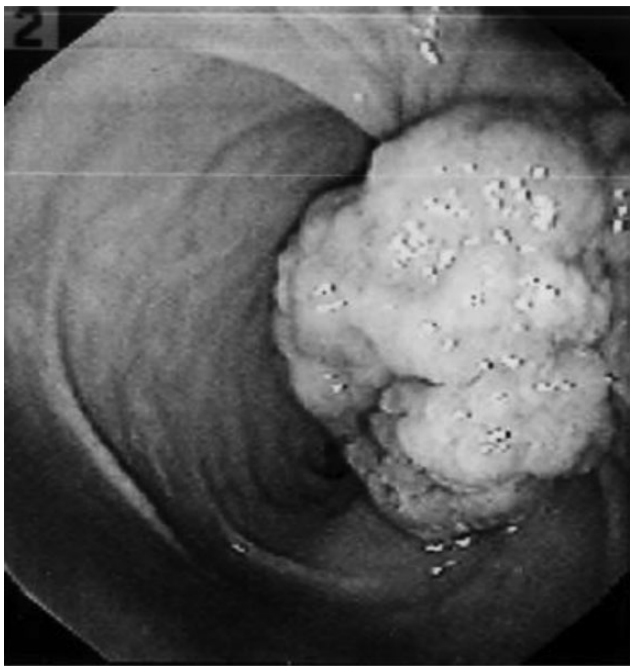


Figure 157.1 Endoscopic view of a periampullary villous adenoma.

Clinical Features

More than two-thirds of patients with periampullary tumors present with painless jaundice and its sequelae, including pruritus, dark urine, and acholic stools [22]. Other clinical findings such as upper gastrointestinal tract bleeding, epigastric pain, early satiety, and gastric outlet obstruction may also be present [23]. Although less common, pancreatitis and steatorrhea from pancreatic insufficiency can lead to fat-soluble vitamin deficiencies and coagulopathy [24,25]. In addition to the stigmata of a jaundice seen on physical exam, Courvoisier's sign and hepatomegaly can also be appreciated.

Laboratory Work-up

Laboratory studies including liver function tests are likely to reveal a hyperbilirubinemia, elevated alkaline phosphatase, and possibly a transaminitis. For patients with hematemesis or melena, anemia may also be present. Prolonged prothrombin time (PT)/international normalized ratio (INR) is another important lab abnormality that may be seen in patients with long-standing biliary obstruction.

Tumor markers including carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) can also aid in the diagnosis and management of periampullary neoplasms. In one large study comparing tumor markers in patients with periampullary tumors, higher CA 19-9 levels correlated with larger tumor size and positive lymph node status. In addition, patients with CA 19-9 levels above 26.6 U/mL had a decreased overall survival (25 months vs 56 months, $P = 0.003$) [26]. Similarly, CEA levels greater than 4.6 ng/mL were associated with decreased overall survival, although this was not statistically significant (25 months vs 43 months, $P = 0.077$). Another study investigating tumor markers in cases of resectable or unresectable periampullary cancer found CA 19-9 to be more sensitive for detecting tumors and predicting unresectable disease than CEA [27]. A final study evaluating tumor markers in ampullary cancers showed that elevated levels of CA 19-9 and CEA were predictive of decreased overall survival in both the intestinal and pancreatobiliary histologic subtypes, but a normal CEA level in intestinal-subtype ampullary cancers had improved survival [28].

It is important to note, however, that biliary obstruction may also produce an elevated CA 19-9 level, and this must be considered during the evaluation of patients with obstructive jaundice [29].

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Diagnostic Modalities

Common diagnostic strategies in the work-up of periampullary tumors include axial imaging and endoscopy. Transabdominal ultrasonography is useful for ruling out cholelithiasis and identifying common bile duct dilation but only has an accuracy of 15% for diagnosing periampullary tumors [30]. By contrast, dual-phase (arterial and venous), thin-cut computed tomography (CT) scan of the abdomen and pelvis or magnetic resonance cholangiopancreatography (MRCP) are more accurate studies for detecting periampullary lesions and have the added benefits of assessing vascular abutment/involvement as well as detecting ascites and metastatic foci (>1 cm) to the liver, omentum, or peritoneum (Fig. 157.2) [31–36].

When determining which imaging modality to utilize, clinicians must be mindful of cost, institutional availability and experience, and the potential for contrast reactions and acute kidney injury.

On imaging, characteristic findings for periampullary tumors include a filling defect at the level of the major papilla and the classic "double-duct" sign, a radiographic feature found in over half of periampullary tumors in which the main pancreatic and common bile duct are

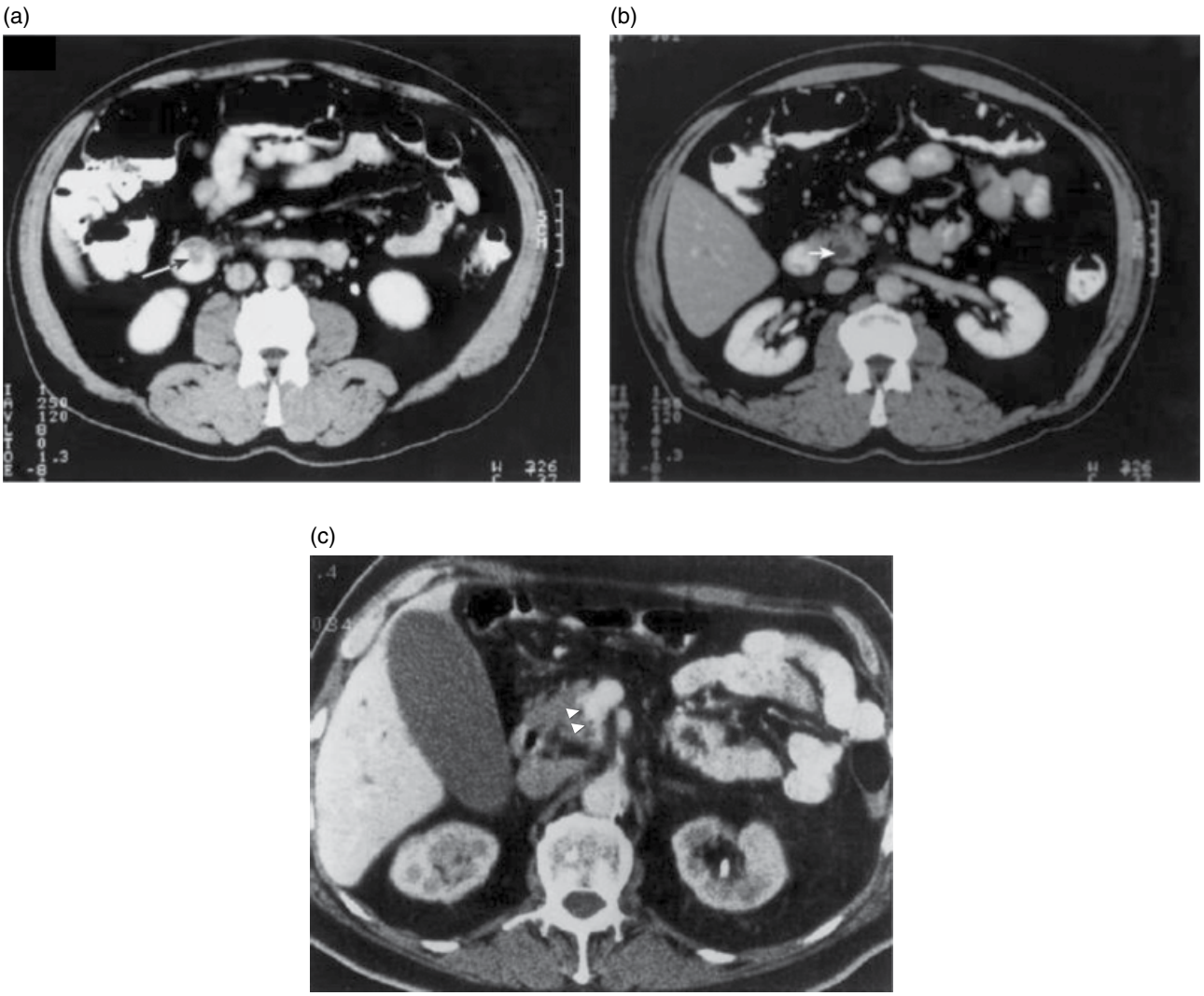


Figure 157.2 CT demonstrating an ampullary carcinoma causing obstructive jaundice. (a) Radiographic appearance of a small ampullary mass. (b) Appearance of distal common bile duct dilation caused by an ampullary lesion. (c) Superior mesenteric vein involvement in addition to abnormal enhancement of the medial border of the head and uncinate process of the pancreas.

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dilated [20,37]. By contrast, isolated common bile duct dilation with an "apple core" appearance may be seen in distal cholangiocarcinoma, whereas a dilated main pancreatic duct with abrupt caliber change is more suggestive of a pancreatic lesion. Note that intrapancreatic lesions can also cause extrinsic compression of the common bile duct and subsequent dilation.

Endoscopic techniques including endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) are other adjuncts used in the work-up of periampullary tumors. EUS is an effective modality for determining tumor (T) and nodal (N) stages as well as vascular invasion in small periampullary lesions [38–42]. Furthermore, tissue sampling either through direct biopsy of mucosal lesions or fine needle aspiration can be performed with this endoscopic technique (Fig. 157.3) [36,43]. EUS findings can also influence clinical management. Specifically, adenomas or mucosal-based (T1) lesions may be candidates for endoscopic or surgical ampullectomy whereas higher tumor stage or tumors with positive lymph nodes should be considered for pancreatoduodenectomy [44–46]. EUS is also valuable for obtaining a tissue diagnosis of cancer prior to initiating neoadjuvant treatment in cases of borderline resectable or locally advanced disease. Importantly, rates of false-negative endoscopic biopsies can be found in up to 25% of patients, and extirpation should be considered to rule out malignancy in an otherwise benign lesion [47,48].

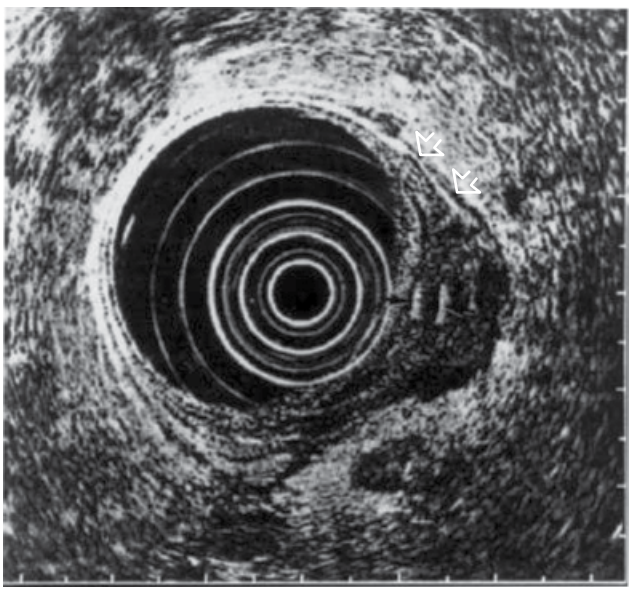


Figure 157.3 EUS of an ampullary tumor, represented by the hypoechoic region on the right. An endoprosthesis (small black arrows) is seen running through the tumor, which infiltrates beyond the muscularis propria (open arrows) and into the pancreas.

Like EUS, ERCP is another endoscopic tool used in the management of periampullary neoplasms. Unlike EUS, however, ERCP allows for characterization of biliary tree anatomy and therapeutic decompression in patients with long-standing biliary obstruction or planned neoadjuvant therapy (Fig. 157.4). ERCP can also be used to perform biopsy or brushings of suspicious or indeterminate biliary strictures. While valuable, surgeons must use ERCP selectively given the increased risk of infectious complications following biliary stenting in addition to the periprocedural risks of pancreatitis, perforation, or hemorrhage, all of which may delay operative intervention or increase operative case complexity [49–51].

In the last decade, another endoscopic adjunct, SpyGlass^{TM} direct visualization cholangioscopy, has been developed and used in the diagnosis of periampullary neoplasms and cholangiocarcinoma. Two studies examined the utility of this emerging technology and found it to be both safe and more efficacious in diagnosing indeterminate biliary strictures compared to conventional ERCP or EUS [52,53]. Additionally, SpyGlass can be used to treat benign biliary pathologies including choledocholithiasis by way of either stone extraction or lithotripsy.

Diagnostic Laparoscopy

While diagnostic laparoscopy has been used in the past for ruling out occult metastatic disease in patients with periampullary tumors, it is less commonly used in contemporary practice [54,55]. Specifically, two studies evaluated the added benefit of laparoscopy for patients with upfront resectable nonpancreatic periampullary lesions but only identified surreptitious metastases in 10% of patients [54,56].

As such, a cost-effective work-up for most patients with a suspected periampullary tumor includes liver function tests, blood counts, serum chemistries, coagulation studies, tumor markers, a dual-phase CT or MRCP, and EUS or ECRP, if tissue diagnosis or biliary stenting is indicated.

Conclusion

In summary, periampullary tumors consist of malignant lesions arising from the head of the pancreas, ampulla of Vater, distal common bile duct, and duodenum. Presenting symptoms include painless jaundice and, in rarer instances, bleeding, gastric outlet obstruction, pancreatitis, and nutritional deficiencies. Further characterization with axial imaging and endoscopic techniques is important for ruling out benign etiologies, establishing

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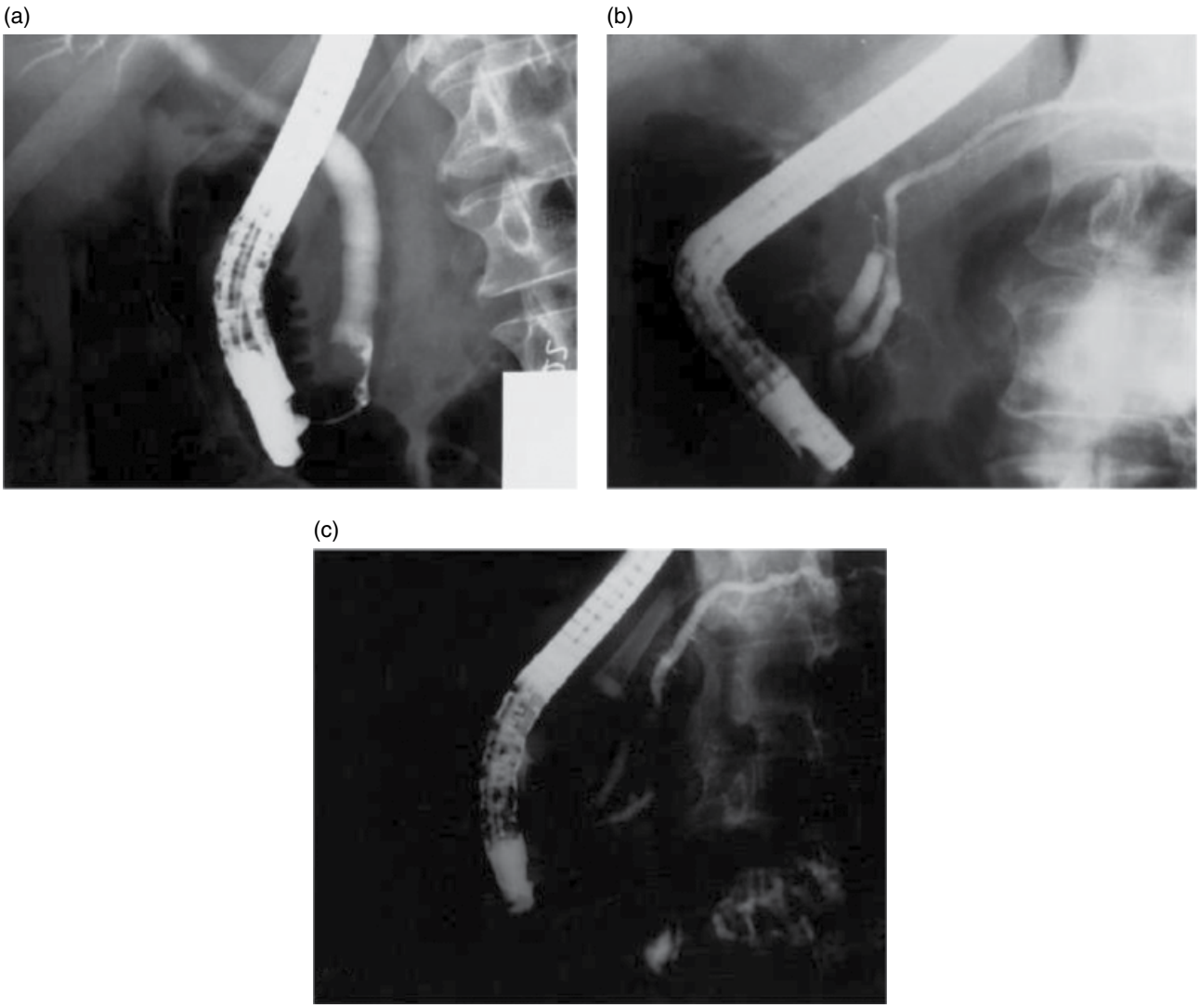


Figure 157.4 ERCP images of three periampullary lesions. (a) A periampullary carcinoma causing obstruction of the distal common bile duct. (b) A distal common bile duct carcinoma with dilated common bile duct and normal-appearing main pancreatic duct. (c) A pancreatic carcinoma, with partial obstruction of the main pancreatic and common bile duct causing a "double-duct" sign.

tissue diagnosis in the setting of preoperative therapy, and providing therapeutic interventions such as biliary stenting. These modalities can also influence clinical decision making and inform providers on whether to pursue a radical or more limited resection of the periampullary lesion.

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Histology and Genetics of Cancer of the Papilla, Distal Common Bile Duct, and Duodenum

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Carcinoma of Papilla (Ampulla of Vater)

The ampulla of Vater is a complex anatomic and histologic structure. Histologically, it consists of four compartments featuring transitional-type epithelia.

- The distal common bile duct (CBD) and pancreatic duct are lined by pancreatobiliary-type epithelium, a simple mucinous epithelium.
- The mucosa of the papilla of Vater (the duodenal protuberance surrounding the ampullary orifice) is covered by a specialized epithelium with features that resemble gastric-foveolar epithelium with scattered goblet cells.
- The duodenal surface of the papilla is virtually identical to the duodenal mucosa elsewhere.
- On the wall of the ampulla is the Oddi musculature within which are pancreatobiliary-type ductules lying individually and in clusters.

These different compartments not only have distinct histologic and functional properties but also their own chemical milieu which makes this small region highly complex and challenging. Thus, it is not surprising that there are vastly different impressions regarding the characteristics of the cancers of this region. Recently, careful analysis of tumors of this area processed with more standardized grossing protocols [1,2] has led to refined classification and elucidated the specific characteristics of tumors arising from different compartments [3–5].

Preinvasive Neoplasms

A significant proportion of the ampullary cancers (estimated at more than a third) arise from adenomatous lesions, i.e., preinvasive mass-forming neoplasia, which are also called tumoral intraepithelial neoplasms [6–9]. By location, these can be regarded in two groups.

- Those arising from the ampullary duodenal surface and thus presenting as obvious mass lesions endoscopically in the ampullary region, appearing as polypoid masses or ulcero-vegetating lesions in the duodenal lumen; almost all of these prove to be intestinal-type adenomas.
- Some arise within the ampullary channel and are termed intraampullary papillary-tubular neoplasm, which are essentially intraampullary counterparts of pancreatic intraductal papillary mucinous neoplasms (IPMNs), and while some are very similar to intestinal-type adenomas, many are hybrid type or pancreatobiliary or gastric lineage [6].

Adenomas of the Ampullary Duodenum

Adenomas with all the characteristics of colonic adenomas also arise from the duodenal surface of the ampulla. They can be sporadic or associated with familial adenomatous polyposis (FAP) syndrome. In fact, the ampulla is a common extracolonic site to be involved by FAP [10–14].

Adenomas of the ampullary duodenum are more likely to harbor an invasive carcinoma than similarly sized colorectal adenomas. Invasive carcinomas that arise in

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adenomas are often hidden in the deep creases of the tumor at the base of the polyp and are difficult to detect in surface biopsies. Microscopically, adenomas of the ampullary duodenum are similar to those that occur in the large intestine but present some challenges in their diagnosis at the pathologic level. For example, reactive changes can mimic adenomas closely [7,8]. More importantly, an underlying invasive carcinoma of the pancreas or bile duct involves the ampullary epithelium by colonization ("cancerization") of the mucosal basement membrane, which simulates *in situ* disease [15,16].

Intraampullary Papillary-Tubular Neoplasms

Intraampullary papillary-tubular neoplasms (IAPNs) are adenomatous (tumoral intraepithelial) lesions that occur almost exclusively within the ampulla [6,17]. They represent the intraampullary counterpart of intraductal neoplasms of the pancreas and biliary tract. Papillary or polypoid tumors can fill the ampullary channel and distal segment of the common bile duct or main pancreatic duct. By definition, involvement of the ampullary duodenum and intramucosal extension into the proximal aspect of the common bile duct and main pancreatic duct is minimal (<25%) [6,9]. The mean age of affected patients is 64 years, with male predominance [6,9].

Gross examination of the ampullary duodenum (the view from the luminal aspect of the duodenum) typically reveals a hemispheric elevation of intact mucosa, often with a patulous papilla orifice from which nodules of friable granular material protrude into the duodenal lumen [1]. Ulceration may be evident, but overt mucinous discharge, characteristic of pancreatic intraductal neoplasms, is seldom encountered. On sectioning the ampullary wall, the tumors are characterized by a prominent exophytic growth pattern in the dilated distal bile duct and pancreatic duct.

Microscopically, IAPNs show various degrees of papillary or tubular growth (Fig. 158.1). Most have a mixture of these patterns. They exhibit a spectrum of dysplasia, and most cases show a mixture of low-grade (the criteria are the same as those used for adenomas of ampullary duodenum) and high-grade dysplasia which is defined as substantial cytologic atypia and architectural complexity. Unlike adenomas of the ampullary duodenum, approximately 50% of IAPNs show mixed (intestinal, gastric, pancreatobiliary) differentiation [6]. Approximately 75% of IAPNs are associated with invasive carcinoma at the time of diagnosis, but the invasive component is usually less than 1 cm in diameter [6]. Invasion is mostly tubular and often shows a mixture of intestinal and gastropancreatobiliary features. These tumors are easily missed and since the invasive carcinoma is often small, proper sampling and examination become crucial. This also pertains to ampullectomy for these cases.

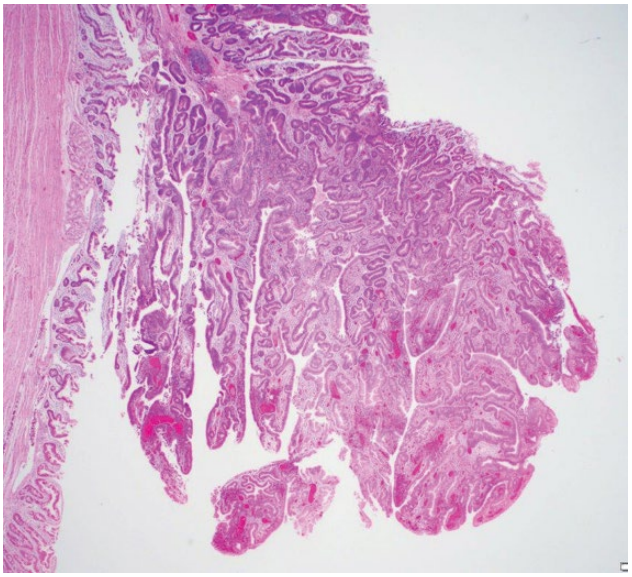


Figure 158.1 Intraampullary papillary tubular neoplasm (IAPN). (a) Grossly, an exophytic mass is located in the dilated distal bile duct and pancreatic duct. (b) Microscopically, IAPNs show various degrees of papillary or tubular growth.

It should be noted here that, because of the complexity of this site, it becomes very difficult to distinguish histopathologically true invasive carcinoma from adenomatous (preinvasive) cells pagetoidly extending into complex glandular units in a pseudoinvasive pattern.

The hybrid cellular nature of these lesions is also reflected in their immunophenotype. More than 50% of cases coexpress CK7 and CK20 [6]. Immunostaining for MUC2 and CDX2 is positive in cases with intestinal differentiation; immunostaining for MUC1, MUC5AC, and MUC6 is positive in cases with gastropancreatobiliary differentiation. However, overlaps are very common, and a significant proportion of the cases reveal mixed immunophenotype [6].

Noninvasive cases have an excellent prognosis. However, cases with extensive high-grade dysplasia can recur and this recurrence can be seen many years after resection [6]. Therefore, long-term follow-up is warranted, even in noninvasive cases. Cases with invasive carcinoma are associated with better survival than conventional (invasive) ampullary carcinomas unaccompanied by an IAPN (three-year survival of 69% versus 44%) [6]. This survival advantage is likely attributable to early detection of invasion but also reflects differences in tumor biology [3,18].

Invasive Adenocarcinomas

Until recently, the definition of ampullary cancer lacked uniformity, which has led to the vastly different impressions expressed regarding their characteristics. Many of

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the studies on the topic have been presented to the literature under the heading of "periampullary cancers" and seemed to have included, on one hand, cases that are noninvasive carcinomas (adenomatous lesions with carcinoma *in situ* [CIS]), and on the other, tumors that arise in neighboring sites including the pancreas and secondarily invading the ampulla. Nonstandardized and limited pathologic evaluation seems to have been the biggest contributor to this variation. Recent refined definitions were provided and have been adopted by the College of American Pathologists (CAP) and American Joint Committee on Cancer (AJCC) [19,20], which currently serve as the main guide for the documentation of ampullary tumors in the United States. Accordingly, four categories are recognized in the section of "ampulla of Vater" cancers and their corresponding clinicopathologic characteristics are as follows [21].

- Ampullary-duodenum cancers arise from the duodenum-facing surface of the ampulla that is lined by intestinal epithelium normally, and typically form bulky ulcero-vegetating lesions readily observed in the duodenal lumen, in which the ampullary orifice is often eccentrically located (Fig. 158.2a). They typically have a prominent adenoma component and their invasive component is most commonly intestinal or mixed mucinous-intestinal phenotype. Although they are usually very large (>4 cm) and produce lymph node metastases (~60%), their behavior is often significantly better than expected.
- Intraampullary papillary-tubular neoplasm-associated carcinomas are characterized by preinvasive nodules located within the ampullary channel (i.e., distal portions of the common bile duct and main pancreatic duct). These can be viewed as an ampullary counterpart of IPMN/ITPN-associated invasive carcinomas. Because by definition they are predominantly intraampullary, these tumors are less impressive from the duodenal perspective; they show a dilated orifice, from which granular material may protrude into the lumen of the bowel. Upon sectioning the ampullary wall, the main bulk of the tumor is elucidated and typically reveals light tan, friable nodules (Fig. 158.2b). Probes placed into the common bile duct and pancreatic duct typically exit into the center of the lesion. They are by default rich in adenomatous components and microscopic examination often reveals only a small invasive carcinoma, and thus, not surprisingly, the prognosis is relatively good (median survival of >10 years), especially if invasion is limited.
- Ampullary duct carcinoma is the other category that can be regarded as an "intraampullary" tumor but they are biologically very different from the intraampullary papillary-tubular neoplasm-associated carcinomas discussed above. In essence, they are the intraampullary counterpart of pacreatic ductal adenocarcinomas (PDACs) and distal common bile duct carcinomas (DCBCs). Ampullary ductal cancers by default do not have a significant adenomatous (preinvasive neoplasm) component, and instead form circumferential scirrhous lesions that constrict the distal end of the common bile duct and pancreatic duct, with preservation (or minimal alteration) of the papilla of Vater and ampullary duodenal mucosa. Therefore, from the duodenal perspective, these tumors are fairly underwhelming, and typically show a button-like elevation of mucosa or a small, subtle ulcerating lesion (Fig. 158.2c) such that endoscopists are not sure if there is a lesion. If proper dissection approaches are not employed, ampullary-ductal carcinomas can easily be missed because they are small and subtle. Microscopically, they often prove to be pancreatobiliary-type carcinomas. Although these tumors are usually less than 2 cm in diameter, they have a high rate of lymph node metastasis (57%) and an aggressive behavior (median, 38 months), the worst among the ampullary carcinoma subtypes but nevertheless significantly better than PDACs.
- Ampullary carcinomas not otherwise specified (ampullary-NOS) include two subsets of tumors. The first is presumed to arise from the papilla of Vater (i.e., the edge of mucosa where the CBD and main pancreatic duct merge into the duodenal mucosa) (Fig. 158.2d) and thus does not qualify for one of the three categories discussed above. The second is those that cannot be confidently placed into one of the above categories because of inadequate processing. In our archival database, this group constituted >50% of the cases, but with improved grossing and classification, currently <10% are placed into this category.

Microscopically, ampullary adenocarcinomas are highly versatile in their morphologic appearance, demonstrating various types, as opposed to pancreatic and DBD carcinomas, the vast majority of which are pancreatobiliary type. Most ACs are tubular type, characterized by glandular arrangement. Some are intestinal-type tumors that are similar to conventional colonic adenocarcinomas (Fig. 158.3a). They are commonly associated with intestinal-type adenomas. An extensive mucinous component (>50% of the tumor volume) justifies a diagnosis of mucinous adenocarcinoma [9]. Those that resemble pancreatic or bile duct adenocarcinomas are called *pancreatobiliary-type adenocarcinomas* (Fig. 158.3b). Most ACs that have an ampullary duct origin prove to be of this type. A significant proportion of ampullary carcinomas (>40% in our experience) have a mixed phenotypic appearance and are difficult to place into one of the

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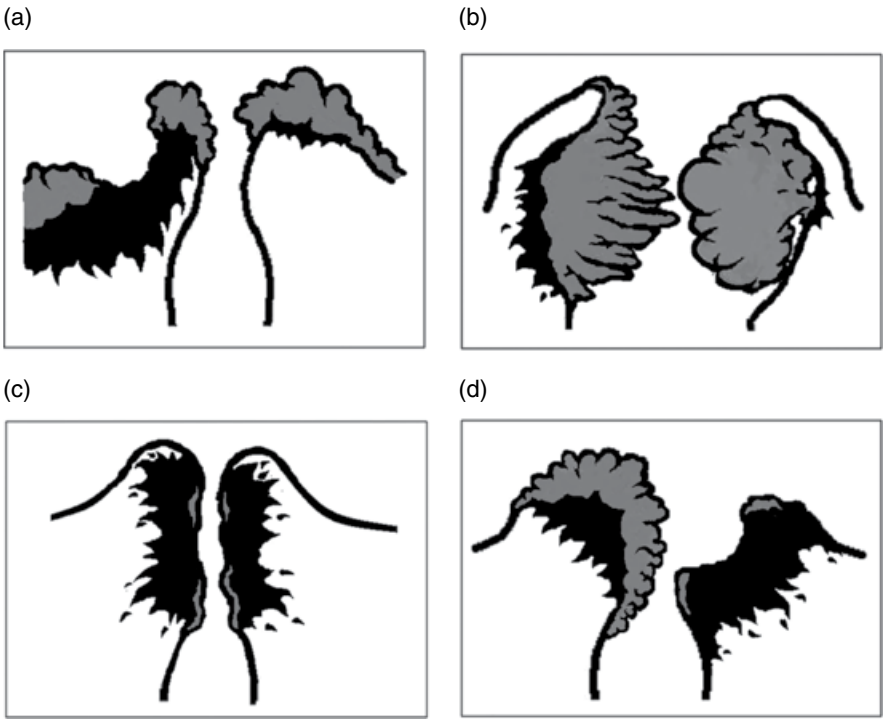


Figure 158.2 Site-specific classification of ampullary carcinomas. (a) (Peri)ampullary-duodenal: these tumors are characterized by substantial exophytic component on the duodenal surface of ampulla, while mostly sparing or only minimally involving the intraampullary segment. Often this vegetating tumor grows distally and leaves the ampullary orifice as an eccentric hole. (b) Intraampullary papillary-tubular neoplasm (IAPN) associated: invasive carcinomas arise from an IAPN. (c) Ampullary-ductal type: these tumors are quite underwhelming, showing mucosa-covered button-like elevations with a central dimple-like depression, or ulceration. (d) Ampullary-NOS type: these tumors are localized in the ampulla, mostly centered in the papilla region of the Vaterian complex, and not showing any of the specifications identified in other subtypes.

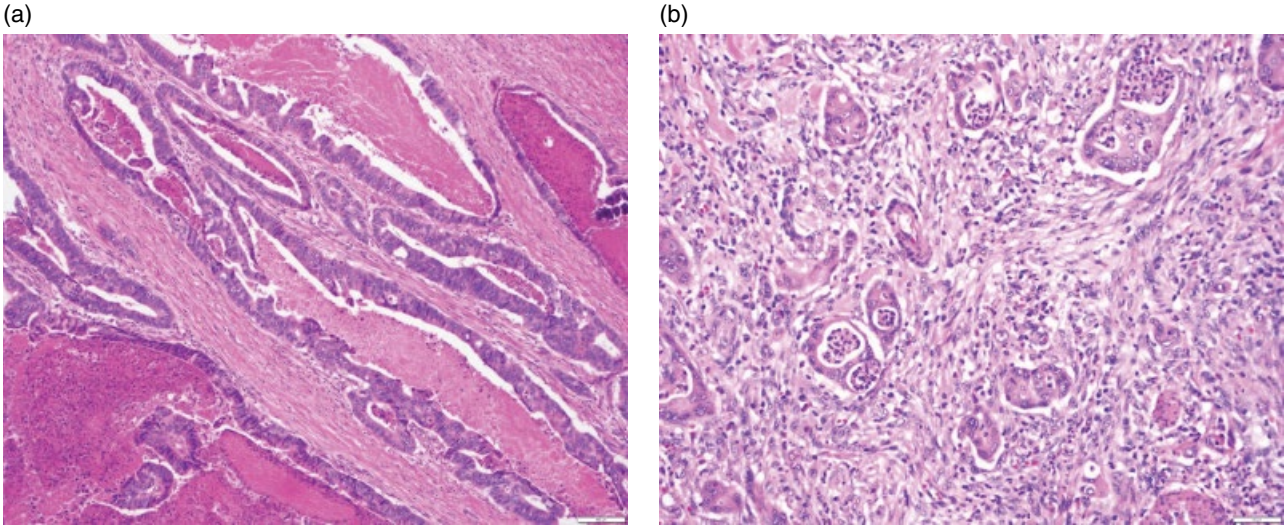


Figure 158.3 Histologic types of ampullary adenocarcinoma. (a) Intestinal type: similar to conventional colonic adenocarcinomas. (b) Pancreatobiliary type: small branching glands surrounded by a desmoplastic reaction.

categories as intestinal or pancreatobiliary [22]. If noninvasive carcinomas and carcinomas of neighboring sites (pancreatic and CBD) are excluded carefully and the true ampullary carcinomas with the refined definition are analyzed separately, the survival advantage of the intestinal type over pancreatobiliary type adenocarcinomas proves to be much less significant than previously reported [23–29].

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Recently, immunohistochemically (IHC)-based classifications of ampullary carcinomas have been proposed [30,31] and are now being utilized by oncologists in management protocols. These panels are based on observations that the intestinal phenotype tends to stain for MUC2, CK20, and CDX2, whereas the pancreatobiliary phenotype stains positively for MUC1. However, in carefully selected cohorts analyzing true ampullary carcinomas with the refined definitions, the putative lineage markers MUC1/MUC2/CK20/CDX2 and their corresponding panels fail to show direct/significant prognosis [32]. There is emerging evidence that MUC5AC, the gastric marker, may prove to be a significant prognosticator of ampullary carcinoma [32].

The frequency of DNA mismatch repair (MMR) deficiency (i.e., immunohistochemical evidence of microsatellite instability) in ampullary cancers is comparable to, if not higher than, that in colon carcinomas [33–36]. MMR-deficient ampullary carcinomas are associated with medullary or pushing-order patterns, peritumoral inflammation (including lymphocytes, neutrophils, and eosinophils), or focal mucin production [33]. They appear to be less aggressive (lower rates of both lymph node metastasis and perineural invasion) and have a significantly better progress compared to MMR-intact ampullary carcinomas [33].

Recently, the introduction of checkpoint immunotherapies has revolutionized the oncologic targeted therapy paradigm in various organs. In ACs, PD-L1 expression appears to occur in the MMR-deficient group, specifically in tumors with medullary-type morphology [33]. Therefore, this subset of ACs may be targets for immunotherapy.

Since ampullary carcinomas are highly heterogeneous, it is difficult to ascertain the validity of molecular alterations identified in subsets [37]. *KRAS* mutations are found in approximately 40% of cases [38–42] and increased expression of p53 is detected in 70% [42–44]. Sixty-four percent of ampullary carcinomas that arise in FAP contain *APC* gene mutations, but only 17% of sporadic ampullary carcinomas carry this type of mutation [45]. Mutations of the β-catenin gene (*CTNNB1*) and alterations of the *SMAD4* (*DPC4*) gene are rare in ampullary carcinomas [46,47]. Like colorectal cancer, intestinal-type ACs show mutation of *APC* in greater than 50% of cases, whereas pancreatobiliary-type ACs show predominant *KRAS*, *TP53*, and *SMAD4* mutations, of similar frequency to PDAC [48–50]. In addition, *ELF3* has been implicated as a novel driver gene in AC [48,49] and, along with *KRAS* and *TP53*, may be mutated in all histologic subtypes, suggesting shared biologic mechanisms in development. *ERBB2* amplification has been shown in up to 23% of ACs and is mutually exclusive with downstream *KRAS/NRAS/BRAF* mutations that are responsible for resistance of therapies targeting *ERBB2* [51].

Ampullary carcinomas have an overall survival rate far better than pancreatic and distal common bile duct cancers. The five-year survival rate is approximately 45% [3,52]. Even the ampullary-duct carcinomas which are mostly pancreatobiliary type adenocarcinomas (i.e., ampullary counterparts of CBDC and pancreatic ductal adenocarcinomas) have a much better prognosis than ordinary PDACs. Invasion size may be an important factor. Ampullary carcinomas often arise from a precursor (adenomatous) lesion, and the mean size of the invasive component is usually significantly smaller than primary pancreatic carcinomas [52]. For instance, IAPN-associated invasive carcinomas often have only a small invasive component (mean 1.5 cm) [6]. Not surprisingly, they have a better prognosis [6]. Positive margins occur in less than 5% of ampullary carcinomas, compared with at least 35% of pancreatic tumors [52]. The carcinomas arising from the four distinct compartments of the ampulla have different biologic behavior, as discussed above.

Other factors associated with prognosis include tumor budding, perineural and lymphovascular invasion [18,53–57]. Among these, tumor budding is increasingly being recognized as an important prognosticator (and possibly stratified) as its value in the remainder of the GI tract is appreciated. In fact, in our study, we found it to be independent prognostic factor.

Uncommon Carcinomas in the Ampulla

There are other carcinoma types that occur in the ampulla, such as poorly cohesive carcinoma (with or without signet ring cells), medullary carcinoma, and mucinous (colloid) carcinoma [9]. These have some specific associations. For example, poorly cohesive carcinomas are usually diagnosed at an advanced stage and behave aggressively [58]. In contrast, medullary carcinomas are closely associated with microsatellite instability, and despite their large size and poorly differentiated appearance, their clinical behavior appears to be similar to, if not better than, that of other ACs [59]. Mucinous carcinomas are often ampullary-duodenal in origin and often present as advanced tumor and with a higher lymph node metastasis rate but their prognosis does not seem to be significantly worse [60]. Unlike their lower GI counterparts, they do not show association with MSI [60].

Distal Common Bile Duct Carcinoma

Distal common bile duct carcinoma (DCBC) is relatively uncommon and thus poorly characterized. Established risk factors for these tumors include parasites and congenital/anatomic variations such as choledochal

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cyst [61,62] and pancreatobiliary maljunction [63–65]. Recently, it was elucidated that DCBC is commonly associated with low (intrapancreatic) union of cystic and common hepatic ducts which suggests a chemical milieu alteration in bile as a factor in their etiopathogenesis [66].

One of the biggest challenges regarding DCBC has been in definition as to what really qualifies for this category. Common bile duct involvement is extremely common in pancreatic ductal adenocarcinomas if careful sampling is performed [67], and can even show focal circumferential involvement. Additionally, ampullary-ductal carcinomas discussed above are often classified as distal CBD carcinoma. Therefore, many studies have included cases from these secondary sites into the analysis of DCBC and vice versa. Careful dissection of the resection specimens and correlation of the findings with the imaging and clinical findings are crucial in establishing the true primary site in many cases [5].

A recent study reported that intrapancreatic tumors symmetrically/concentrically involving the common bile duct are likely to be DCBCs, which are frequently associated with high-grade biliary dysplasia, lack *KRAS* mutations, and have a superior prognosis with an actual five-year overall survival of 35%, whereas asymmetric/eccentric involvement generally implies pancreatic ductal adenocarcinoma, which are commonly associated with high-grade PanIN, *KRAS* mutations, and a poor five-year overall survival of 17% [68]. Microscopically, DCBCs commonly exhibit a small tubular pattern, sharing the similar morphology with pancreatic ductal adenocarcinoma. In addition, intraglandular neutrophil-rich debris is often seen [69]. Median survival is better than for pancreatic ductal adenocarcinoma, but worse than for ampullary carcinoma; however, the survival advantage over pancreatic carcinoma may be less when the tumors are size matched [69,70]. Poor prognostic indicators include node metastasis, lymphovascular invasion, size of invasion, and margin positivity [69]. T-staging of tumors based on depth of invasion or size is shown to be much more applicable and prognostically relevant [65,69].

The vast majority of biliary tract cancers are adenocarcinomas of the pancreatobiliary type. These are very similar to ordinary pancreatic ductal adenocarcinomas and are often histologically indistinguishable from each other except for subtle differences [69].

Incipient Cancers

Biliary intraepithelial neoplasia (BilIN) is defined as microscopic flat or micropapillary lesions of atypical bile duct epithelium. These flat lesions cannot be detected by preoperative image analysis or macroscopic examination. In the current WHO (5th edition), the BilIN classification scheme employed a two-tiered approach as low- and high- grade dysplasia, based on nuclear to cytoplasmic ratio, and loss of cellular polarity [71]. Since BilIN is most commonly detected incidentally in association with invasive carcinoma, its biological behavior and natural history have been difficult to evaluate. There are no data regarding the risk of progression of BilIN in the absence of invasive carcinoma. Low-grade dysplasia is largely believed to be clinically inconsequential; however, high-grade dysplasia is believed to be a significant lesion that may be associated with (or progress into) invasive carcinoma with relatively high risk, and thus warrants careful clinical attention [71]. BilINs are detected in >10% resected choledochal cysts, with or without an accompanying invasive carcinoma component [62].

An estimated 10% of biliary tract carcinomas arise in mass-forming preinvasive neoplasms (tumoral intraepithelial neoplasms [TIN]). Just as in the pancreas [4,72], ampulla [6], and gallbladder [73], the carcinomas arising from tumoral intraepithelial neoplasm, namely intraductal papillary neoplasm of the bile duct (IPNB) [74,75] and intraductal tubulopapillary neoplasm (ITPN) [76], show highly distinctive characteristics.

Intraductal papillary neoplasm of the bile duct (IPNB) shows a papillary proliferation of atypical epithelium that fills the bile duct and may lead to a fusiform or cystic dilation of the affected duct segment [74]. IPNB can be detected by imaging and gross examination. The degree of cytologic atypia is graded with the criteria used for BilIN. Similar to intraductal papillary neoplasm of the pancreas, IPNB is classified into gastric, intestinal, pancreatobiliary, and oncocytic types [74]. When the pancreatobiliary type becomes invasive, it usually shows the pattern of a tubular adenocarcinoma; intestinal-type IPNB, if invasive, often produces a mucinous (colloid) adenocarcinoma; the gastric and oncocytic-type IPNBs, if invasive, have a tubular type-associated carcinoma [71].

Intraductal tubulopapillary neoplasm is now recognized as a distinct group in the bile ducts as in the pancreas. ITPNs are distinguished from IPNBs by their tubular growth pattern with only minimal, if any, papilla formation [76]. Another important defining characteristic of ITPN is the mucin-poor nature of the cells. On gross examination, the bile ducts are filled with nodules. Foci of invasion are typically represented by firm, white scirrhous lesions with irregular borders [76]. Punctate or geographic foci of necrosis can be present. At the microscopic level, all ITPNs are characterized by large, smooth-contoured nodules composed of prominent, relatively small, back-to-back tubular units. In addition to their typical tubular pattern, solid areas or abortive papillae are seen. Necrosis is common, predominantly focal and with a "comedocarcinoma-like pattern" [76].

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ITPNs show a pancreatobiliary epithelial phenotype with MUC1 (80%) and MUC6 (30%) expression and negativity for MUC2 and MUC5AC [76]. Most ITPNs are associated with invasive carcinomas.

Overall, these have a more indolent behavior, partly attributable to the early detection of invasive carcinomas that are tagged by the massive intraductal component that leads to obstruction and early symptomatology. However, there is also evidence that even when stage matched, these invasive carcinomas arising from TINs behave better than those arise from BilINs, which indicates a different biology. This is also supported by the molecular alterations seen in these tumors [76]. Of note, as in the pancreas, those arising in oncocytic examples are currently classified as oncocytic variant of IPNB, but are increasingly being recognized as a separate entity of intraductal oncocytic papillary neoplasm (IOPN) as in the pancreas [77,78]. IOPNs have been shown to have a distinct molecular phenotype with rearrangements of PRKACA and PRKACB [79,80].

Nonampullary Duodenal Carcinoma

Nonampullary duodenal carcinomas (NADCs) are rare, and frequently have been grouped with jejunoileal adenocarcinoma. However, they have several distinctive characteristics. The distal duodenal carcinomas can be associated with intestinal-type adenomas; however, especially the proximal examples often form plaque/ulcero-plaque-like lesions arising from large vegetating adenomatous lesions [81]. Mismatch repair protein deficiency was found in 13% of NADCs overall, and more commonly in those with the plaque-like growth and pushing-border infiltration [81]. Proximal examples closer to the stomach also appear to be closer to gastric cancer in their nature, maybe arising from Brunner glands or metaplastic gastric-like epithelium. Additionally, NADCs, similar to ampullary carcinomas, are seldom pure "intestinal" type, and instead often exhibit a striking degree of morphologic versatility, with the gastropancreatobiliary being the predominant type and also unusual carcinoma types not described in the remainder of the GI tract [81,82]. This is reflected also in the frequency of the hybrid immunophenotype with less than 50% expressing "intestinal lineage markers" MUC2, CDX2, and CK20 [81]. The presence of gastric-pancreatobiliary histology appears to be associated with more aggressive behavior [82] and thus it is important to attempt to recognize and report this lineage (no matter the quantity) in any NADC case.

The prognosis of NADCs is fairly similar to ampullary-duodenal cancers and better than the ampullary-ductal cancers discussed above (five-year survival 29% vs 57%) [81]. More importantly, the prognosis of NADC is incomparably better than that of pancreatic ductal adenocarcinoma [81]. This is important because, for NADC that occurs close to the pancreas, pancreatic ductal adenocarcinoma with secondary invasion into duodenum becomes an important and highly challenging differential and the latter has been shown to have highly aggressive behavior.

Pathologic Staging of Cancers of This Region

The current eighth edition (2017) of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and updated CAP Cancer Protocol for Carcinoma of the Ampulla of Vater [19,20] are based on the invasion of cancer into different compartments of this complex area. Into Oddi (T1a), duodenal submucosa (T1b), duodenal muscularis propria (T2), superficial pancreas (≤0.5 cm) T3a, peripancreatic soft tissue or duodenal serosa (T3b); or involvement of the celiac axis, superior mesenteric artery, and/or common hepatic artery (T4).

Lymph node (pN) staging is subdivided into N1 (1–3 positive nodes) and N2 (±4 positive nodes). A minimum of 12 regional lymph nodes is required for optimal staging in a pancreatoduodenectomy specimen, although with careful dissection typically more than 15–20 lymph nodes are harvested. A recent analysis of the AJCC classification system showed that the two-tier reclassification of positive lymph nodes was linked to significant differences in survival (including recurrence-free survival) between T3a and T3b tumors (but not between T1b and T2 or between lymphatic/venous invasion/node metastases) [83]. These results raise the question of the need for a size-related staging.

Neuroendocrine Neoplasms and Related Tumors

Neuroendocrine neoplasms should be regarded in two distinct groups: well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (PDNECs). Well-differentiated neuroendocrine tumors constitute a heterogeneous group of neoplasms [9], including what were previously called ordinary carcinoids (often showing serotonin production), "ampullary somatostatinomas" (glandular psammomatous carcinoids with somatostatin positivity at the cellular level), gastrinomas and other hormonal types as well as nonfunctional tumors [84,85].

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Ampullary somatostatinomas merit specific mention because they seem to be fairly unique to the ampulla, and conversely, a significant proportion of NETs in the ampulla prove to be of this type. These can be associated with neurofibromatosis and gastrointestinal stromal tumors. Although they are low-grade tumors, they are often infiltrative and show lymph node metastasis in close to half of the cases, but seem to behave in a very protracted fashion nevertheless [86–88]. Neuroendocrine tumors are graded based on the mitotic activity and Ki67 index. Accurate counting of Ki67 can be challenging. Eye-balling is discouraged. We find manual count performed on camera-captured printed images of tumor hot spots to be the most practical approach [89].

A distinct but related entity is duodenal gangliocytic paraganglioma, a neoplasm that combines features of a well-differentiated neuroendocrine tumor with those of a nerve sheath tumor admixed with ganglion cells [90–93]. This is a very peculiar entity that is almost unique to the ampulla and duodenum in the vicinity of the ampulla. The vast majority of cases seem to be benign with only rare cases showing lymph node metastasis, and even those seem to have benign behavior.

Poorly differentiated neuroendocrine carcinomas of this region need to be distinguished from the well-differentiated neuroendocrine tumors. They often occur in association with adenocarcinomas or glandular preinvasive neoplasms (adenomatous lesions). They are typically high-grade carcinomas, recognizable as such by morphology, showing highly atypical cytology (with differential diagnosis of other poorly differentiated carcinomas) as well as brisk mitotic activity and necrosis. Ki67 labeling index is typically higher than 50%. Retinoblastoma gene alteration is common, represented as loss of nuclear expression at the immunohistochemical elevel. Recent studies suggest that such tumors warrant cis-platinum treatment, as opposed to the well-differentiated NETs which grow slowly and not only do not require cis-platinum but also do not benefit much from it. They have a highly aggressive behavior.

Pseudotumors That Commonly Mimic Cancer

One of the most common types of pseudotumor in this region is paraduodenal ("groove") pancreatitis. This type of pancreatitis has been described under various names in the literature; here we use the term paraduodenal pancreatitis [94,95]. This particular pancreatic inflammation is found predominantly in male patients (40–50 years) with a history of alcohol abuse [96,97]. Grossly, there is either thickening and scarring of the duodenal wall, particularly in the area corresponding to the minor papilla, that extends to the adjacent pancreatic head tissue, and/or sieve-like cystic changes in the duodenal wall. Most cysts contain clear fluid, but others may have more granular white material and even stones. Microscopically, the chronic inflammatory process resides in the duodenal submucosa, the duodenal wall, and the adjacent pancreatic tissue. Typically, there are several small foci of necrosis surrounded by dense proliferation of myoid cells, which show all the features of myofibroblasts and are positive for muscle markers. A common finding associated with the inflammatory changes is Brunner's gland hyperplasia, which contributes to the thickening of the duodenal mucosa.

Fibroinflammatory biliary stricture (FIBS) is a rare benign tumor-like myofibroblastic lesion of the extrahepatic bile duct of unknown etiology that masquerades as cholangiocarcinoma. It is unrelated to autoimmune pancreatitis, primary sclerosing cholangitis, cholangiocarcinoma, prior bile duct injury or repair, and choledocholithiasis [98]. Histologically, the FIBS lesion is composed of spindle cells, fibroblasts, and myoblasts with varying degrees of fibrosis and lymphoplasmacytic inflammatory infiltrate [98]. If a defined mass is present, it is firm and lacks a capsule. By comparison with patients having bile duct cancer, FIBS patients present at a significantly younger age, are more likely to be female, and have a high incidence of coexisting autoimmune diseases [98]. The malignant potential of FIBS remains unknown due to the rarity of this disease. These lesions can masquerade as cholangiocarcinoma due to reactive epithelial hyperplasia, perineural extension, and involvement of vascular structures and adjacent organs. These features can be particularly misleading when examining intraoperative frozen sections due to the limitations of sample processing and the time constraints of immunohistochemistry. A subset of these cases appear to represent IgG4-related sclerosing cholangitis, which is a part of the autoimmune pancreatitis spectrum. Because preoperative cytology is not diagnostic of FIBS, surgical resection remains the mainstay of diagnosis and treatment, while immunosuppression may reduce the risk of recurrence.

Secondary Tumors

Virtually every malignant neoplasm described in the body can also occur in this region. These include melanomas, lymphomas, sarcomas, and germ cell tumors, all of which can mimic primary cancers and thus ought to be considered in the differential diagnosis of more common adenocarcinomas, at both clinical and pathologic evaluation.

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Adenoma and Adenocarcinoma of the Ampulla of Vater: Diagnosis and Management

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Introduction

Ampullary neoplasms refer to a family of periampullary tumors, which arise from the ampulla of Vater. The significant premalignant potential and a unique anatomic location of ampullary neoplasms make them special. Typically, ampullary tumors are classified as benign and malignant. Benign tumors account for less than 10% of periampullary tumors [1], and ampullary carcinomas are the second most common periampullary carcinomas (after pancreatic adenocarcinoma) [2]. Although ampullary adenomas are classified as benign, they tend to progress to malignant transformation. True ampullary cancer is usually difficult to distinguish from other periampullary malignancies. It is generally diagnosed at an earlier stage, meaning that it has a better prognosis than periampullary cancers originating from the bile or pancreatic duct [3]. An aggressive diagnostic and therapeutic approach is therefore warranted for these tumors.

Epidemiology and Biologic Behavior

In autopsy studies, periampullary neoplasms prevalence is reported to be 0.04–0.12 [3,4]; however, the prevalence increases with the widespread availability of flexible endoscopy and screening programs. Currently, periampullary malignancies account for 5% of all newly diagnosed gastrointestinal tumors [5]. The incidence of ampullary carcinomas is 4–6 cases per million population, representing 0.2% of all gastrointestinal tumors and accounting for approximately 20% of all periampullary cancers [6,7]. Caucasian people are most affected, there is a male predominance, and the peak incidence is in the seventh decade [8]. Both benign and malignant ampullary tumors can occur in the setting of a genetic syndrome or, more commonly, sporadically.

Familial adenomatous polyposis (FAP) is the most common genetic predisposition [9], and most patients with FAP manifest some degree of dysplasia in the ampulla [10]. Periampullary cancers have become a leading cause of death in patients with FAP since prophylactic colectomy became the standard of care [11]. Gardner syndrome, Lynch syndrome, neurofibromatosis type 1, and Muir–Torre syndrome are the other reported genetic predispositions for ampullary carcinoma [12–15]. Ampullary adenomas progress to cancer through an adenoma to carcinoma sequence, similar to what is known with colon polyps. This interval allows a lead time for investigation and excision of these lesions before carcinoma development [16].

Thankfully, screening and early resections of these lesions have become more common worldwide. The current European Society of Gastrointestinal Endoscopy guideline recommends starting endoscopic surveillance at the age of 25 and continuing at intervals determined by the characteristics of previously found lesions [17]. The effective use of a side-viewing duodenoscope with random biopsies has increased duodenal and ampullary adenoma detection rates [17]. On the other hand, local factors play an essential role in sporadic tumors. The earliest histopathologic changes are seen in the common pancreaticobiliary channel, followed by the pancreatic duct. Concentrated bile produces mutagenic effects on ductal epithelium, resulting in epithelial apoptosis promoting malignant transformation [18]. Also, chronic liver fluke infection is a risk factor for ampullary carcinoma [19].

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Histologic Features

Ampullary neoplasms are macroscopically classified as (i) intraampullary (intramural protruding), (ii) periampullary (extramural protruding), or (iii) ulcerating ampullary (19). Ulcerating ampullary lesions have a high lymph node metastasis rate and are mostly diagnosed at an advanced stage. Adenocarcinoma accounts for 75% of all ampullary neoplasms, followed by benign adenomas (20%) (Fig. 159.1) and neuroendocrine tumors (5%) [2]. Villous and tubulovillous adenomas are the most common benign lesions; the others include hemangioma, lipoma, leiomyoma, lymphangioma, and leiomyofibroma [1,9].

Histologically, Kimura and colleagues classified ampullary carcinomas into two subtypes: intestinal and pancreaticobiliary [20]. The intestinal type classically arises from an adenoma; however, a premalignant precursor lesion is often absent in the pancreaticobiliary type [19]. In 2010, the World Health Organization revised this classification, adding mixed as a third subtype [21]. Currently, histologic ampullary carcinoma classification includes three subtypes: intestinal, pancreaticobiliary, and mixed [21,22]. Typically, intestinal-type carcinomas have fewer invasive components and a less frequent perineural and lymphovascular invasion, which has been related to a better prognosis than the pancreaticobiliary type [23,24]. The mixed type overlaps with intestinal and pancreaticobiliary subtypes, ranging from 20% to 40% of ampullary carcinomas, showing features not attributable to a single phenotype [25].

Immunohistochemical stains can potentially distinguish between intestinal and pancreaticobiliary types. Intestinal epithelium expresses intestinal markers such as cytokeratin 20 (CK20), mucin 2 (MUC2), and caudal-related homeodomain transcription factor 2 (CDX2) plus or minus cytokeratin 7 (CK7), whereas pancreaticobiliary adenocarcinoma is positive for CK7 and mucin 1 (MUC1). Other potentially useful immunohistochemical stains to differentiate the subtypes include mucin 5AC (MUC5AC) and S100 calcium-binding protein (S100P) [26] (Table 159.1).

Genetic Features

Most ampullary neoplasms occur sporadically; however, the presence of FAP has been associated with a 200-fold higher risk of ampullary cancer compared with the general population, similar to colorectal cancer [27]. Several recent studies have provided an impressive amount of molecular information about hepatobiliary-pancreatic tumors, including ampullary cancers (ACs) [28,29]. Two landmark studies reported by Yachida et al. and Gingras et al. emphasized the presence of specific mutations, such as *KRAS*, *APC*, *TP53*, and *SMAD4*. Moreover, these two studies investigated putative associations between gene mutations and histologic subtypes [30,31]. Similar to colorectal cancer, intestinal-type ACs show APC gene mutations, whereas pancreaticobiliary-type ACs show *KRAS*, *TP53*, and *SMAD4* gene mutations, predominantly. In addition, the tumor suppressor gene *ELF3* has been implicated as a novel driver gene in ampullary cancer due to its role in the regulation of epithelial differentiation [30,32].

It seems that molecular profiling can drive therapeutic decisions since some features have been suggested to have a putative prognostic value. A study conducted by Mafficini et al. recently linked the presence of *KRAS* and *TP53* mutations with a more aggressive clinical course, regardless of histology [33]. However, few data are currently available, and further studies are warranted to make clinical decisions based on molecular features.

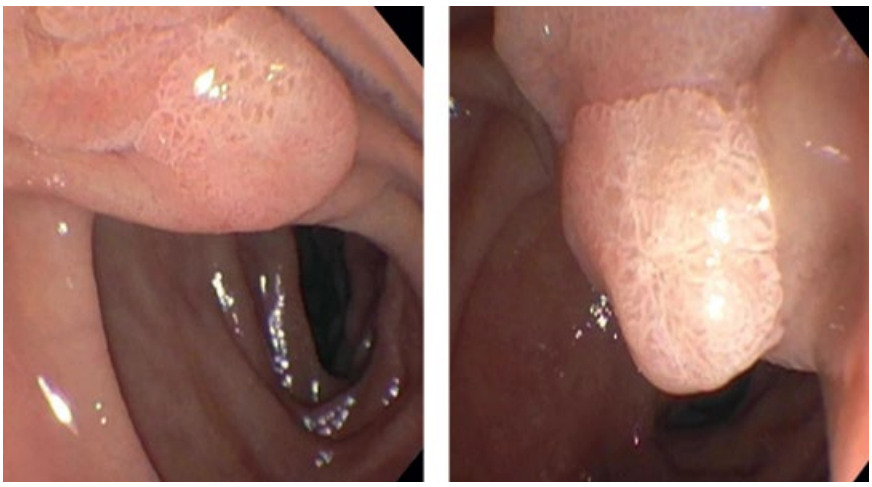


Figure 159.1 (a,b) Endoscopic views of an ampullary adenoma on forward-viewing endoscopy.

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Table 159.1 Immunohistochemical classification and genetic mutations of ampullary cancer.

Histologic type	Positive stains	Other stains	Reference
Intestinal	MUC2, CK20, CDX2, ± CK7	-	[26]
Pancreaticobiliary	MUC1, CK7, ±MUC5AC	S100P+, SMAD4 loss	[26]
Mixed	Might show a combination of the above stains		[26]
	Gene mutations		
Intestinal	APC (49%), TP53 (39%), KRAS (39%), CTNNB1 (26%), ARID2 (18%)		[30]
	TP53 (64%), KRAS (46%), APC (41%), PIK3CA (26%), SMAD4 (20%)		[31]
Pancreaticobiliary	KRAS (67%), TP53 (67%), SMAD4 (20%), CTNNB1 (15%), ERBB3 (14%)		[30]
	TP53 (71%), KRAS (65%), SMAD4 (18%), CDKN2A (16%), PIK3CA (13%)		[31]
Mixed	KRAS (49%), APC (50%), TP53 (41%), SMARCA4 (27%), PIK3CA (23%)		[31]

Clinical Features

As with ampullary adenomas, the presenting symptoms and signs of ampullary adenocarcinomas are nonspecific, as frequently observed in pancreatic adenocarcinoma and extrahepatic cholangiocarcinoma (the most common symptom is painless obstructive jaundice, which is seen in two-thirds of patients) [34,35]. Occult gastrointestinal bleeding, diarrhea, fatigue, weight loss, and duodenal obstruction may be the symptoms associated with ampullary cancer. Due to cholestasis, 25% of ampullary adenomas develop common bile duct stones [36]. Furthermore, small distal intraductal benign tumors can mimic an ampullary malignancy and cause significant biliary obstruction [37]. Physicians should keep these lesions in mind when seeing a patient with atypical abdominal symptoms since there are no specific symptoms that are pathognomonic for ampullary lesions.

Diagnosis and Staging

The primary concern in evaluating ampullary lesions is to rule out malignancy risk, since ampullary adenomas have a premalignant potential. Also, an occult focus of carcinoma may be present within an adenoma [38,39]. Diagnosis is usually established by combining radiology, endoscopy, and histology, similar to evaluating ampullary adenoma and carcinoma. However, it is generally challenging to differentiate between them without complete resection.

Ampullary carcinomas are frequently diagnosed with a macroscopic appearance on endoscopy and histopathologic examination of the obtained biopsy specimens. Most ampullary lesions are apparent endoscopically. Ulcerated masses, lesions >3 cm, ampullary rigidity, and nonlifting of the periampullary component with submucosal injection are highly suspicious features for malignancy. However, the ampulla is best examined and biopsied with a side-viewing duodenoscope. Endoscopic retrograde cholangiopancreatography (ERCP) does not only help obtain biopsies, but it also excludes an associated stricture or stone and allows evaluation of the extension of the tumor into the pancreatic or biliary duct (Fig. 159.2). As a general rule, negative endoscopic biopsy for malignancy does not entirely exclude a malignant focus in an adenoma. Therefore, the diagnostic accuracy of biopsies can be increased by obtaining at least six biopsies, preferably at least 48 hours following sphincterotomy [40,41], and by complete resection of ampullary adenomas (endoscopic ampullectomy). Therefore, endoscopic ampullectomy is considered an integral part of the diagnostic process and may also be curative in highly selected cases, such as *in situ* carcinoma, low-grade dysplasia, and early adenocarcinoma [42–44].

In terms of differential diagnosis, primary ACs must be distinguished from other cancer types, including pancreatic cancer, distal cholangiocarcinoma, and small bowel cancers [45,46]. Endoscopic ultrasound (EUS), ERCP, and fine-needle aspiration cytology (FNAC) are the major diagnostic modalities. On the other hand, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET/CT) of the chest, abdomen, and pelvis are the basic tools for the staging of ACs [44,47]. In patients with obstructive jaundice, transabdominal ultrasound (TUS) is the first choice of imaging to rule out other causes such as choledocholithiasis and pancreaticobiliary tumors; however, it rarely reveals the neoplasm itself.

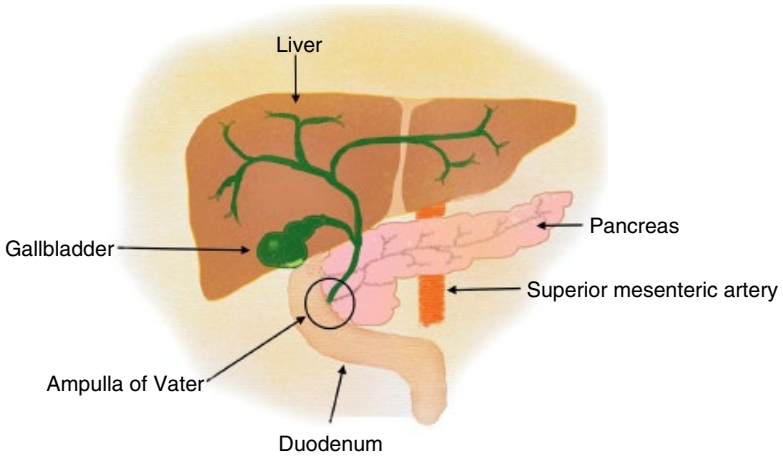
The complex and strategic anatomic structure of the ampulla of Vater, a crossroads of the three different

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Figure 159.2 (a) Ampullary adenoma on forward-viewing endoscopy. (b) CT image of the same lesion. (c) Endoscopic retrograde cholangiopancreatography of the same patient showing distally complete obstruction of bile duct.

Figure 159.3 Schematic representation of the ampulla of Vater.



epithelia (intestinal, ductal pancreatic, and biliary), makes tumor staging highly difficult [45,46] (Fig. 159.3). The American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) updated the TNM staging system in 2018 (8th edition) [46,48]. According to the last edition, the T stage is subclassified based on the depth of duodenum and pancreas invasion, and the N classification has been splatted into N1 (1–3 lymph nodes) and N2 (four or more) (Table 159.2).

Cross-sectional techniques and EUS are usually preferred in staging and preoperative evaluation, as well as differentiating an ampullary adenoma from carcinoma [44]. With its ability to place an ultrasound transducer close to the ampulla, EUS is superior to CT, MRI, and TUS for tumor staging and is as sensitive as duodenoscopy in detecting small ampullary tumors [49] (Fig. 159.4). EUS and intraductal ultrasonography provide detailed information about the endoscopic appearance, tumor size, localization, tumor extension, and the existence of metastatic lymph nodes. These data help the preoperative staging of ampullary malignancy [50,51]. Furthermore, EUS-guided fine needle aspiration (EUS-FNA) can provide tissue from the ampulla, lymph nodes, and surrounding deeper structures. However, it does not rule out a malignant focus within an adenoma [52,53]. EUS is the best modality for T-staging ampullary carcinoma and vascular invasion, while the accuracy for N-staging is lower [53,54].

Although CT is superior to TUS in evaluating ampullary lesions, it is not sensitive enough for staging and detecting small lesions. On the other hand, CT is highly accurate in detecting distant metastasis, which usually involves lymph nodes, peritoneum, liver, bone, and lungs. However, MRI can provide more detailed images of the ampulla and periampullary tissue [55]. Ampullary cancers are usually hypodense distinct masses on MRI with magnetic resonance cholangiopancreatography (MRCP). A "double-duct" sign (dilation of both pancreatic and bile duct) or only the dilated bile duct can be observed mainly; however, single dilation of the pancreatic duct is rare [56].

Another staging modality is PET/CT, which has not been well studied in detecting ampullary malignancies; it

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Table 159.2 The 8th edition of the TNM staging system by AJCC/UICC.

TNM stage	Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Limited to sphincter of Oddi
T1b	Invasion into duodenal submucosa
T2	Invasion into duodenal muscularis propria
T3a	Invasion into pancreas ≤0.5 cm
T3b	Invasion into pancreas >0.5 cm
T4	Involvement of celiac or superior mesenteric artery
NX	Lymph nodes cannot be assessed
N0	No lymph node involvement
N1	Metastasis in 1–3 lymph nodes
N2	Metastasis in 4 or more lymph nodes
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage group	
Stage 0	Tis N0 M0
Stage IA	T1a N0 M0
Stage IB	T1b 2 N0 M0
Stage IIA	T3a N0 M0
Stage IIB	T3b N0 M0
Stage IIIA	T1a,1b,2,3a,3b N1 M0
Stage IIIB	T4 AnyN M0 or AnyT N2 M0
Stage IV	AnyT AnyN M1

is highly sensitive in detecting distant metastasis [57]. In a recent study comprising 44 patients, Watanabe et al. assessed the usefulness of fluorodeoxyglucose PET (FDG-PET) for preoperatively predicting tumor invasion in ampullary cancer, retrospectively. They reported that PET performance correlated with tumor invasion and lymph node metastasis and speculated that FDG-PET could be a helpful modality for preoperative staging and treatment strategy [47]. In another study, Chuang et al. investigated the effectiveness of preoperative dual-phase 2-[18F] FDG PET-CT for poor survival in 54 patients with ampullary carcinoma receiving pancreaticoduodenectomy. They reported that dual-phase PET scan with bowel distention could better delineate the ampulla of Vater and characterize tumor physiology. Therefore, 2-[18F] FDG PET-CT offers good survival prediction before surgery in primary malignant neoplasms at the ampulla of Vater, providing better preoperative risk stratification along with improved treatment planning [58].

Management and Treatment

Endoscopic Management and Surgery

It can be difficult to differentiate an ampullary adenoma involving a carcinoma focus and true ampullary carcinomas from other periampullary cancers. Furthermore, there is no consensus regarding the optimal management of patients with ampullary adenomas. It is not clearly defined who requires endoscopic or surgical excision and who should be followed up with surveillance endoscopy. However, American Society for Gastrointestinal Endoscopy (ASGE) guidelines for the role of endoscopy in ampullary and duodenal adenomas attempt to make it easier and update the recommendations for management. The ASGE guideline recommends ERCP before resection attempts. The initial assessment in diagnosis is looking for a sign of malignancy with ERCP, which is also helpful in the differential diagnosis. These guidelines also recommend EUS before resection, as EUS is superior to other imaging modalities for the accuracy of primary tumor staging [16,59]. However, CT/PET and MRI should be completed before

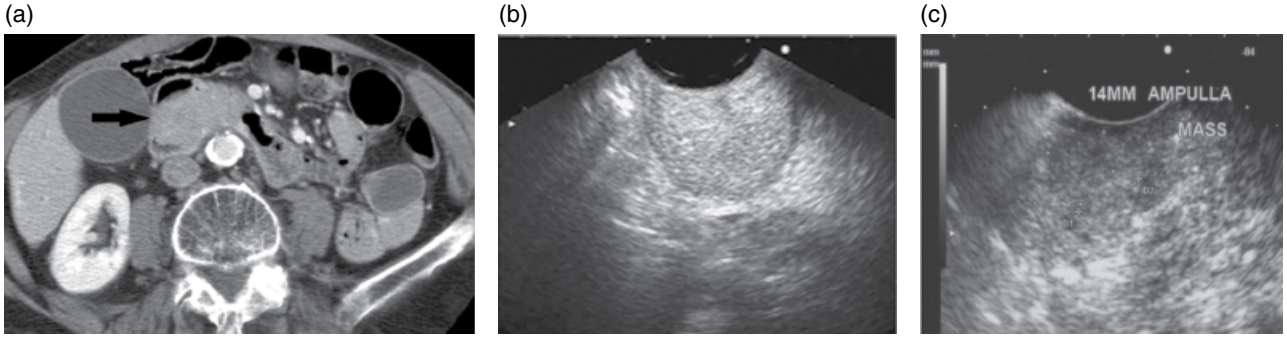


Figure 159.4 (a) A large soft tissue mass consistent with ampullary cancer in duodenal wall on CT. (b) Ampullary adenoma on endoscopic ultrasound (EUS). (c) 14 mm ampullary cancer on EUS.

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resection attempts since these modalities have been shown to be superior for detecting small, distant metastases and nodal metastases [57,60].

Removal of the adenoma is suggested in cases with sporadic adenoma, especially those that have high-grade dysplasia or are causing any symptoms. Endoscopic surveillance with biopsies every 6–12 months may be advised when a patient declines excision of the lesion. In cases with FAP, excision should be suggested since the prognosis seems better compared with sporadic cases. On the other hand, removing ampullary adenoma does not eradicate cancer risk because multiple upper intestinal adenomas are usually present in patients with FAP.

There are three excision options for ampullary neoplasms: endoscopic ampullectomy (Fig. 159.5), surgical ampullectomy (local surgical excision), and Whipple's procedure (pancreaticoduodenectomy). The decision is made based on the degree of surgical risk, life expectancy, stage of malignancy, and patient preference. Although there are no definite criteria on which approach is best for a random case, especially in centers that are not experienced in advanced endoscopy, patients with large lesions, adenomas containing carcinoma, lymph node involvement, and adenoma ingrowth into the bile duct or pancreatic duct on EUS should be referred to surgery. Endoscopic ampullectomy should only be attempted in patients with adenocarcinoma staged as Tis, while other stages should be referred for surgical resection [16].

There are comparable reports in the literature on the size of the lesion for endoscopic removal. The current recommendations suggest that removing ampullary adenomas <4–5 cm in maximal diameter is judicious. Resection of Tis ACs can be curative, although the most recent ASGE guideline does not endorse it in routine management [16,59]. Certain endoscopic features, including nonlifting with injection, ulceration, firmness, and presence of depression, suggest a possible malignancy, which are indications to refer for surgical resection [42,43].

The only curative treatment of carcinoma which eliminates histologic progression to carcinoma and eradicates a malignant focus within an adenoma is R0 (margin-negative) resection. Although pancreaticoduodenectomy (PD) has been associated with higher morbidity and mortality rates compared to surgical ampullectomy, it achieves curative excision for ampullary adenomas with almost no local recurrence risk, and has 90% successful resection rates for carcinomas. Curative surgery is deemed possible in approximately 50% of cases [61,62]. Moreover, surveillance endoscopies are not recommended after curative surgery. On the other hand, since a higher proportion of complications frequently burdens the postoperative course, several minimally invasive approaches have been explored, including robot-assisted and laparoscopic surgery; however, the real benefit of these modalities remains unclear [63–65].

Patients with evident malignancy on an adenoma should be referred for pancreaticoduodenectomy rather than endoscopic or local surgical excision. Although some studies report that endoscopic ampullectomy has lower morbidity and similar efficacy rates (46–93%) compared to surgical ampullectomy (0–30%), the role of endoscopic ampullectomy is still controversial [66]. Complete removal of the neoplasm is the aim of the procedure, and *en bloc* excision is the preferred method since occult carcinoma and also negative margins should be ensured entirely. However, due to the frequent local and locoregional lymph node involvement, this technique should be used in selected patients with noninvasive forms [67].

The quoted technical success rate for complete resection varies significantly from 42% to 92%, depending on individual endoscopists' experience with ampullectomies. Literature also reports comparable recurrence rates



Figure 159.5 (a) Ampullary adenoma in a patient with familial adenomatous polyposis. (b) Endoscopic appearance of the lesion two weeks after endoscopic ampullectomy. (c) Endoscopic appearance of the lesion three months after endoscopic ampullectomy.

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ranging from 2% to 33% following resection [42,68,69]. Patient and lesion features play a significant role in technical success, and therefore patient selection is critical. Predictors of success include male sex, age >48, lesion diameter <24 mm, and absence of FAP [3].

Postprocedure Surveillance

Patients with ampullary adenoma who have been treated with either endoscopic or surgical ampullectomy are at risk of recurrence and require endoscopic surveillance. In contrast, surveillance is not recommended after pancreaticoduodenectomy except for patients with FAP. All patients who undergo ampullectomy are invited for a follow-up diagnostic endoscopic procedure with side-viewing scopes in one week to one month. If this first endoscopy shows no residual lesion, routine endoscopic follow-up is suggested for surveillance at either three-month or six-month intervals for two years. After two years, some institutions may continue surveillance for much more extended periods [16]. Since patients with FAP are at risk of developing upper intestinal polyps other than ampullary adenomas, they require regular endoscopic surveillance according to the Spigelman classification [70]. In patients with ampullary cancer who undergo local surgical excision, endoscopic surveillance may be recommended, similar to endoscopically resected ampullary adenomas, although no guidelines are available.

This topic requires further study to identify the optimal interval and duration of postprocedural surveillance.

Medical Treatment

Although radical surgery is known as a curative modality for early-stage AC, tumor recurrence is still high (up to half of the patients). Therefore, the effectiveness of the postoperative approaches, including chemotherapy, radiotherapy, or chemoradiation, have been investigated over the years [71,72]. In a recent retrospective study comprising 4190 patients with ACs from the National Cancer Database, Nassour et al. highlighted that adjuvant chemotherapy and adjuvant chemoradiation therapy were associated with improved survival [73]. On the other hand, Ecker and colleagues reported that adjuvant chemotherapy is not associated with improved clinical outcomes, neither for intestinal nor for the pancreaticobiliary types of ACs [74].

There is a need for randomized controlled trials (RCTs) on this topic; however, conducting RCTs in AC patients is difficult because of several reasons, including the rarity of the disease and frequent misclassifications. Given the lack of RCTs supporting the use of adjuvant chemotherapy and chemoradiotherapy, the optimal regimen for ACs in both adjuvant and metastatic settings remains to be explored.

Recently, in a retrospective cohort study including 214 patients, Bolm et al. reported that pancreatobiliary-type ACs that received adjuvant therapy had an improved median overall survival (adjuvant treatment 85 months versus no adjuvant treatment 65 months); moreover, adjuvant therapy was found to be an independent prognostic factor in multivariate analysis. In contrast, there was no benefit of adjuvant therapy in intestinal-type AC patients, suggesting that adjuvant treatment might be indicated in pancreaticobiliary or mixed-type ACs [75].

Systemic chemotherapy represents the gold standard in patients with advanced AC with distant metastases. Some landmark studies conducted in biliary tract cancers might be guidance for this purpose, supporting the increase of median overall survival [76–79]. Studies focusing their attention on the molecular features of ACs may also be helpful to translate the results obtained in other biliopancreatic malignancies. For example, WNT pathways and PI3K alterations have been reported in more than 30% of all ACs regardless of histologic subtype. The anticancer agents found to be effective in the case of PI3K mutations, such as everolimus and temsirolimus, are also under evaluation in ACs [33,80]. Large-scale, prospective randomized clinical trials are still warranted to identify the role of systemic treatment in this setting.

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Endoscopic Treatment of Adenomas of the Ampulla of Vater: Techniques, Results, Benefits, and Limitations

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Introduction

Tumors of the ampulla of Vater are relatively rare and arise from the duodenal papilla. Symptoms of an ampullary tumor include biliary colic, obstructive jaundice, recurrent cholangitis, and pancreatitis. These symptoms arise due to obstruction of the bile or pancreatic ducts. Occult bleeding is relatively common. However, most ampullary tumors are asymptomatic and are often found incidentally by screening endoscopy. Ampullary tumors are thought to develop either from the intestinal epithelium or the epithelium covering the pancreaticobiliary ducts. Most ampullary tumors are adenomas or adenocarcinomas [1]. The results of familial adenomatous polyposis (FAP) surveillance suggest that an ampullary adenoma is associated with the progression of adenoma to carcinoma and is recognized as a premalignant lesion, such as colonic adenoma [2–4]. Although the natural history of ampullary adenoma has not been well investigated in sporadic lesions, many endoscopists advocate resecting ampullary adenomas [1].

Indications for Endoscopic Papillectomy

Endoscopic papillectomy was first documented by Suzuki et al. in 1983 in Japanese [5] and by Binmoeller et al. in 1993 in English [6]. It involves resecting the mucosa and submucosa of the duodenal wall in the area of the anatomic attachments of the ampulla of Vater, including the tissues around the bile duct and the pancreatic duct orifices [7].

Surgical resection (pancreaticoduodenectomy or transduodenal ampullectomy) is recognized as the gold standard for treating ampullary tumors. However, no prospective study has compared endoscopic papillectomy with surgical resection. Surgical resection has a low recurrence rate but is too invasive for cases of localized ampullary adenoma. Endoscopic papillectomy has been accepted as a less invasive alternative to surgical treatment and is increasingly performed in cases of adenoma [8].

The indications for endoscopic papillectomy have not been established. The European Society of Gastrointestinal Endoscopy guidelines recommend endoscopic papillectomy for patients with ampullary adenoma without intraductal extension [9]. The 2015 American Society for Gastrointestinal Endoscopy guidelines did not provide specific criteria for endoscopic papillectomy [8]. Intraductal involvement of the lesion is considered a noncurative lesion, or one with a high risk of recurrence [10]. Additionally, surgical transduodenal ampullectomy is suitable for cases of large (>40 mm) lesions and a periampullary diverticulum for technical reasons. Endoscopic resection is not recommended for ampullary cancer because of the risk of lymph node metastasis. In contrast, high-grade dysplasia or carcinoma restricted to the mucosal layer is reportedly suitable for endoscopic papillectomy, but there is a rare risk of lymph node metastasis [11].

Preprocedural Evaluation

The purpose of the preprocedural evaluation is to evaluate extension to the bile duct or pancreatic duct after apparent advanced adenocarcinoma is excluded. The preprocedural diagnosis of ampullary tumor is based on endoscopic appearance, biopsy, endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP) with intraductal ultrasonography (IDUS).

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Endoscopic Appearance and Pathologic Diagnosis

A side-viewing endoscope (duodenoscope) is generally used to visualize or treat ampullary tumors. Cap-assisted endoscopy is suggested when the ampulla is not observed by forward-viewing endoscopy [12]. The typical endoscopic finding of ampullary adenoma is a villous tumor. The characteristic features distinguishing adenoma and adenocarcinoma are the presence of ulceration, spontaneous bleeding, depressed area, friability, and rigidity, which have often been observed in patients with malignancy [13]. The fold convergence of the duodenum wall around the ampulla indicates invasion of the tumor into the duodenal wall.

However, ampullary adenomas cannot always be distinguished from ampullary adenocarcinomas based on endoscopic appearance alone. Observing the ampullary tumor with dye and narrow-band imaging is reportedly helpful for providing endoscopic images of microvessels and the surface structure of tumors [14] or to enhance tumor margins [15]. A biopsy is very important for differentiating adenoma from carcinoma and other tumors. However, the accuracy of biopsy is reportedly low, at approximately 70% [16–19]. It is thought that severe atypism is observed in the ampullopancreatobiliary common duct rather than in the ampulla–duodenum. Therefore, the biopsy must be taken from the deep portion of the orifice. Some reports have suggested that biopsy followed by endoscopic sphincterotomy has better accuracy when adenocarcinoma is suspected [20]. However, the sensitivity of biopsy does not change after sphincterotomy [21].

Tissue sampling by EUS-guided fine needle aspiration (EUS-FNA) is one of the options for pathologic confirmation when the tumor is not exposed to the surface of the duodenum. EUS-FNA is suitable when an invasive adenocarcinoma is suspected that has a negative histopathology initially. In one retrospective study of 35 patients, the accuracy of EUS-FNA for suspected primary ampullary lesions was 88.8% [22]. Thus, endoscopic papillectomy is occasionally performed as a diagnostic treatment or as a major biopsy before surgery, as the preoperative confirmation of the histopathologic diagnosis is not always accurate.

Endoscopic Retrograde Cholangiopancreatography, Intraductal Ultrasonography, and Endoscopic Ultrasound

Endoscopic retrograde cholangiopancreatography, including an evaluation of the biliary and pancreatic ducts, should be performed at the time of endoscopic resection to assess evidence of extension into either ductal system. IDUS is performed via the working channel of the duodenoscope and into the bile and pancreatic ducts after cholangiopancreatography. IDUS may be useful for imaging the detailed anatomy of the ampulla. EUS is essential for deciding whether or not endoscopic resection is indicated. It provides information on the presence of invasion into the muscularis propria, intraductal extension of the lesion, and metastasis to regional lymph nodes. EUS is superior to computed tomography (CT), magnetic resonance imaging (MRI), and transabdominal ultrasonography as diagnostic modalities [23,24]. A metaanalysis showed that the pooled sensitivity and specificity of EUS for the diagnosis of T1-stage tumors were 77% and 78%, respectively [25]. The combination of EUS and IDUS improves the accuracy of preprocedural diagnosis [23]. It is uncertain whether all cases of ampullary adenoma require EUS before endoscopic resection. Some experts suggest that EUS is not required when the tumor is ≤1 cm in diameter, or when no obvious endoscopic signs of malignancy are present [26].

Techniques

In general, endoscopic papillectomy is performed using a duodenoscope in the same manner as polypectomy using a snare, followed by stenting of the pancreatic duct for prophylaxis of postprocedural pancreatitis. Although no data have compared the safety or recurrence rates between *en bloc* and piecemeal resection, achieving *en bloc* resection without complications is fundamental when performing endoscopic papillectomy (Fig. 160.1). Piecemeal resection is performed for large lesions, aiming to decrease complications and recurrence. However, a complete pathologic evaluation is important to evaluate the resected margins or malignant foci with invasiveness, as the previous pathologic diagnosis is often incomplete. *En bloc* resection can potentially shorten the procedure time, requiring less cautery time. A large retrospective study concluded that *en bloc* resection is strongly associated with a higher rate of complete resection (odds ratio [OR] 4.05, 95% confidence interval [CI] 1.71–9.59, P <0.001) [27]. Balloon catheter-assisted papillectomy has been documented to facilitate *en bloc* resection in a few case reports [28,29].

Submucosal Lifting

Submucosal injection with epinephrine diluted in saline solution and indigo carmine before endoscopic papillectomy has been reported [30,31]. The mucosal tissue at the ampullary lesions does not lift because of tethering by the biliary and pancreatic ducts. After lifting the submucosa, the central lesion becomes comparatively depressed by the elevated mucosal tissue around the papilla, which makes snaring difficult.

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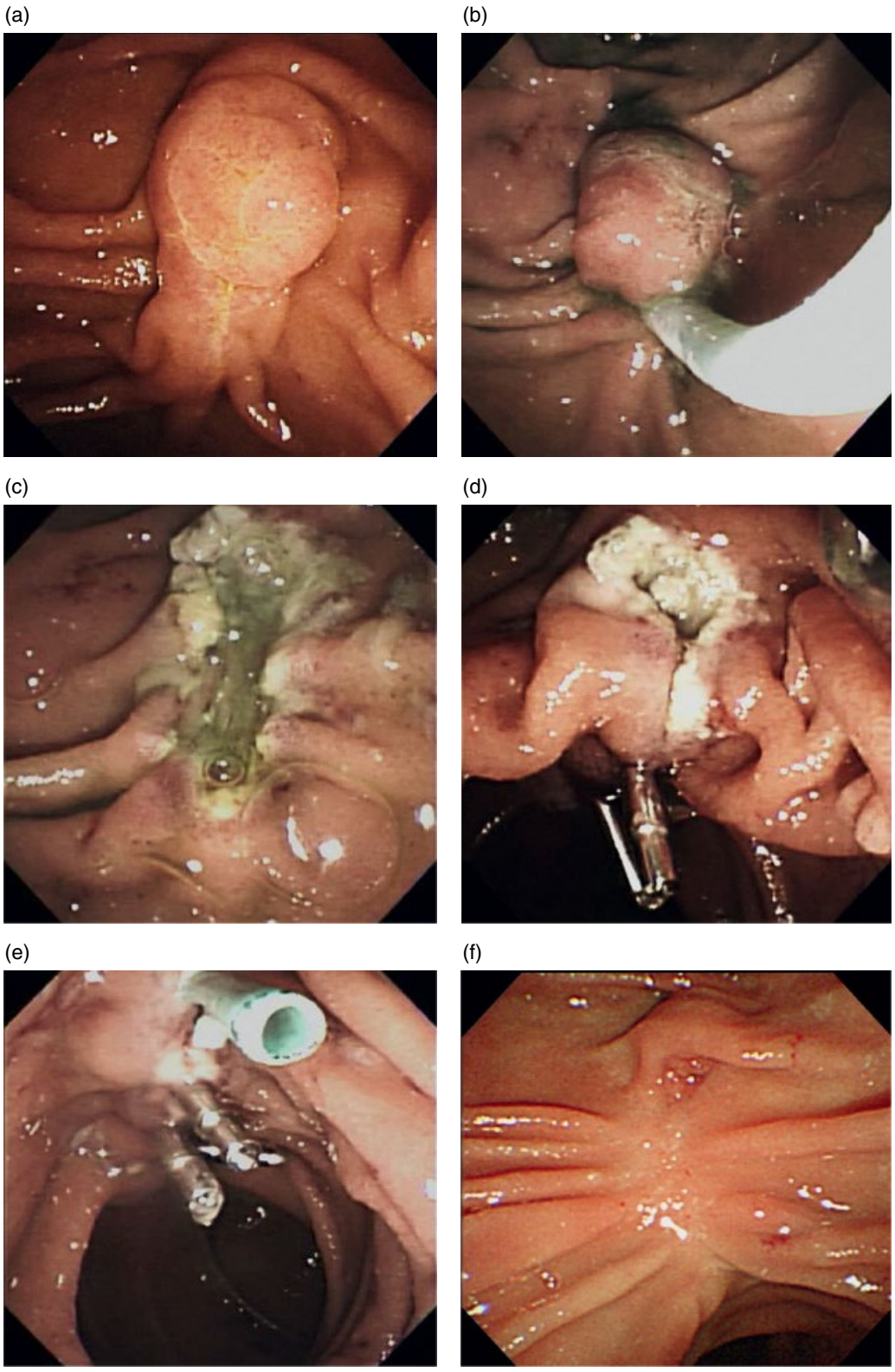


Figure 160.1 *En bloc* papillectomy by snaring. (a) Endoscopic view of the ampullary adenoma. (b) The adenoma is grasped with a snare. (c) The adenoma is resected. (d) The anal side of the ulcer is closed by clipping to prevent bleeding. (e) A 5 Fr pancreatic stent is placed to prevent obstructive pancreatitis. (f) Endoscopic view one year after resection.

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A randomized control trial compared papillectomy with submucosal injection and simple papillectomy for small lesions [32]. Among 50 patients with papillary adenomas, the complete resection rates were 80.8% (21/26) in the simple papillectomy group (12 mm mean tumor size) and 50.0% (12/24) in the submucosal injection group (9.29 mm) ($P = 0.02$). No differences were observed among postprocedural bleeding, delayed bleeding, and pancreatitis. The authors concluded that simple papillectomy may be a recommendable technique. Therefore, mucosal injection is not routinely suggested for small lesions. However, it may be useful for cases with predominantly lateral periampullary extension [33]. Underwater ampullectomy without lifting of the submucosa has been reported for lateral spreading tumors rather than submucosal injection [34].

The effectiveness of these techniques is still under investigation.

Snaring and Transection

Electrosurgical snare resection is the most common snaring and resection technique. There is no specific type or size of snare for endoscopic ampullectomy. The snare is often placed with the tip on the oral side of the lesion. The snare is closed at the base and the lesion is resected. Although no general recommendations regarding the optimal current and power output have been provided, there are reports of both pure cutting and blended cutting. Many endoscopists prefer the "blended" or Erbe Endocut® mode, which decreases bleeding by coagulation. In a pilot randomized controlled trial (N = 60), Iwasaki et al. reported that both pure cutting current (Autocut® mode) and blended cutting current (Endocut mode) have similar efficacy and safety for endoscopic papillectomy, and that the Endocut mode may prevent immediate bleeding of large tumors. The incidence rates of delayed bleeding (13.3% vs 16.7%, $P = 1.00$) and pancreatitis (27% vs 30%, $P = 0.77$) were similar between the Autocut and Endocut procedures. Immediate bleeding in the resection of tumors >14 mm in diameter was more common in the Autocut than in the Endocut group (88% vs 46%, P = 0.04) [35].

A novel "hybrid-ESD papillectomy" technique has been introduced recently. This involves a circumferential incision with partial submucosal dissection and subsequent snare resection. The *en bloc* resection and complete resection rates were 100% (N = 8) and 63%, respectively. A clear lateral margin was achieved in all cases [36]. This may be a treatment option when the lateral margin of a tumor is difficult to confirm by grasping with snare forceps. Another study reported the effectiveness of submucosal dissection for recurrent laterally spreading papillary lesions [37].

Retrieval of Resected Tumors

Retrieving a specimen is very important for accurately evaluating and staging the tumor. Immediately after transection, the specimen is grasped with a snare and removed from the body to avoid intestinal migration. A basket catheter or net forceps should be used for large specimens. It is important that the tissue is not collected by aspiration through the endoscope, as this will cause the specimen to fragment, making it impossible to evaluate the cut end histopathologically.

Sphincterotomy/Pancreatic and Biliary Stent Placement

Cannulation and sphincterotomy of the bile and pancreatic ducts are occasionally performed during papillectomy. Cholangiography and pancreatography are performed before papillectomy to rule out intraductal extension and to ensure easy recannulation after resection. Some experts have included methylene blue in the contrast injected into the pancreatic duct to assist in identifying the pancreatic orifice and preserve access to the pancreatic duct [38]. Sphincterotomy is often performed using the Delphi process after papillectomy according to an expert consensus [39].

Placing a pancreatic stent is strongly recommended to prevent postprocedural pancreatitis [8,9]. Pancreatic stenting aims to maintain the pancreatic duct orifice and prevent obstruction of the pancreatic duct. However, pancreatic damage caused by thermal ablation cannot be prevented.

The only prospective, randomized, controlled trial to evaluate the role of prophylactic pancreatic duct stenting to reduce the rate of post-ERCP pancreatitis after endoscopic papillectomy was conducted by Harewood et al. [40]. That study enrolled 19 patients who underwent *en bloc* papillectomy, 10 of whom were randomized to placement of a pancreatic stent. A significant decrease in the rate of postprocedural pancreatitis was observed in the stent group compared with the conventional group (33% vs 0%, $P = 0.03$). A systematic review of 23 retrospective cohort studies demonstrated a nonsignificant reduction in the rate of postpapillectomy pancreatitis (OR 0.71, 95% CI 0.36–1.40, $P = 0.325$) [41]. A metaanalysis by Spadaccini et al. showed that the only factor affecting acute pancreatitis as an outcome was the placement of a same-session prophylactic pancreatic stent (OR −1.72, 95% CI −2.95 to −0.50, $P = 0.006$) [42]. In general, a 5 Fr or 3 Fr diameter pancreatic stent is used after papillectomy. A metaanalysis of the size of the pancreatic stent after ERCP showed superiority of a 5 Fr pancreatic stent [43].[43] A long (7 cm) pancreatic stent is more useful than a short (5 cm) stent to decrease the incidence of pancreatitis [44].

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Other than the conventional method of placing a pancreatic stent after papillectomy, the techniques of biductal sphincterotomy with placement of a pancreatic duct stent before resection [45], pancreatic duct wire-guided endoscopic papillotomy, or retrieval of an intraductal migrated pancreatic stent after endoscopic papillectomy [46,47] have been introduced. Apart from the risk of postprocedural pancreatitis, obstructive cholangitis does not frequently occur except when caused by a clot obstruction due to major bleeding.

Treatment of Remnant Tissue/Intraductal Extension

Snares, biopsy forceps, and thermal ablation, such as argon plasma coagulation, are used to treat remnant tissue. Argon plasma coagulation is the most common technique and is useful for ablating remnant tumor as well as for hemostasis or prophylaxis of postprocedural bleeding. However, it must be applied carefully to the tissues around the pancreatic and bile duct orifices because it may induce a bile duct obstruction or pancreatitis due to the thermal effect.

Treatment of intraductal extension has not been well discussed. Several studies have reported the efficacy of endobiliary radiofrequency ablation (RFA) for intraductal residue after papillectomy [48]. Rustagi et al. reported the results of RFA for intraductal extension of ampullary tumors in 14 patients [49]. Additional modalities (thermal probe, argon plasma coagulation, and/or photodynamic therapy) were used in seven patients, and prophylactic stents were routinely placed. Treatment success was 92%, including 100% of those treated with RFA alone. Adverse events occurred in 43% of patients and included ductal strictures (five patients) and a retroduodenal abscess (one patient), which were successfully treated endoscopically. RFA should be used selectively in patients for whom treatment of an intraductal lesion is appropriate, as other endoscopic modalities are likely to be insufficient.

Clinical Results

Curative resection by endoscopic papillectomy is reportedly achieved in 52–92% of cases [6,16,18,30,50–53]. Multiple procedures may be required to completely remove all adenomatous tissue. Larger lesions are more likely to be incompletely excised during the initial endoscopic procedure. Jaundice, intraductal extension, occult adenocarcinoma in the resected specimen, and piecemeal resection are associated with lower rates of complete resection [27]. The recurrence rate of ampullary adenoma after endoscopic papillectomy ranges from 0% to 33%, over a median follow-up period of 19–65 months. Recurrence of benign lesions occurred in up to 33% of patients depending on the tumor size, final histology, presence of an intraductal tumor, coexistence of familial adenomatous polyposis, and endoscopist experience [16,18,27,51–53].

Complications

Endoscopic papillectomy is considered a less invasive option than surgery but is a high-risk endoscopic procedure. Therefore, the procedure requires the expertise of a specialist. Careful observation after the procedure is important to detect acute complications. Endoscopic papillectomy is associated with an increased risk of postprocedural pancreatitis, which is reported to occur in 3–25% of cases [16,18,51,52]. A systematic review with a pooled analysis by Spadaccini et al. reported that the overall adverse event rate was 24.9%. The most common adverse event reported after endoscopic papillectomy was postprocedural pancreatitis in 11.9%, followed by bleeding in 10.6%. Perforations and cholangitis were reported in 3.1% and 2.7% of cases, respectively. Long-term adverse effects of papillary stenosis occurred in 2.4% of cases. The mortality rate was 0.3% [42].

Pancreatitis occurs due to an obstruction of the pancreatic duct and thermal damage to the pancreatic parenchyma. As described earlier, a pancreatic stent should be placed, although it does not prevent pancreatitis in all cases. Postprocedural bleeding is a serious complication. The duodenal papilla is a hypervascular area, and bleeding is often observed on the anal side of the resected margin [54]. Postprocedural bleeding is treated with adrenaline injection, argon plasma coagulation, or clipping. Hemostatic procedures may cause a perforation or pancreatitis; therefore, excessive hemostasis should be avoided.

Perforations usually occur in the retroperitoneal area. The patient may not have signs of peritoneal irritation. However, pancreatitis or bleeding is often observed concurrently with a perforation. CT evaluation is informative for suspected perforations. If a perforation occurs, surgery may be considered, but select patients can be treated conservatively with antibiotics [16,18,30].

Late adverse events include the development of pancreatic or papillary stenosis [16,18,30,52,53,55], which can be treated endoscopically by stenting or balloon dilation.

Postprocedural Surveillance

Although there is no consensus, postprocedural surveillance is important for detecting local recurrence. The European Society of Gastrointestinal Endoscopy guidelines recommend long-term monitoring of patients.

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Postprocedural surveillance is recommended within the first three, six, and 12 months and yearly thereafter for at least five years after endoscopic papillectomy or surgical ampullectomy, based on duodenoscopy with biopsies of the scar and any abnormal area [9].

Some reports indicate that there is a higher risk of developing colorectal neoplasia in sporadic cases of duodenal adenoma including ampullary adenoma [56]. Screening colonoscopy should be performed in patients with duodenal or ampullary adenomas [8].

Conclusion

Endoscopic papillectomy has been established as the first-line treatment for ampullary adenoma without ductal extension. The indications have expanded due to the development of endoscopic techniques and devices. The management of complications and the treatment of remnant or recurrent lesions have also made significant progress. No consensus exists on preprocedural assessment, endoscopic papillectomy technique, management of complications, or postprocedural surveillance.

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161

Surgical Treatment of Papillary and Ampullary Tumors: Management and Long-term Results

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Introduction

If papillary and ampullary tumors are examined from a surgical point of view, it is important to achieve a sustainable treatment success for the patient through the operation. This is a crucial contribution in an interdisciplinary concept, as the surgeon chooses between local excision of the tumor in the sense of a papillectomy or ampullectomy and the oncologically radical procedure of partial pancreatoduodenectomy. In this respect, ampullary carcinomas must be distinguished from pancreatic head carcinomas near the papilla and distal bile duct carcinomas. The ampulla of Vater represents a special challenge for every surgeon because in this very circumscribed region, there are a large number of anatomic variants in the confluence, course, and joining area of the main bile duct and main pancreatic duct.

Although "carcinoma of the papilla" and "ampullary carcinoma" are usually used synonymously in clinical practice, the technical terms "ampulla" and "papilla" must be clearly distinguished from each other. They describe different depths of penetration of tumorous lesions within the duodenal wall to the head of the pancreas. This chapter outlines the surgical approach, strategically and surgically and against the background of macroscopic appearance and growth form of the tumor, and postoperative long-term results.

Surgical Management of Papillary and Ampullary Tumors

The indication for circumscribed operations of the ampulla is adenomas with missing or varying degrees of histologically proven dysplasia, in which endoscopic removal is not possible. The surgical presentation of these patients is therefore often prompted by gastroenterologists. Their often expressed fear that surgical intervention represents overtherapy of the relatively small lesions must be refuted within the framework of intensive cooperation. Even small lesions must be removed *in toto*. It is undisputed that radical tumor resections come to the fore with increasing T-stage ampullary neoplasms.

Anatomic Variations of the Periampullary Region

Figure 161.1 illustrates the main variant of the ampulla of Vater present in about 85% of all cases with prepapillary union of bile duct and pancreatic main duct and subsequent common channel with or without ampullary dilation. The papilla itself forms only the small elevation above the ampulla with a sphincter (M. sphincter of Oddi). It can protrude a few millimeters into the duodenum and can thus be easily identified either endoscopically or surgically after duodenotomy on the posterior wall of the pars descending about 8–10 cm distal of the pylorus. In about 10%, there is the possibility of a separate mouth of bile and pancreatic main duct. In 5% of cases a common mouth is formed by a single papilla even though the ducts are separated by a septum. In this case a proper ampulla does not exist [1].

Detailed knowledge of these evolutionary variations is particularly important because intraoperatively the ducts must be explored via their confluence points. In this context, it is also essential to obtain information by previously performed duodenoscopy about the formation of a papilla minor, which is usually located proximally. This is where the ductus Santorini ends, which embryonally drains the dorsal bud of the pancreatic

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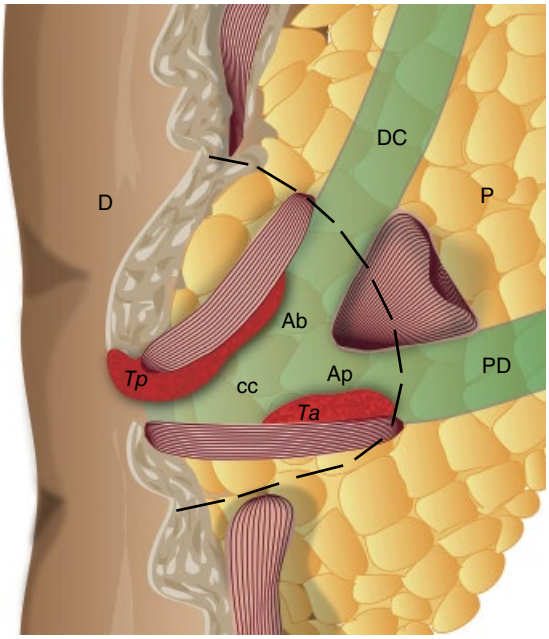


Figure 161.1 Schematic depiction of tumors in the area of the ampulla of Vater. Confluence of ductus choledochus (DC) and pancreatic duct (PD) via an ampullo-biliary (Ab) and ampullo-pancreatic (Ap) segment to a common channel (cc); P, pancreas; D, duodenum; dotted line, ampullectomy. Based on the macroscopic appearance, tumors of the papilla surface (*Tp*) and ampullary tumors (*Ta*) with intramural or intraductal growth can be differentiated. *Source:* Fischer and Zhou [3].

system and can be of varying size. Studies on resectates show that the accessory duct mostly ends blind in the papilla minor, which is then covered by duodenal mucosa [2]. If a lumen can be detected, this must also be intubated with a probe during the operation.

Indications for Surgical Papillectomy/Ampullectomy

In adenomas of the papilla of Vater, malignant tumor cells are frequently detectable. The dysplasias appear to follow an adenoma–carcinoma sequence analogous to colorectal cancer [3]. Biopsies histopathologically confirmed carcinomas in small adenomas in over 20% of cases and in up to 60% in villous adenomas [4]. It is therefore recommended to biopsy lesions even in the presence of endoscopic benign criteria such as soft consistency and sharp limitation, if necessary also in several places and repeatedly, so as not to miss components of a carcinoma located in deeper layers [5,6]. However, biopsy shows poor diagnostic accuracy with a high rate of false-negative results [7].

According to their localization, the following entities can be discriminated (see Fig. 161.1).

- Exposed tumors with polypous growth on the papilla or through the papilla's orifice.
- Intramural, ampullary tumors with polypous growth.
- Intraductal tumors that grow polypously into the lumen of the common channel.

Due to increasing expertise and technical developments, endoscopic removal of adenomas has now come to the fore even in this not always easily approachable region of the gastrointestinal tract [8]. In general, endoscopic papillectomy is considered demanding due to the complex anatomy, thin duodenal wall and very well-perfused tissue layers and is complicated in untrained hands, which is why it should be performed at a center with experience [9]. This makes interdisciplinary cooperation all the more important, as most lesions are discovered incidentally, as part of the further clarification of (endo)sonographically proven pancreatic or bile duct dilation or within a screening program (e.g., familial adenomatous polyposis or a hereditary nonpolyposis-associated colorectal carcinoma).

In the case of a carcinoma finding (bioptic or after endoscopic ablation), it is necessary to initiate a full oncologic TNM staging. Despite modern diagnostics, such as intraductal ultrasound which seems to be superior to endoscopic ultrasound [10], the exact diagnosis of early cancer and particularly the distinction between Tis and T1 remain extremely difficult. Data from a metaanalysis on endoultrasound show a sensitivity (95% CI) and specificity (95% CI) of 77% (0.69–0.83)/78% (0.72–0.84) for T1, 72% (0.65–0.80)/76% (0.71–0.83) for T2, 79% (0.71–0.85)/76% (0.71–0.83) for T3, and 84% (0.73–0.92)/74% (0.63–0.83) for T4 carcinomas [11]. However, this differentiation is important insofar as studies of T1 carcinomas already show locoregional lymph node metastases in up to 9% [12]. Therefore, intraductal tumors, which are often incompletely resected by endoscopy and have a high probability of recurrence [13] and carcinomas, remain clearly a domain of surgery.

The European Society of Gastrointestinal Endoscopy (ESGE) recently presented a corresponding guideline. According to this, for a lesion size of 20–30 mm with high-grade dysplasia or generally a size >40 mm, a surgical procedure is favored. This also applies to carcinomas (starting from carcinoma *in situ*) and a bile or pancreatic duct progression >20 mm [14,15]. However, it is difficult to endoscopicallyremove an adenoma which grows up to 20 mm along the bile or pancreatic duct. Therefore, we strongly favor a surgical approach in these cases. The American Society for Gastrointestinal Endoscopy no longer recommends endoscopic papillectomy in the case of a diagnosed carcinoma [16]. On the other hand, there

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Table 161.1 Indications for surgical papillectomy/ampullectomy.

Functional pathology
• morphologic sphincter Oddi dysfunction / *endoscopic failure or technically unfeasible*
Inflammatory pathology
• inflammatory / fibrotic stenosis of Papilla of Vater or common channel of bile / pancreas duct / *endoscopic failure or technically unfeasible*
• stenosis of minor papilla (e.g. pancreas divisum) / *endoscopic failure or technically unfeasible*
Neoplasia
• villous and tubulovillous adenoma / *endoscopic failure or technically feasible,* or >40mm or 20-30mm and high grad dysplasia [14]
• adenoma with intraampullary / intraductal extension 20mm [14]
• carcinoma in situ [14]
• (T1a, N0, M0, G1/2 carcinoma) [15]
• severe co-morbidities (making pancreaticoduodenectomy not feasible)

are no clear recommendations for adenoma recurrences after endoscopic removal. In this context, however, it should be pointed out that the risk of recurrence increases more than tenfold if the lesion cannot be removed in one session [17].

Finally, a surgical ampullectomy may also be indicated in the case of inflammatory stenosis in the area of the common course of the bile/pancreatic duct or its orifice into the duodenum (Table 161.1).

Essential Surgical Steps of Papillectomy/ Ampullectomy

The head of the pancreas and the duodenum must be prepared as far as technically possible to be assessed manually from all sides in order to exclude a locally advanced tumor manifestation. This can be achieved by an extensive Kocher maneuver. In most cases, the papilla region can be palpated and if necessary, for example, a catheter can be pushed antegrade to the papilla via an incision of the bile duct (e.g., by cholecystectomy or choledochotomy).

After sufficiently extensive longitudinal incision of the duodenum in the pars descendens, the papilla is now *exposed* (Fig. 161.2a). Holding threads may help to mark the resection area around the tumor region. In the case of a large or villous adenoma, probing of the bile duct should be carried out for orientation. The actual *papillectomy* defines the separation and circumferential detachment of the sphincter after incision of the mucosa (Fig. 161.2b). This can also be performed in case of large-scale but superficial lesions. The a*mpullectomy* also includes sharp dissection of the bile and pancreatic ducts in their common course and muzzle area with subtle coagulation of mucosal bleeding. These structures should also be stretched with retaining threads to avoid retraction into the parenchyma of the pancreas. Intraductal tumor expansion determines the extent of excision of both the bile and pancreatic duct. A tumor-free resection margin is important, which is why a frozen section procedure is done during the operation. The reinsertion of both ducts into the duodenal wall is usually carried out as a common ostium. For this purpose, both structures are adapted with simple interrupted stitches (Fig. 161.2c), and the existing holding threads are now circumferentially used for the so-called "duct-to-mucosa" anastomosis with the duodenal wall (Fig. 161.2d). It is important to check the resistance-free opening of both ducts with a probe. Finally, the duodenum is closed with a continuous double row suture.

Besides postoperative bleeding, complications include local abscess formation, bile or pancreatic duct leakage, and sometimes severe pancreatitis. Pancreatic fistulas, which appear in less than 10% after local excisions and in about 16% after radical partial pancreatoduodenectomy, must be treated as serious complications. Overall, the surgery-related complications rate for ampullectomy is lower than for partial pancreatoduodenectomy, which is reported to be between 30% and 50% [18]. However, ampullectomy is an infrequently performed operation compared to partial pancreatoduodenectomy and therefore should be limited to one or two surgeons in an appropriate center. Complications after ampullectomy rarely require surgical revision.

Considerations of Ampullectomy Versus Partial Pancreatoduodenectomy

The aim of the surgical procedure is the complete removal of the papilla/ampullary tumor. Well-established surgical procedures are available for this purpose: local excision of the tumor by papillectomy/ampullectomy or oncologically radical, partial pancreatoduodenectomy. The latter procedure is explicitly discussed elsewhere in this book. It is considered the standard procedure for periampullary pancreatic head and distal bile duct carcinomas and is performed in ampullary carcinoma starting at least at tumor stage T1b or detection of lymph node metastases [19]. It includes resection of the duodenum (possibly with antrum of the stomach), distal bile duct, gallbladder, and pancreatic head as well as an oncologic lymph node dissection. Occasionally, alternative

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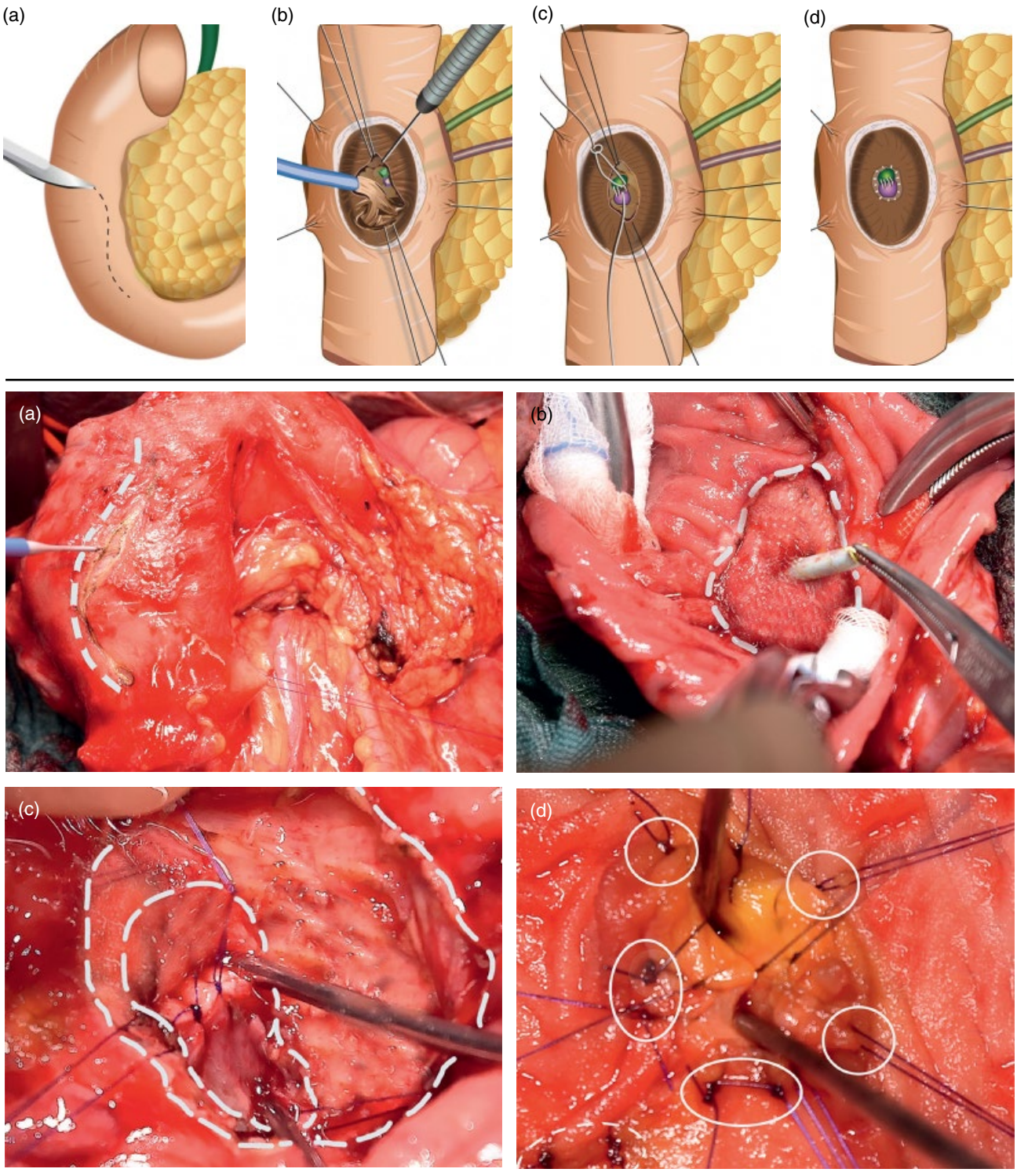


Figure 161.2 Operative steps of ampullectomy. (a) Longitudinal, S-shaped duodenotomy (dashed line) and exposure by means of retaining threads. (b) Probing of the papilla and circumferential opening of the papilla (dashed line). (c) Ampullectomy (outer line), creation of a common ostium of both duct structures (inner line) and subsequent (d) reinsertion of the common ostium into the duodenal wall (circles) and adaptation of mucosa defects (dashed line).

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options such as pancreatic head resection in combination with a segmental duodenectomy or a complete resection of the extrahepatic common bile duct and the ampulla are also indicated [20,21].

Due to their exposed location, papilla/ampullary carcinomas can become evident with obstructive jaundice at an early stage. Nevertheless, only about 40% of patients qualify for a surgical procedure after diagnosis [22]. General recommendations for or against local resection of an ampullary tumor have not been published in any surgical guidelines. While patients with a carcinoma *in situ* benefit from limited intervention, there are different views on the extent of surgery in case of a T1a staged cancer. Although isolated reports describe a combination of local lymphadenectomy and ampullectomy [15,23], it must always be taken into account that the initial surgical intervention sets the course for the patient's prognosis. Remaining tumor tissue or affected lymphatic tissue *in situ* is at least associated with a possibly harmful time delay of the subsequent, oncologically radical second intervention. In addition, it must be borne in mind that a local excision procedure cannot provide a reliable lymphadenectomy, especially in the pancreatic head area.

From the curative point of view, there must be no compromises in the choice of surgical procedure, although ampullectomy is a less invasive procedure and is associated with lower morbidity and mortality compared to partial pancreatoduodenectomy [24,25]. In this regard, it has been shown that the age of the patient alone has no influence on morbidity after partial pancreatoduodenectomy and therefore must not be the limiting factor in therapy decision making [26].

The risk for postoperative complications is clearly associated with the texture of the pancreatic parenchyma (soft, firm) and the diameter of the pancreatic duct (≤3 mm, >3 mm). However, these two parameters influence morbidity after ampullectomy or partial pancreatoduodenectomy in the same way.

Whenever a positive lymph node status or a tumor-affected resection margin is revealed during ampullectomy, a change of strategy (if possible intraoperative) towards a partial pancreatoduodenectomy must be determined. In order to avoid this method of therapy escalation in patients with Tis or T1a carcinomas who qualify for a local surgical procedure, attempts have been made in recent years to define preoperative tumor characteristics (such as size, histologic differentiation, or morphology) as predictive factors for lymph node metastases or deeper infiltration of pancreatic parenchyma and common bile duct. These approaches have not succeed.

Winter et al. studied the ampullary tumor size of 450 patients and showed an even more circumscribed growth pattern for adenocarcinomas compared to adenomas (median 2.0 versus 2.9 cm) [27]. In addition, another study revealed lymph node metastases and ductal involvement in 5% and 10% for early carcinomas (Tis, T1, <1 cm), respectively [12]. Therefore, it must be noted again that the procedure of ampullectomy as described in this chapter must be considered as an exception after diagnosis of ampullary carcinoma.

Surgical experience shows that there is often an advanced intraoperative tumor finding that could not be adequately determined in preoperative imaging, hence disqualifying for a local procedure. In many centers, therefore, the detection of a tumor that exceeds carcinoma *in situ* stage (by definition limited to the mucosa) is the indication for partial pancreatoduodenectomy. Postoperative morbidity and surgery-related lethality are comparable to the results after partial pancreatoduodenectomy for pancreatic cancer [12,27]. In contrast to the latter tumor entity, ampullary carcinomas are much less likely to develop portal venous or arterial infiltration [28]. This finding and a frequently observed lower mediodorsal tumor infiltration depth may explain the high R0 rate of over 95% [29].

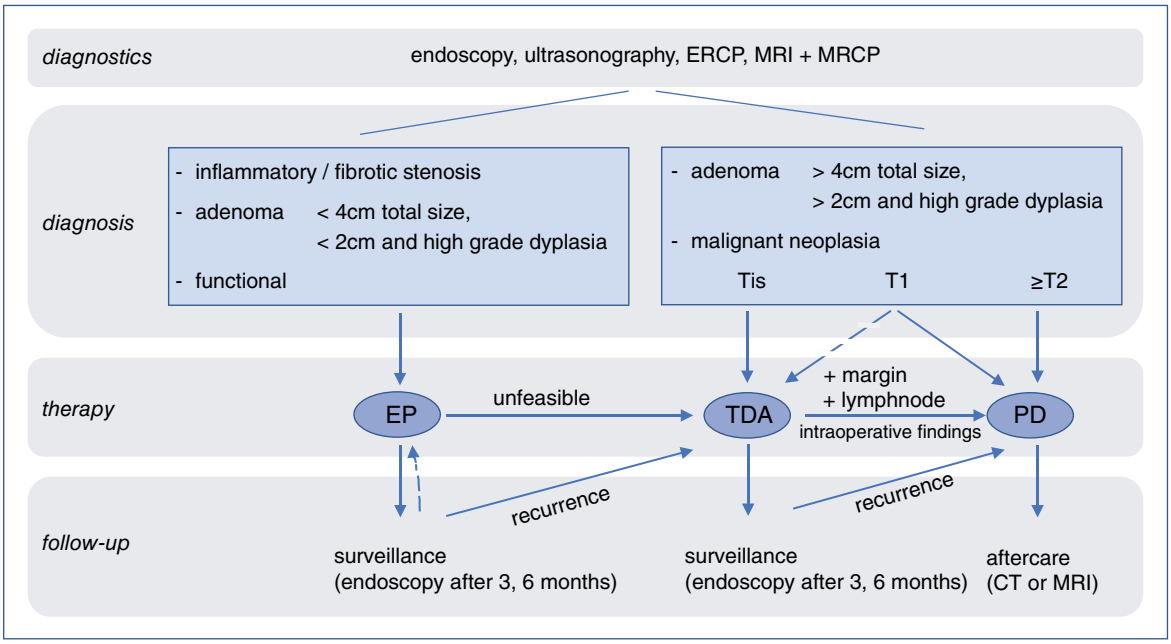
Currently, there is no evidence for the benefit of neoadjuvant therapy with a curative approach of ampullary carcinoma if surgical resection is possible [30]. Analogous to pancreatic head carcinomas, there is also no indication for preoperative drainage of the bile duct system from the surgical point of view. A timely operation should be sought, as the operation's outcome is not improved by a stent insert [31]. Figure 161.3 outlines a potential algorithm for the treatment of ampullary tumors.

Extension of Lymphadenectomy

As one of the first lymph node stations, the posterior pancreatoduodenal group is affected by lymphogenic metastases [32]. The potential extent of lymph node dissection along the superior mesenteric artery allows the distinction into three levels. Level I leaves the lymphatic tissue surrounding the artery with separation of the mesopancreas, level II additionally includes radicular resection of the inferior pancreatic duodenal artery, the first jejunal artery, and an *en bloc* resection of the mesopancreatic lymph nodes, and level III further includes dissection of the periarterial nerve tissue. Due to the potential involvement of the pancreatoduodenal lymph node groups, radical surgical resection of an ampullary carcinoma should include level II dissection [33].

The classic Whipple procedure and the pylorus-preserving variant of partial pancreatoduodenectomy are presented in detail elsewhere in this book. It should be noted that both methods should be regarded as equivalent both oncologically as well as with regard to

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EP: endoscopic papillectomy, TDA: transduodenal ampullectomy, PD: partial pancreatoduodenectomy
ERCP: endoscopic retrograde cholangiopancreatography, MRCP: magnetic resonance cholangiopancreatography
MRI: magnetic resonance imaging, CT: computed tomography

Figure 161.3 Algorithm of endoscopic or surgical approach of pathologies of the ampulla of Vater.

morbidity and postoperative quality of life [34] if the bulb or pyloric region is proven to be free of tumor.

Long-term Results After Operative Therapy

In the presence of benign adenomas, the endoscopic papillectomy, which found its way into the clinic in the 1980s [35,36], has prevailed with a low morbidity rate and good feasibility. To date, however, there are no randomized controlled trials that compare endoscopic procedures and transduodenal ampullectomy surgery in terms of outcome, recurrence, and reintervention rate in both benign and malignant processes. Morbidity is roughly comparable for both procedures (28.3% for ampullectomy versus 24.7% for endoscopic resection) [37,38].

A recently published metaanalysis presents at least an indicative comparison of both therapeutic approaches (surgical ampullectomy or partial pancreatoduodenectomy versus endoscopic papillectomy) for noninvasive lesions, carcinoma *in situ*, and T1 lymph node-negative adenocarcinoma. However, the study comments on the enormous difficulties with regard to meaningful analyses that arose in the course of heterogeneous patient populations, different dysplasia or tumor stages (low grade versus high grade versus T1 with intact or nonpreserved submucosal layer) and various histopathologic tumor entities (intestinal versus pancreaticobiliary) [37].

Overall, there is an obvious superiority of surgery over endoscopy in terms of complete resection (pooled R0 rate 96.4% for ampullectomy versus 76.6% for endoscopic resection versus 98.9% for partial pancreatoduodenectomy). The recurrence rate of benign neoplasms after endoscopic intervention is about 20%, which is higher than after surgical ampullectomy, which is reported to be less than 10% [39].

The postinterventional and surgical control of patients is important, all the more in those cases where a local excision procedure was done despite a malignant lesion. CT scans or MR tomographic cross-sectional imaging, ERCP, and endosonography are limited with regard to accurate statements about the involvement of the distal common bile duct and pancreatic duct beyond the periampullary region. Moreover, despite the lack of evidence of lymphadenopathy, lymph node metastases cannot be excluded in cases of tumor stage of T1a or higher [12]. In the literature, there are only small numbers of cases of endoscopic therapy of T1 adenocarcinomas [40]. The medical societies reflect on these circumstances and accordingly derive their recommendations for surgical therapy of malignant lesions of the ampulla. However, even transduodenal ampullectomy cannot be a standard treatment for T1 carcinomas. When using this local procedure, it is essential to achieve a tumor-free resection margin and negative lymph node status, which was proven by the data of Beger et al. [15]. During a mean

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follow-up period of nearly three years, especially those patients with R1 tumor resection showed tumor recurrence. Particular emphasis must be placed on the potential risk of a generalized tumor manifestation at the time of recurrence diagnosis with involvement of other organs, particularly the liver [41].

After partial pancreatoduodenectomy (performed with curative intent), the five-year survival rate across all tumor stages is about 45% [42]. Compared to periampullary carcinomas of the head of the pancreas and distal bile duct, ampullary carcinomas postoperatively show a comparatively favorable prognosis with a longer survival time. This was the result of the evaluation of the American National Cancer Institute database. Within AJCC stages, median survival is 55 months (stage I and II), 26 months (stage III) and 21 months (stage IV) respectively [43,44]. Besides tumor stage, positive lymph node status and perineural sheath invasion, histopathologic differentiation and thus the subtype of ampullary carcinoma play essential roles in the long-term postoperative course [44,45]. The five-year survival rates are below 30% for the pancreatobiliary subtype and over 60% for intestinally differentiated ampullary cancer [46]. The added value of adjuvant chemotherapy seems to be given (if at all) for pancreatobiliary ampullary carcinoma [47].

Conclusion

Ampullectomy and partial pancreatoduodenectomy are standardized surgical procedures for ampullary tumors and carcinomas. Strictly speaking, it makes no sense to compare both operations in terms of long-term outcome from an oncologic point of view because they do not replace each other, but they represent the appropriate treatment concept at different times of a periampullary tumor disease. Ideally, the operation achieves the least invasive but at the same time sufficiently radical procedure, as a fundamental prerequisite for sustainable treatment success for the patient. Of course, in addition to this important decision, surgically independent factors, such as tumor biology and subtype of ampullary carcinoma, play an essential role in long-term prognosis. Both surgical procedures are demanding, so it is essential that they are performed at a center with pancreatobiliary surgical expertise.

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Surgical Treatment of Duodenal Cancer

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Duodenal cancer is a rare disease. Primary, nonampullary duodenal adenocarcinomas account for about 0.5% of all gastrointestinal cancers. The incidence of duodenal cancer is 5.4 per 1 000 000 people [1]. It accounts for 60–100% of all duodenal malignancies and 30–45% of all small intestinal malignancies. Besides sporadic duodenal adenocarcinoma, other causes of adenocarcinoma include gastrointestinal polyposis syndromes with a genetic background, such as familial adenomatous polyposis, Peutz–Jeghers syndrome, and duodenal polyposis. Early duodenal cancer, which is classified into mucosal and submucosal types, is usually asymptomatic and is typically diagnosed on endoscopic check-ups. Although mucosal tumors with no lymph node metastasis could be treated by endoscopic complete resection [2], feasibility of endoscopic resection for duodenal lesion depends on location, depth, and size of tumor [3].

Long-term survival with submucosal or more advanced tumors, however, requires complete surgical resection. The standard surgical procedure for the disease is pancreatoduodenectomy (PD) with regional lymph node dissection (lymphadenectomy) [4]. The regional lymph nodes include nodes along the inferior pancreatoduodenal artery and first jejunal artery, infra- and suprapyloric nodes, nodes along the common hepatic artery, and nodes on the posterior and superior surface of the pancreatic head. Since these pancreatoduodenal lymph node stations are commonly involved in duodenal adenocarcinoma [4], *en bloc* regional node dissection requires total mesoduodenum excision. Segmental resection (limited resection: LR) of the duodenum can be performed in some cases, depending on the location and extent of the tumor. Partial segmental resection can achieve negative margins in tumors in the proximal (first part) or distal part (distal third or fourth part) of the duodenum, and the long-term survival outcome of LR for selected patients with such tumors, especially those located in the third or fourth portion of the duodenum and those with T1a/T1b stage cancers, is comparable between PD and LR [5–7].

The most significant prognostic factor for duodenal cancer is resectability. In the absence of distant metastasis, curative resection (R0 resection) determines the outcome in patients with duodenal cancer. Since the year 2000, the five-year survival rate after curative surgery has been reported to be 17–74% (Table 162.1) [1,4,8–18]. The results obtained are 40–60% reproducible, as reported by a large (more than 100 cases) series [10,12,13,15–17]. In another report, the TNM stage was higher in patients with nonampullary duodenal cancer than in patients with ampullary duodenal cancer [14]. Deep extension of the primary tumor (T), presence of nodal metastases (N), margin-positive resection (R), large size of tumor, poor histologic grade, and higher age are reportedly associated with a poor prognosis after resection [6,16,19]. However, after adjusting for TNM stage, no significant difference in survival was observed between ampullary and nonampullary duodenal cancer [14].

Database analysis of the largest series of stage I–IV cancers [19] showed five-year survival rates of 65.9%, 50.4%, 31.4%, and 11.9%, respectively, for the four cancer stages. The common recurrence sites were locoregional, intraabdominal distant organs, including the liver and peritoneum, and extraabdominal distant organs, including the lungs.

Systemic chemotherapy or chemoradiotherapy is administered after resection of advanced disease to prevent relapse in the setting of good postoperative performance status. However, the role of adjuvant therapy and/or neoadjuvant therapy for patients with duodenal cancer has not yet been established [6,20,21]. Additionally, survival outcomes after resection of duodenal cancer

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Table 162.1 Survival rates after resection of duodenal cancer.

First author	Year	No. of patients	Five-year survival (%)
Ryder [8]	2000	49	43
Kaklamanos [9]	2000	63	40
Bakaen [10]	2000	101	54
Sarela [11]	2003	72	74
Gold [12]	2007	106	68
Cecchini [13]	2012	103	42
Zenali [14]	2013	68	56
He [15]	2014	158	49
Solaini [16]	2015	150	43
Buchbjerg [1]	2015	28	27
Jiang [17]	2016	128	44
Sakamoto [4]	2017	51	67
Lee [18]	2018	49	67

have not changed significantly over the past few decades (see Table 162.1). Hence, further work is urgently needed to improve the survival outcomes of duodenal cancer following multimodal treatment, including surgery.

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Surgical Treatment of Distal Cholangiocarcinoma

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Introduction

Extrahepatic bile duct tumors have been conventionally classified into perihilar and distal tumors from a surgical standpoint. The standard procedures are major hepatectomy for the former and pancreaticoduodenectomy for the latter. According to the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, tumors with their center located between the confluence of the cystic duct and common hepatic duct and the ampulla of Vater are considered distal bile duct tumors [1]. The TNM staging system of distal tumors is separate from perihilar tumors because their pathologic features, surgical approach, and prognosis are different.

Distal cholangiocarcinoma is a relatively uncommon disease, comprising approximately 30% of all cholangiocarcinomas [2]. Although pancreaticoduodenectomy is commonly selected as a surgical procedure for pancreatic head cancer and distal cholangiocarcinoma, a minor procedure for each type of tumor is necessary as biologic behavior is different. Because the prevalence of distal cholangiocarcinoma is lower than that of pancreatic head carcinoma, a limited number of publications focus solely on the clinicopathologic features of distal cholangiocarcinoma. Hospital mortality after resection in high-volume centers for distal cholangiocarcinoma is 0–7% (Table 163.1) [3–11]. The most common surgery-related complication is pancreatic fistula (7–53%) (see Table 163.1) [3,5,8,9,12] because patients have a normal soft pancreas with a thin main pancreatic duct in most cases of distal cholangiocarcinoma.

The five-year overall survival after resection of distal cholangiocarcinoma ranges from 24% to 50% (see Table 163.1) [3–13]. Lymph node metastasis is commonly observed (22–68%) (see Table 163.1), and this is a major factor that determines prognosis after surgery [3–14]. Other important prognostic factors are depth of invasion [6,8,10,12], pancreatic invasion [3,4,6–10,14], perineural invasion [3,4,6–8,14], tumor histology [4–6,8,9], and resection margin status [4–7,9–12,14]. Therefore, the surgical approach for distal cholangiocarcinoma should be carefully modified depending on tumor location, longitudinal or extramural tumor extension, lymph node status, and perineural involvement.

Pyloric Ring Preservation Versus Resection

Pylorus preservation or resection is a major option in pancreaticoduodenectomy. One of the merits of removing the pyloric ring is the removal of lymph nodes in the perigastric region. However, perigastric lymph node metastasis is not frequently involved in distal cholangiocarcinoma [15]. Based on these observations, pylorus-preserving pancreaticoduodenectomy is indicated in almost all patients with distal cholangiocarcinoma. Randomized controlled trials comparing the clinical outcome between pylorus-preserving pancreaticoduodenectomy and conventional pancreaticoduodenectomy (thus removing perigastric lymph nodes) for patients with periampullary carcinoma showed no significant difference in long-term survival between the two procedures [16,17]. However, this concept is not applicable in patients with a tumor in the middle region of the extrahepatic bile duct because the tumor is generally proximate to the duodenal bulb. Therefore, removal of the duodenal bulb together with the pyloric ring may be the method of choice for obtaining a safe surgical margin.

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Table 163.1 Surgical outcome of distal cholangiocarcinoma.

Author	Year	N	Nodal involvement (%)	Overall 1/3/5-year survival (%)	Mortality (%)	Morbidity (%)	Pancreatic fistula (%)
Kayahara [12]	1999	50	68	–/47/35	–	30	26
Sasaki [13]	2001	59	39	–/43/34	–	–	–
Yoshida [11]	2002	27	58	65/37/37	4	22	–
Sakamoto [10]	2005	55	53	78/52/24	7	–	–
Cheng [9]	2006	112	22	86/51/25	4	19	7
Murakami [7]	2007	36	24	75/54/50	0	–	–
Ebata [8]	2007	100	38	75/47/35	5	54	42
Kawai [14]	2010	62	61	–/–/–	–	–	–
Kiriyama [6]	2015	370	42	–/54/41	5	–	–
Chua [5]	2017	28	68	68/49/24	0	43	7
Miura [3]	2017	88	40	81/51/43	2	17	53
Maeta [4]	2017	453	57	–/52/42	4	68	–

This procedure is necessary for a case with severe extramural tumor growth.

Lymph Node Dissection

Lymph node metastasis is one of the most important factors affecting survival of patients with distal cholangiocarcinoma [3–6,8,10–14]. The five-year overall survival after resection is 4–36% in patients with nodal involvement and 30–73% in those without [3,4,6–12,14]. In addition, the number of involved nodes works as a determinant of cancer progression in distal cholangiocarcinoma 7,11,13,14,18–21]. In a report by Kiriyama et al. analyzing 370 patients with distal cholangiocarcinoma [6], the median survival time shortened with increasing number of involved lymph nodes: 2.2 years in patients with 1–3 metastatic nodes and 1.3 years in those with four or more (Fig. 163.1).

The total lymph node count (TLNC), defined as the total number of lymph nodes examined histologically, is another important predictor of survival because inadequate assessment of lymph nodes, due to either an insufficient extent of resection or pathologic examination, results in understaging of cancer [22,23]. It should be noted that TLNC substantially differs depending on the extent of lymphadenectomy and additional organ resection. In particular, TLNC can vary depending on

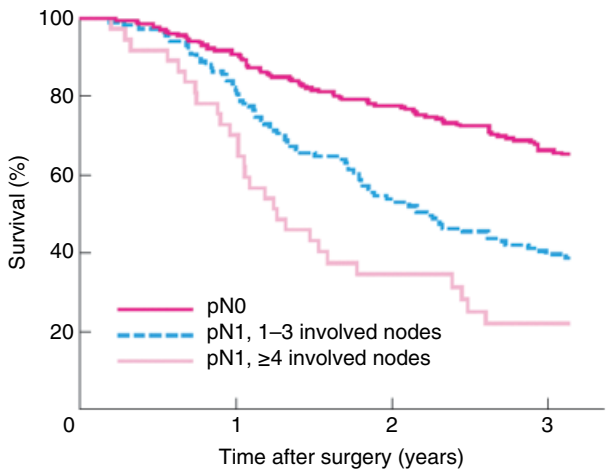


Figure 163.1 Overall survival according to the number of involved nodes in 370 patients. $P < 0.001$ (pN0 versus pN1, 1–3 involved nodes; pN0 versus pN1, 4 or more involved nodes) (log-rank test). *Source:* [6]/Oxford University Press.

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the extent of lymphadenectomy for the perigastric and mesenteric lymph nodes. The AJCC recommends a "12-node minimum" for distal cholangiocarcinoma to prevent inadequate staging [1], but the supporting evidence for this number is ambiguous. Kiriyama et al. reported that TLNC considerably affected survival among 206 patients with pN0 disease who underwent R0 resection, who were divided into three groups according to TLNC (less than 10, 10–19, 20 or more). The three-year survival rates were 50%, 68%, and 71%, respectively [6]. Hence, a minimum of 10 nodes may be sufficient for pathologic nodal assessment in distal cholangiocarcinoma.

The total lymph node count also changes the lymph node ratio (LNR) results, calculated as a ratio between the number of lymph node metastases and TLNC because the greater the TLNC is, the lower the LNR. According to the report by Kiriyama et al., the median (range) TLNC was 19 (3–59) [6]. Nodal metastasis occurred in 157 patients (42.4%); the median (range) number of involved nodes was 2 (1–19), and the LNR was 0.11 (0.02–0.80). An LNR lower than 0.17 was associated with a significantly shorter median survival (1.3 vs 2.2 years). Another report by Kawai et al. indicated that an LNR >0.2 is an important factor for predicting survival after resected distal cholangiocarcinoma [14].

For distal cholangiocarcinomas, the location of nodal involvement differs among tumor locations, according to the report by Kayahara et al., which compared the lymph node stations between the middle third (N = 14) and lower third (N = 36) of cholangiocarcinomas [12]. In the former tumor, nodes along the common hepatic artery, in the hepatoduodenal ligament, and in the posterior pancreatoduodenal region were frequently involved with an incidence of 7%, 50%, and 7%, respectively. Interestingly, there was no lymph node metastasis in nodes around the superior mesenteric artery. In contrast, there was less nodal involvement in nodes along the common hepatic artery and more involvement in posterior pancreatoduodenal nodes in patients with lower-third cholangiocarcinoma. Notably, in 28% of patients with lower-third cholangiocarcinoma, there was lymph node metastasis in nodes around the superior mesenteric artery, with the highest frequency in nodes at the origin of the inferior pancreatoduodenal artery.

These differences in the state of cancer spreading through lymphatic vessels and lymph nodes should be considered preoperatively when planning a surgical approach for distal cholangiocarcinoma. Lymph node dissection along the superior mesenteric artery is recommended for the lower-third cholangiocarcinoma rather than the middle tumor. A thorough lymph node dissection along the superior mesenteric artery requires combined resection of the mesentery along the first jejunal artery and vein.

Skeletonization of the Hepatoduodenal Ligament and Dissection of Pancreatic Head Neural Plexus

Neural plexus invasion is a potential prognostic factor in cholangiocarcinoma ([4,6]. According to the recent extensive study by Maeta et al. (N = 453), the overall incidence in distal cholangiocarcinoma was 67% [4]. The five-year survival rate for patients with perineural invasion was significantly lower than those without (56% vs 33%) [4]. Neural invasion was observed more frequently with tumor progression [24]. Therefore, skeletonization of the hepatoduodenal ligament, including removal of the neural plexus around the hepatic artery and portal vein, is recommended for the treatment of advanced distal cholangiocarcinoma.

In this procedure, the proximal bile duct was transected basically at the level of the right hepatic artery or more proximally, as needed. Regional lymph node dissection was undertaken as far as possible (Fig. 163.2) [25].

Bile Duct Cut Margin

It is now widely recognized that margin status is one of the robust predictors of long-term survival in cholangiocarcinoma [26]. After surgical resection for extrahepatic cholangiocarcinoma, invasive carcinoma at ductal resection margins appears to have a substantial adverse effect on patient survival. Superficial spreading, defined as a noninvasive cancer extension of more than 20 mm, is sometimes observed in cholangiocarcinoma, accounting for approximately 15% of all tumors, according to Igami

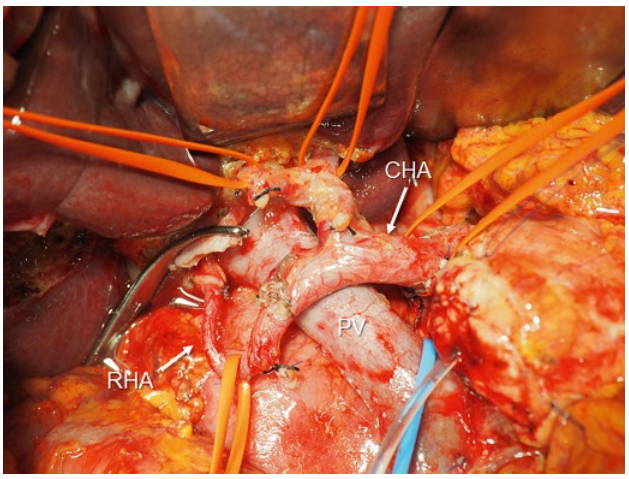


Figure 163.2 Skeletonization of the hepatoduodenal ligament. RHA, right hepatic artery; CHA, common hepatic artery; PV, main portal vein.

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et al. [27]. Histologically, superficial spreading is more commonly observed in papillary and well-differentiated adenocarcinomas than in other types of carcinoma [27]. Because superficial spreading has a high risk at positive ductal margins, the extent of superficial spreading from the main tumor should be carefully examined using cholangiography, intraductal ultrasonography, and/or biliary biopsy. It is also important to examine the proximal bile duct cut margin by intraoperative frozen section histology.

Nonetheless, extensive spread of cancer beyond the macroscopic tumor mass is often observed in cholangiocarcinoma. Ebata et al. proposed that a 10 mm margin for invasive cancer and 20 mm margins for noninvasive components are required on the ductal stump to accomplish R0 resection [28].

Notably, the clinical significance of residual carcinoma *in situ* at the bile duct cut margin is controversial. Several reports have indicated that residual carcinoma "*in situ*" in the proximal cut margin of the bile duct does not have an impact on survival [27,29,30]. However, a positive margin with "invasive" carcinoma is an independent risk factor for poor survival after surgery for distal cholangiocarcinoma [6,11,12]. Importantly, residual carcinoma "*in situ*" in the ductal stump potentially progresses to local recurrence and shortens postoperative survival in patients with early-stage cholangiocarcinoma. However, this prognostic effect was less severe than that of residual "invasive" carcinoma. Residual carcinoma "*in situ*" should be avoided as much as possible in surgery for early-stage cancer [31].

Tumor Depth

The T classification is used exclusively for pathologic staging, but it cannot be used to determine local unresectability and subsequent surgical procedures. However, because it is commonly associated with several prognostic factors, a preoperative assessment of T classification is needed.

In the eighth edition of the AJCC cancer staging classification [1], the T system for distal cholangiocarcinoma has been revised from a layer-based to a depth-based approach. Hong et al. first proposed a depth-based approach for the T system using the measured depth of invasion (DOI), with cutoff values of 5 and 12 mm [32]. DOI was defined as the vertical distance between the basal laminae of the adjacent normal/dysplastic bile duct and the advancing infiltration of cancer cells (Fig. 163.3). However, DOI was measurable in less than half of the patients because it is necessary to observe the clear basal lamina bounding the tumor with the most extensive cancer infiltration on the same histologic slide for accurate measurement of DOI [24]. Cancer infiltration, associated cholangitis, and catheter placements evoke fibrosis inside and outside the bile duct wall, often precluding clear visualization of the basal lamina.

The low frequency of measurability of DOI in bulky tumors and the high frequency in papillary tumors suggest that DOI cannot easily be measured in advanced tumors. In this regard, invasive tumor thickness (ITT), defined as the maximal vertical distance of the invasive cancer component, was measured (see Fig. 163.3).

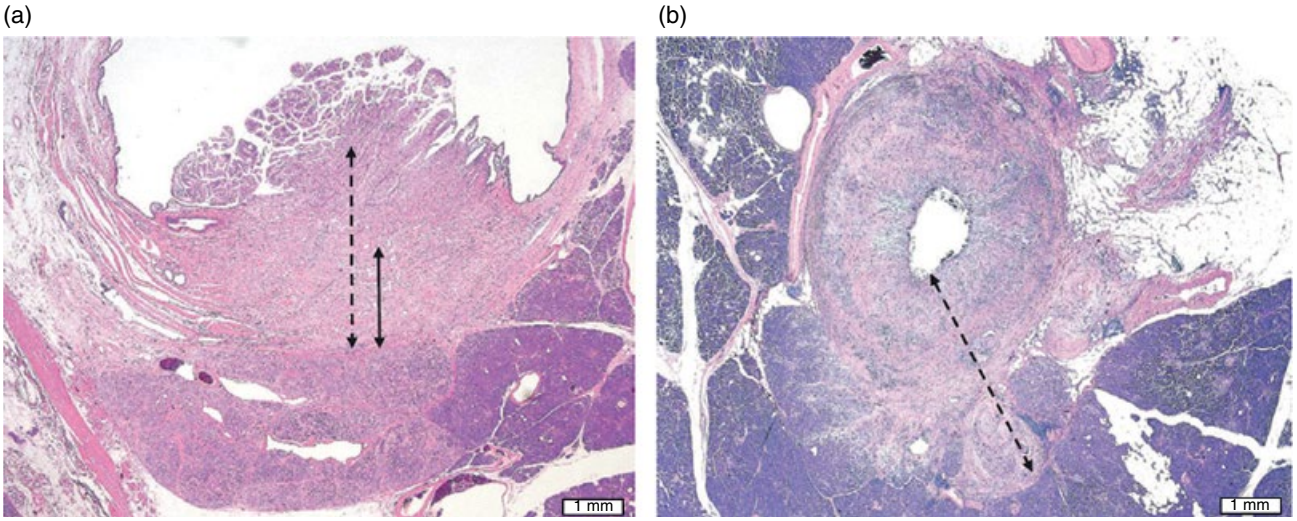
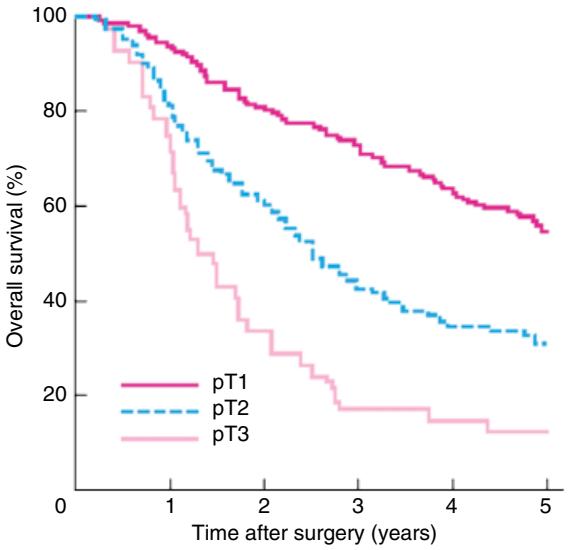


Figure 163.3 Depth of invasion (solid line) and invasive tumor thickness (dotted line) in (a) papillary and (b) nonpapillary tumor morphology. Both specimens were sectioned axially to the bile duct. Depth of invasion is not measurable in (b) because the basal lamina of the bile duct is not observed in the circumferentially thickening tumor (hematoxylin and eosin stain; scale bar 1s>mm). *Source:* [24], John Wiley & Sons.

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No. at risk

pT1	167	158	123	92
pT2	195	162	87	62
pT3	42	32	7	5

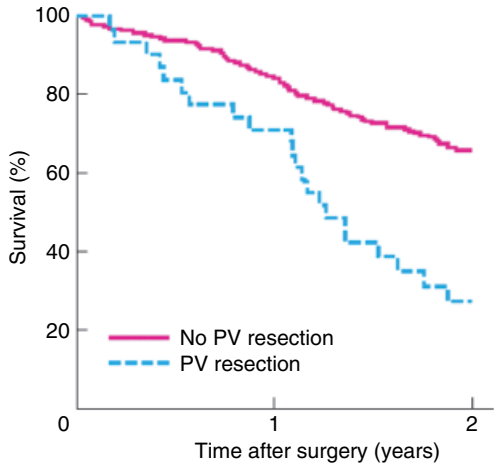
Figure 163.4 Overall survival stratified by T systems of AJCC eighth edition. In 222 patients with a missing depth of invasion (DOI), invasive tumor thickness (ITT) was used as an alternative to DOI for T assignment. $P < 0.001$ (pT1 versus pT2), $P = 0.001$ (pT2 versus pT3) (log-rank test). *Source:* [24]/Oxford University Press.

Survival curves according to T classifications of the AJCC eighth edition stratified by ITT are shown in Figure 163.4.

Portal Vein Resection

Pancreaticoduodenectomy combined with portal vein (PV) resection is an extended procedure that is often undertaken for pancreatic head cancer but is rarely performed for distal cholangiocarcinoma. Maeta et al. investigated the clinicopathologic features associated with PV resection using 453 patients who underwent pancreaticoduodenectomy, which is the largest series of PV resections in patients with distal cholangiocarcinoma [4]. Of these, 31 (6.8%) had combined PV resection. Postoperative morbidity and mortality were not different in those with or without PV resection. Portal vein invasion is associated with locally advanced disease. Consequently, the incidence of R1/2 resection was higher in this group (32% vs 12%). Survival among the patients with PV resection was worse than for the patients without PV resection (15% vs 42% at five years) (Fig. 163.5).

Considering the poor survival of patients with PV resection, distal cholangiocarcinoma with suspected PV invasion may be categorized as a borderline resectable tumor,



No. at risk

No PV resection	422	352	274
PV resection	31	22	7

Figure 163.5 Overall survival curves for patients who underwent pancreaticoduodenectomy for distal cholangiocarcinoma, stratified by surgery with or without portal vein resection. $P < 0.001$ (log-rank test). *Source:* [4]/Oxford University Press.

and the establishment of neoadjuvant chemotherapy and adjuvant chemotherapy for such patients seems urgently needed [4].

Surgery-Related Complications of Pancreaticoduodenectomy

The morbidity and mortality rates after resection of distal cholangiocarcinoma are 17–69% and 0–7%, respectively (see Table 163.1) [3–12]. Patients generally have a normal soft pancreas with a small main pancreatic duct. Therefore, the rate of pancreatic fistula is higher in patients with distal cholangiocarcinoma (7–53%; see Table 163.1) than in patients with pancreatic head cancer [3,5,8,9,12]. Other common complications include biliary fistula (0.1–3%) [8,9], delayed gastric emptying (0.1–7%) [5,8,9], and bleeding (3–11%) [5,8,9,11].

Bile Duct Resection as a Minimally Invasive Surgical Procedure

Bile duct resection can be considered an alternative approach in high-risk patients with middle-third distal cholangiocarcinoma but provides a worse long-term outcome [25,33]. Jikei et al. reported a detailed surgical comparison between bile duct resection and pancreaticoduodenectomy [25]. Bile duct resection was characterized by shorter operation time, less blood loss, less

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frequent complications, and lower mortality. However, the incidence of positive surgical margins was 26.3% in bile duct resection, in contrast to 5.6% in pancreaticoduodenectomy. The survival rate after bile duct resection was significantly worse than that after pancreaticoduodenectomy (38.8% versus 54.8% at five years). Meanwhile, "tumor length <15 mm" and "ductal margin length ≥10 mm" were favorable factors in bile duct resection. Therefore, it was proposed that a clinical guide for optimal candidates for bile duct resection included either or both of these favorable factors [25].

Conclusion

When a surgeon performs a pancreaticoduodenectomy for distal cholangiocarcinoma, dissection of the pyloric ring (pylorus-preserving, subtotal stomach-preserving, or conventional pancreaticoduodenectomy), the extent of lymph node dissection (dissect lymph nodes along the superior mesenteric artery or not), skeletonization of hepatoduodenal ligament, and the proximal cut line of the bile should be carefully designed based on tumor location as well as tumor extension.

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164

Adjuvant and Palliative Chemotherapy of Periampullary Cancers

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Introduction

The term "periampullary cancer" encompasses three pathologically distinct tumor subtypes which are in close anatomic proximity to the pancreatico-ampullary apparatus, including tumors arising from the distal common bile duct, ampulla of Vater, and duodenum. The incidence of these tumors remains low, with European figures ranging between 0.3 to 0.84 per 100,000 population, placing them within the European Union definition of rare cancers [1,2]. These tumors possess different biologic and molecular characteristics, but they are often grouped together as their curative surgical approach would usually mandate a pancreaticoduodenectomy [3,4]. Occasionally, the true pathologic origin of the malignant process is difficult to establish until full histologic assessment of the specimen is performed [5]. The heterogeneity of the histologic and biologic profiles has profound implications for their long-term survival rates and response to available chemotherapy regimens [5,6].

Periampullary tumors demonstrate a higher resectability rate, in contrast to pancreatic tumors. The ideal treatment is surgical resection, which offers a chance of cure and prolonged survival in 60–80% of patients with resectable disease on presentation [7]. The remainder usually present with manifestations consistent with locally advanced disease or evidence of distant widespread metastasis. The mainstay of therapy in this setting is palliation of symptoms, with relief of jaundice, alleviation of pain, and provision of nutritional support [8]. The focus on prolonging survival by the use of adjuvant and palliative treatments should not overlook the psychologic and emotional aspects for patients affected with this debilitating disease.

At present, the overall prognosis remains bleak despite adequate tumor clearance by surgical resection as the locoregional and distant relapse incidence rates are known to be high in these tumors [9]. Surgical resection alone is associated with five-year survival rates of 20–30%. The worst prognosis is associated with positive local lymph nodes and involved surgical margins [5,10,11]. Given the above, attempts to improve long-term survival by the addition of adjuvant chemotherapy have been tested in various clinical studies.

Most of the evidence in published literature on the use of adjuvant and palliative chemotherapy is limited to institutional retrospective case series and often contains a mixture of periampullary and pancreatic tumors with limited randomized controlled trials. The heterogeneity and quality of the evidence can lead to conflicting results about the genuine value of chemotherapy in periampullary cancers. The inherent rarity of these tumors has governed the paucity of published useful data that could be translated into effective clinical and oncologic management paradigms.

Distal Cholangiocarcinoma

Adjuvant Therapy

Patients with distal cholangiocarcinoma have the worst prognosis among periampullary cancer patients. The long-term survival figures resemble those achieved in pancreatic adenocarcinoma. Tumors arising within the intrapancreatic portion of the distal bile duct account for approximately 27%–40% of all cholangiocarinomas cholangiocarcinomas [12,13]. These are closely linked to tumors arising in the proximal pancreatic duct as they

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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share the same embryologic origins with common phenotypic and functional characteristics. This supports the hypothesis that they should be considered as a congruent disease entity [14].

Takada et al. [15] conducted one of the first phase III randomized controlled trials in Japan with adjuvant 5-fluorouracil (5-FU) and mitomycin C in 508 patients with resected pancreaticobiliary tumors (including 139 patients with cholangiocarcinomas) compared to surgery alone and concluded that adjuvant chemotherapy compared to surgery alone did not have an impact on the five-year survival rate (26.7% vs 24%).

Following this, the European Study Group for Pancreatic Cancer 3 (ESPAC-3) periampullary trial was designed to explore the benefit of adjuvant chemotherapy on overall survival in patients with resected periampullary cancer [16]. In this study, 428 patients (of whom 96 had cholangiocarcinomas) were randomized to either fluorouracil or gemcitabine-based chemotherapy versus surgery alone. The use of adjuvant treatment was associated with a potential survival advantage that did not reach statistical significance (median 43 months vs 35 months; hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.66–1.11) but on multivariable analysis and after adjusting for prognostic variables, a statistically significant survival benefit was demonstrated with adjuvant chemotherapy with HR 0.75 (95% CI 0.57–0.98; $P = 0.03$). The median survival of patients with cholangiocarcinoma assigned to observation, fluorouracil plus folinic acid, or gemcitabine arms was 27.2, 18.3, and 19.5 months, respectively.

More recently, the BILCAP study [17] was a phase III randomized controlled trial conducted within the UK, primarily assessing survival outcomes between adjuvant capecitabine or observation alone following resection for confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer. In this trial of 447 patients (of whom 156 had distal cholangiocarcinomas), no statistical significance was noted on overall survival in the intention-to-treat analysis. However, sensitivity analyses in this population proved a statistical significance following adjustment for prognostic factors (nodal status, grade of disease and sex, and minimization factors resulting in an overall survival HR of 0.71 (95% CI 0.55-0.92; $P = 0.010$). A statistically significant advantage was demonstrated for overall survival in the per-protocol analysis population in which median overall survival was 53 months and 36 months for capecitabine and observation respectively (HR 0.75; 95% CI 0.58–0.97; $P = 0.028$).

Concurrent with the BILCAP study, the PRODIGE 12-ACCORD 18 (UNICANCER GI Group) study [18] was a randomized phase III trial conducted in 33 centers in France with a total of 194 patients, to investigate beneficial outcomes with adjuvant gemcitabine and oxaliplatin chemotherapy (GEMOX) over observation following resection of biliary tract cancers (of whom 55 had distal cholangiocarcinomas). This study primarily investigated disease-free survival (DFS) following adjuvant GEMOX or observation and no statistically significant result was noted (median 30.4 months vs 18.5 months; HR 0.88; 95% CI 0.62–1.25; $P = 0.48$). No significant result was noted with overall survival either (median 75.8 months vs 50.8 months; HR1.08; 95% CI 0.70–1.66; $P = 0.74$).

These studies have demonstrated evidence for the use of adjuvant therapy (Table 164.1). Horgan et al. [11] conducted a large metaanalysis of 20 studies, which included a randomized trial of chemotherapy, two registry, and 17 institutional series. The treatment protocol contained chemotherapy alone in three studies, radiotherapy only in nine, while eight studies contained radiation and chemotherapy combinations. There was a total of 6712 patients, of whom 1797 received some form of adjuvant treatment during the course of their disease and 4915 in the surgery-only group. In this metaanalysis, the improvement in five-year survival with any adjuvant therapy was not statistically significant (pooled odds ratio [OR] 0.74; 95% CI 0.55–1.01); however, the survival benefit from adjuvant therapy was statistically significant when the data from the two large registry series (N = 1233 patients) were excluded (OR 0.53; 95% CI 0.39–0.72). Pooled data extracted from the studies confirmed a statistically significant overall survival advantage for any adjuvant therapy in node-positive disease (OR 0.49; 95% CI 0.30–0.80) and patients with margin-positive disease (OR 0.36; 95% CI 0.19–0.68).

These studies have demonstrated survival benefit for the use of adjuvant treatment in patients with cholangiocarcinoma, especially in those with poor prognostic indicators [22,23]. Currently, there are two randomized controlled trials under way of adjuvant therapy in patients with resected cholangiocarcinoma. The ACTICCA-1 trial compares adjuvant combination therapy with gemcitabine and cisplatin against the standard treatment of capecitabine and is due to publish it's findings by 2024. The ASCOT trial, which compares adjuvant S-1 chemotherapy versus observation alone, has completed recruitment and the results are due to be published.

Palliative Therapy

The benefits of systemic chemotherapy in addition to best supportive care in patients with metastatic and recurrent distal cholangiocarcinoma are well established. Patients treated with chemotherapy were noted to have a significantly better median overall survival of more than six months with a better quality of life. The reported high incidence of local relapse and distant recurrence would

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Table 164.1 Studies of adjuvant treatments in resected periampullary cancers.

		Subdivision of tumor types					
Study, year	**Total no. of patients (N)**	**Distal cholangiocarcinoma**	**Duodenal adenocarcinoma**	**Ampullary carcinoma**	**Treatment**	**Median survival (months)**	**Five-year survival (%)**
Bakkevold et al., 1993 [17][a]	61	–	–	14	5-FU/Dox/MMC	23	4
					Surgery	11	8
Takada et al. [15][a]	436/508 evaluated	118	–	48	5-FU/MMC	–	26.7 vs 24.1 months (distal cholangio)[c]
					Surgery		28.1 vs 34.3 months (ampullary)[c]
ESPAC-3, 2012 [16][a]	428	96	10	297	Gemcitabine	45.7	44
					5-FU/FA	38.9	40
					Observation	35.2	36
Poultsides et al. [18][b]	122	–	122	–	5-FU + Rx	–	47
					Observation		48
Bhatia et al., 2006 [19][b]	125	–	–	125	5-FU + Rx	–	48
					50.4 Gy		
					Observation		11
BCAT, 2018 [32][a]	226	123	–	–	Gemcitabine	62.3	51
					Observation	63.8	51
BILCAP, 2019 [17][a]	447	156	–	–	Capecitabine	51.1	49
					Observation	36.4	42
PRODIGE 12-ACCORD 18 (UNICANCER GI Group), 2019 [18][a]	196	55	–	–	GEMOX	75.8	57
					Observation	50.8	59

[a] Randomized controlled trial.
[b] Case series.
[c] Log rank test = NS.
GEMOX, gemcitabine and oxaliplatin; DOX, doxorubicin; MMC, mitomycin C; 5-FU, 5-fluorouracil; FA, folinic acid; NS, nonsignificant.

advocate early referral for palliation treatment in patients with satisfactory performance status [22,24].

Eckel and Schmid [25] performed a pooled analysis of 104 trials examining the role of chemotherapy in advanced biliary tract cancer, which showed combination treatment to have a better effect compared to monoagent therapies. The gemcitabine- and platinum-based combinations demonstrated the greatest benefit in the pooled analysis.

The randomized phase III ABC-02 study [26] of up to six months of gemcitabine versus gemcitabine and cisplatin recruited 410 patients (73 distal cholangiocarcinomas) with unresectable, recurrent, or metastatic biliary tract carcinoma (Table 164.2).This trial demonstrated a significant overall survival advantage with the combination arm versus the gemcitabine arm (11.7 months vs 8.1 months; HR 0.64; 95% CI 0.52–0.80) and a median progression-free survival of 8.0 months versus 5.0 months (HR 0.63; 95% CI 0.51–0.77), respectively. Patients who received the combination therapy were 36% less likely to die at any time compared to those who received gemcitabine alone (HR 0.64; 95% CI 0.52–0.80). Grade 3 and 4 toxicities occurred with similar frequency in both study arms without any substantial difference. The combination of gemcitabine and cisplatin is the first-line treatment of choice recommended by

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the European Society of Medical Oncology (ESMO) [31] in patients with favorable performance status (PS 0–1). Patients with PS 2 should be considered for gemcitabine monotherapy while oxaliplatin could be substituted for cisplatin in patients with impaired renal function.

Following the findings of the ABC-02 trial, the ABC-06 study [30] was completed recently. This was a phase III randomized controlled trial that compared second-line chemotherapy consisting of FOLFOX and active symptom control (ASC) versus ASC alone in patients with advanced or metastatic biliary tract cancers who had already undergone first-line chemotherapy with cisplatin and gemcitabine. A total of 162 patients were analysed (out of whom 45 had extrahepatic cholangiocarcinoma) and a statistically significant outcome was observed in overall survival. Median overall survival of 6.2 months and 5.3 months was noted in adjuvant FOLFOX and ASC and ASC-only cohorts respectively (HR 0.69; 95% CI 0.50–0.97; P = 0.031). Grade 3 and 5 toxicities were 69% in the FOLFOX and ASC cohort and 52% in the ASC-only cohort, with the most frequently reported adverse event being neutropenia.

Duodenal Adenocarcinoma

Adjuvant Therapy

Complete surgical resection with regional lymphadenectomy confers prolonged survival for patients with duodenal cancer. Important prognostic factors include the degree of tumor differentiation and local lymph node involvement. Several studies have shown no survival benefit for the routine use of adjuvant chemotherapy in completely resected, nodal disease-free duodenal adenocarcinoma [33,34].

The global low incidence of duodenal adenocarcinoma and challenges in conducting adequately powered future studies were reflected in the ESPAC-3 trial which contained only 10 patients with duodenal adenocarcinoma in addition to 25 nondescriptive periampullary tumors out of the original study cohort (see Table 164.1). The eight patients who were assigned to observation in this group survived a median of 28.7 months (95% CI 4.7–∞ months); 12 patients in the fluorouracil plus folinic acid group survived 22.4 months (95% CI 9.6–54.6 months), and 15 had high but not estimable survival with gemcitabine therapy [16].

There is currently no agreed regimen as a first-line therapy but many centers would advocate the use of adjuvant oxaliplatin-based chemotherapy in patients with high-risk features (e.g., nodal metastasis) similar to the recommendations for resected colonic adenocarcinoma. Other regimens which demonstrated disease-related activity are capecitabine and oxaliplatin (CAPOX), 5-FU and leucovorin with oxaliplatin (FOLFOX), and 5-FU and leucovorin with irinotecan (FOLFIRI) [28,29,35]. To date, there are no randomized controlled trials testing the superiority of any of these combinations.

Chemoradiation has been tested in the adjuvant setting and showed improvement in locoregional control but this did not translate into any survival benefit [36]. In a retrospective series published by Poultsides et al. [21] from a single institution, 122 patients with local lymph node involvement showed no difference in overall survival with adjuvant chemoradiotherapy compared to patients who underwent surgery alone (five-year survival 47% vs 48%; P = 0.82) [37].

An international collaboration for the study of rare tumors has launched an open-label, randomized controlled multicenter trial (BALLAD) to assess the efficacy of six months of adjuvant chemotherapy compared to observation only in stage I–III resected small bowel adenocarcinoma. The study will also compare fluoropyrimidine monotherapy versus fluoropyrimidine plus oxaliplatin. Recruitment into the study is currently ongoing and is expected to finish by 2022.

Palliative Therapy

A number of studies support the use of palliative chemotherapy in patients with recurrent and metastatic duodenal adenocarcinoma (see Table 164.2) as it adds a clear survival benefit over best supportive care [33,38,39]. The Eastern Cooperative Oncology Group (ECOG) published one of the early studies on 31 patients with locally advanced and metastatic small bowel tumors who received combination treatment 5-FU, doxorubicin, and mitomycin C with a median survival of eight months [27].

Zaanan et al. [28] published results of a retrospective study of 99 patients with advanced and metastatic small bowel adenocarcinoma (55 duodenal) comparing first-line treatments with FOLFOX, leucovorin–FU, FOLFIRI, and leucovorin–FU–cisplatin. In the report, 48 patients with advanced cancer who received FOLFOX as front-line therapy had a median progression-free survival of 7.4 months and median overall survival of 17.8 months. A study by Overman et al. [29] conducted at the M.D. Anderson Cancer Center evaluated the combination of capecitabine and oxaliplatin (CAPOX) in 30 patients with either metastatic or locally advanced small bowel or ampullary adenocarcinoma. In the 18 patients who had small bowel adenocarcinoma, the response rate was 61%, with a median time to progression of 9.8 months and median overall survival of 20.4 months. Of note, 10% of treated patients had a complete radiographic response to CAPOX therapy. The treatment combination of fluoropyrimidine and oxaliplatin was also reported to have a better disease activity in phase II randomized con-

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Table 164.2 Studies of palliative treatments in locally advanced and metastatic periampullary cancers.

Study, year	Type of tumor	No. of patients	Treatment	Median survival (months)	Median progression-free survival (months)
ECOG, 2005 [27][a]	Small bowel/ampullary	31	5-FU/DOX/MMC	8	–
ABC-02, 2010 [26][b]	Biliary (some ampullary)	204	Gem + cisplatin	11.7	8
		206	Gem + cisplatin	8.1	5
Zaanan et al. [28][a]	Small bowel	10	LV/5-FU	13.5	7.7
		48	FOLFOX	17.8	6.9
		19	FOLFIRI	10.6	6
		16	LV/5-FU/cisplatin	9.3	4.8
Overman et al., 2009 [29][c]	Small bowel/ampullary	30	CAPOX	20.4	11.3
ABC-06, 2021 [30][b]	Biliary (some ampuallary)	81	FOLFOX/ASC	6.2	4
		81	ASC	5.3	–

[a] Case series.
[b] Randomized controlled trial.
[c] Phase II trial.
DOX, doxorubicin; MMC, mitomycin C; Gem, gemcitabine; 5-FU, 5-fluoruracil; CAPOX, capecitabine and oxaliplatin; LV, leucovorin; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; ASC, active symptom control.

trolled trials. Three studies, including that by Overman et al., combining fluoropyrimidine with oxaliplatin have shown similar activity, with response rates of 42–50% and a median time to progression ranging from 7.8 to 9.8 months [29,40,41].

Other studies have tested different agents, including irinotecan- and gemcitabine-based treatments which were found to have some disease activity in a small number of patients [28]. Targeted therapies such as antivascular endothelial growth factor receptor (VEGFR) or antiepidermal growth factor receptor (EGFR) therapies have not been evaluated in any formal study as yet and therefore there is currently no evidence to support their use outside the context of experimentation in a clinical trial.

Ampullary Carcinoma

Adjuvant Therapy

Ampullary carcinomas constitute 0.2% of the tumors arising in the gastrointestinal tract. These tumors show different immunohistochemical differentiation and molecular characteristics, including alterations of *KRAS*, *SMAD4*, and *APC* genes. The intestinal subtype mimics behavioral and oncogenic responses similar to duodenal adenocarcinoma, while the pancreaticobiliary subtype tends to be more aggressive, resembling pancreatic ductal adenocarcinoma with poor prognosis and unfavorable outcomes [42–45].

One of the earliest randomized controlled trials was published by Bakkevold et al. in 1993 [20]. This study demonstrated a median survival of 23 months versus 11 months ($P = 0.02$) using adjuvant combination chemotherapy agents 5-FU, doxorubicin, and mitomycin C in 61 patients (14 ampullary, 47 pancreatic tumors) who underwent a radical resection versus observation but with limited five-year survival (4 vs 8 years, respectively) and increased treatment-related toxicity.

ESPAC-3 [16] remains the landmark study in evaluating the role of adjuvant chemotherapy in periampullary carcinomas (see Table 164.1). There were 297 patients with ampullary adenocarcinoma who were randomized to observation, 5-FU/leucovorin, or gemcitabine. The use of adjuvant chemotherapy demonstrated a trend toward improved overall survival, favoring the chemotherapy group versus observation (median overall survival 43 vs 35 months; $P = 0.25$). Moreover, when the analysis was limited to patients with ampullary cancer, those treated with gemcitabine had a remarkable survival that was almost double that in the observation group (median 71 vs 41 months). Subsequent analysis did not show different treatment responsiveness between intestinal and pancreaticobiliary subtypes.

The ESPAC-4 trial [46] randomized 730 patients with resected pancreatic cancer between gemcitabine and combination therapy with gemcitabine and capecitabine (GemCap). The median survival was 25.5 months (95% CI 22.7–27.9) for gemcitabine and 28.6 months (95% CI 23.5–31.5) for GemCap. The hazard ratio was 0.82 (95% CI 0.68–0.98; $P = 0.032$) with a substantial difference in

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five-year survival of 28.8% versus 16.3% in the combination group. The ampullary arm of ESPAC-4 (comparing adjuvant gemcitabine with gemcitabine plus capecitabine) is currently recruiting and has a target of 346 patients and is anticipated to complete follow-up and report by 2022.

A number of retrospective series examined the benefit of chemoradiotherapy as an adjuvant treatment [47,48]. In a study coordinated by the European Organisation for Research and Treatment of Cancer (EORTC), 218 patients with resected pancreatic and periampullary cancers were randomized to postoperative radiotherapy plus concurrent 5-FU (25 mg/kg per day by continuous infusion) or observation. There were 104 patients with periampullary cancers (which included cancers of the ampulla, distal common bile duct or duodenum), and there was no difference in the two-year survival rate (67% radiotherapy vs 63% observation) or in the incidence of locoregional recurrence in the postoperative radiotherapy group compared to controls. This was contrary to the findings from another series at the Mayo Clinic of 29 out of 125 patients with ampullary cancer who underwent curative surgical resection in addition to 5-FU and concurrent radiotherapy with a median total radiation dose of 50.4 Gy (range 45.0–54.0 Gy) while the remainder underwent surgery alone. The five-year survival figures of 48% vs 11% were in favor of the adjuvant chemoradiation group [19].

Results from the ESPAC-4 ampullary trial will help inform future adjuvant therapy options for this patient group.

Palliative Therapy

Systemic chemotherapy remains the mainstay to halt disease progression and prolong survival in unresectable and metastatic ampullary carcinoma. Survival figures beyond 3–6 months are dismal without additive palliative therapy. Most of the existing evidence is extrapolated from large studies that contained a mixture of periampullary tumors, with ampullary tumors forming a subset. Agents that have been examined in this disease include antimetabolites (fluoropyrimidine and/or gemcitabine) with or without a platinum compound (cisplatin or oxaliplatin) with variability in response rates ranging from 10% to 40% [49,50]. A phase II study evaluating CAPOX in patients with advanced adenocarcinoma of the small bowel or ampulla reported a response rate of 33% with improved overall survival (20.4 vs 15.5 months in patients with metastasis). The primary site of disease was the ampulla of Vater in 12 out of 30 patients [29].

In the ABC-02 trial (see Table 164.2) which randomly assigned 410 patients with locally advanced or metastatic biliary tract cancer to receive combination cisplatin and gemcitabine versus gemcitabine alone [26], there were 206 patients in the gemcitabine group (ampullary: 11 cases) and 204 patients in the cisplatin plus gemcitabine group (ampullary: nine cases). The median progression-free survival was eight months in the cisplatin plus gemcitabine versus five months in the gemcitabine-only cohort. The overall median survival was 11.7 months vs 8.1 months, respectively. The ABC-06 trial [30] analysed 162 patients (of whom 11 were ampullary carcinoma) in which second-line chemotherapy, FOLFOX with ASC was compared to ASC alone in patients who had advanced or metastatic biliary tract cancer treated initially with first-line gemcitabine and cisplatin. A statistically significant benefit to median overall survival was proven in the ASC plus FOLFOX group (6.2 months), when compared to ASC alone (5.3 months) with an adjusted hazard ratio of 0.69 (95% CI 0.50–0.97; $P = 0.031$).

Conclusion

Periampullary tumors constitute a diverse group of tumor subtypes. Despite the advances in diagnostics and clinical cancer care, their treatment remains challenging for clinicians and oncologists worldwide. The rarity of these tumors, in addition to disparity of the published data, has slowed the advances made in the field. There is a high unmet need for these patients. Future randomized trials should be of high quality and use efficient novel study designs to ensure that the best clinical evidence is available for these patients.

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Long-term Survival After Resection of Periampullary Cancer

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Introduction

Periampullary cancers are grouped as heterogeneous malignant lesions arising from anatomic sites around the ampulla of Vater. They consist of pancreatic head cancer, ampullary region cancer, distal bile duct cancer, and duodenal cancer. Because of their anatomic proximity, periampullary cancers share similar clinical presentations. In addition, when they invade surrounding tissue, it is often hard to distinguish between then. On the other hand, the treatment strategy is similar and surgical resection is the most effective treatment for all diseases. Pancreaticoduodenectomy represents the most applicable surgical procedure, although limited resection, such as pancreas-preserving duodenectomy, is indicated for some patients.

The incidences and long-term survival rates after surgical resection are very different according to the type of cancer. This chapter mainly focuses on long-term survival after surgical resection in patients with periampullary cancers other than pancreatic cancer, especially presenting recent studies. We elucidate the incidence and survival of periampullary cancer, then describe current data regarding survival and factors indicating long-term survival in each disease.

Incidence and Survival of Periampullary Cancer

As mentioned above, periampullary cancer contains different types of tumors. However, it is often hard to distinguish between them. Pomianowska et al. reported that pathologic reevaluation changed the diagnosis in 55 cases (27%) within 207 resected periampullary adenocarcinomas [1]. Several reports have shown the incidence and survival of periampullary cancers by comparing each disease.

Hester et al. reported the incidence and survival of these diseases by analyzing the National Cancer Database in the United States [2]. This analysis included 116705 patients over 18 years with the histologic diagnosis of adenocarcinoma characterized by four anatomic subtypes. Pancreatic head adenocarcinoma was the most frequent (82%), following ampullary adenocarcinoma (9%), duodenal adenocarcinoma (6%), and distal cholangiocarcinoma (3%). Resection was performed in 73% cases of ampullary adenocarcinoma, 52% duodenal adenocarcinoma, 44% distal cholangiocarcinoma, and 42% pancreatic head adenocarcinoma. Reflecting the high resection rate, patients with ampullary adenocarcinoma showed the most prolonged median survival of 26.3 months. Although the other three diseases showed similar resection rates, the pancreatic head adenocarcinoma patients showed the worst median survival of 8.1 months, compared with duodenal adenocarcinoma (13.3 months) and distal cholangiocarcinoma (11.5 months). Within surgically resected cases, tumors originating from the pancreatic head showed a more aggressive character with a higher incidence of lymph node metastasis and a higher rate of positive microscopic margins than other tumors. The multivariate analysis showed that duodenal adenocarcinoma was associated with improved survival compared with other sites. The resected ampullary, pancreatic head, and duodenal adenocarcinoma within the study period demonstrated significantly improved survival with increasing receipt of adjuvant therapy. These results showed the different biologic characteristics of periampullary cancer in various sites.

Shmuck et al. also showed different characteristics of periampullary cancer by detailed analysis [3]. They analyzed the clinicopathologic factors of 472 patients with

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surgically resected periampullary cancer located within 2 cm from the ampulla of Vater. Patients were divided into three groups: distal cholangiocarcinoma, pancreatic adenocarcinoma, and ampullary carcinoma. The study showed that pancreatic cancer had larger tumor sizes, more frequent R1 resection, and a higher rate of nodal and perineural invasion compared to other tumors. Ampullary cancer showed a much longer median survival at 31.9 months, compared with distal cholangiocarcinoma (19.9 months) and pancreatic cancer (17.2 months). Other studies have also described the more prolonged survival of ampullary cancer and duodenal cancer than other cancers [4,5].

These reports emphasize that periampullary cancer includes heterogeneous tumors, and patients should be treated considering the characteristics of each disease.

Distal Bile Duct Cancer

Overall Survival (Table 165.1)

Few reports describe the clinicopathologic data of patients with distal bile duct cancer. According to the Biliary Tract Cancer Registry in Japan [6], 4091 patients with distal duct cancer were registered from 2008 to 2013. Of these patients, 3800 (92.9%) underwent surgical resection. Based on the Japanese classification of biliary tract cancers, T3a disease, which invades the gallbladder, liver, pancreas, duodenum, or other adjacent organs, was the most frequently seen (53.4%), followed by T2 disease, which invades beyond the bile duct wall to the surrounding tissue (28.6%). In this patient population, the five-year survival rate was 39.1%. The following report demonstrated, by analyzing the same database, that the five-year survival rate of 1748 patients who underwent curative surgery with pancreatoduodenectomy was 47.4% [7].

A retrospective multicenter study from five German and Russian academic centers showed that the five-year survival rate of 228 patients with distal bile duct carcinoma was 27% and the median overall survival was 29.3 months [8]. The Nagoya Surgical Oncology Group from Japan [9] and the French group [10] also reported the five-year survival rate of patients with surgically resected distal bile duct cancer as 40.8% and 34%, respectively.

In high-volume single-center studies, a report from Heidelberg University Hospital in Germany described that the five- and 10-year survival rates and median overall survival time of patients with bile duct cancer who underwent pancreatoduodenectomy were 40.3%, 30.5%, and 36.8 months, respectively [11]. A report from the University of Verona Hospital in Italy described that the median survival time of 54 patients with resected distal bile duct cancer was 35 months [12]. Previous reports from the Johns Hopkins Medical Institution, USA [13], and the Samsung Medical Center in South Korea [14] also stated that the median survival/five-year survival rates of those patients were 18%/20.3 months (147 patients) and 48.3%/73.0 months, respectively. Our institutional experience showed similar rates: five-year survival rate and median survival time were 38.2% and 46.0 months (173 patients). According to these reports, the five-year survival rate and the median survival time of patients with resected distal bile duct cancer were approximately 40% and 40 months. No significant change was found in the last five years.

Table 165.1 Published series of survivals after surgical resection of distal bile duct cancer.

Authors	Reference	Country/institution	Study period	No. of patients	Five-year survival rate	MST (months)
Nationwide study						
Ishihara et al.	6	Japan	2008–2013	3800	39.1%	ND
Multiinstitutional study						
Petrova et al.	8	Germany, Russia	1994–2015	228	27%	29.3
Kiriyama et al.	9	Japan	2001–2010	370	40.8%	42
Bourgouin et al.	10	France	2001–2011	55	34%	24
Single-center study						
Tjaden et al.	11	Heidelberg University, Germany	2001–2017	196	40.3%	36.8
Hong et al.	13	Johns Hopkins Medical Institute, USA	1984–2004	147	18%	20.3
Chung et al.	14	Samsung Medical Center, Korea	1995–2011	237	48.3%	73
Our experience		Chiba University, Japan	2000–2015	75	38.2%	46

MST, median survival time; ND, not determined

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Prognostic Factors (Table 165.2)

The most critical factor for the long-term survival of distal bile duct cancer is surgical resection with a negative cancer margin. The Heidelberg University group showed the importance of complete tumor clearance [11]. Among 196 patients who underwent pancreaticoduodenectomy for this disease, R0 resection with more than 1 mm surgical margin (R0 >1 mm) was achieved in 113 patients (58%). The median overall survival of R0 >1 mm was significantly longer (77.5 months) than that of R1 (≦1 mm) (24.2 months) and R1 (direct) (21.9 months). Interestingly, there were no differences between R1 (≦1 mm) and R1 (direct). Surgical resection with absolute negative margin status is one of the most important prognostic factors for distal bile duct cancer.

Several studies revealed prognostic factors for distal bile duct cancer by multivariate analyses: age >70, ASA III, operative blood loss (>1000 mL), lymph node metastasis, perineural invasion, tumor grade, occurrence of postoperative pancreatic fistula, and grade C complication, in addition to margin status [8,9,11,12,15,16].

Most of the studies indicated lymph node metastasis as a prognostic factor. The number of lymph node metastases was also important. Analysis of Japanese registration cases of biliary surgery revealed that the five-year survival rates of N0, N+(1 or 2), N+(3 or more) were 61.2%, 29.5%, and 21.7%, respectively. Another study also reported similar results regarding the number of lymph node metastases [17].

The Nagoya University group emphasized the importance of cancer invasion depth as a prognostic factor [16]. They showed that invasion depth of 8 mm beyond the bile duct was the only independent prognostic factor determined by multivariate analysis of 121 surgically resected cases.

On the other hand, adjuvant treatment did not show a survival benefit. Analysis of the Japanese registry [7] and a metaanalysis including 2063 patients [15] did not show a significant difference between patients treated with or without adjuvant therapy. This might be because the regimen was not standardized and did not have enough power to prevent cancer spread. This problem should be dissolved by future prospective studies with current chemotherapy protocols.

Several recent reports included inflammatory parameters as prognostic factors, such as platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and systemic immune-inflammation index determined by platelet count and neutrophil-to-lymphocyte ratio [18–20]. These results may indicate the involvement of inflammation and immune status in spread of distal bile duct cancer.

Recurrence

A few studies have reported on cancer recurrence after pancreaticoduodenectomy. Recurrence occurred in 39–67% of patients. The time to recurrence was 13–21 months. The most frequent form of recurrence was distant metastasis (mainly liver metastasis) and local recurrence [11,14,21,22].

Ampullary Cancer

Overall Survival (Table 165.3)

Survival in patients with ampullary cancer is favorable compared with other diseases of periampullary cancer. A population-based study in the Netherlands, including all patients with newly diagnosed malignancies, reported

Table 165.2 Published series of prognostic factors after surgical resection of distal bile duct cancer.

Authors	Reference	Study period	No. of patients	Prognostic factors (multivariate)
Tjaden et al.	11	2001–2017	196	Age>70, ASA III, blood loss >1000 mL, lymph node metastasis, positive resection margin
Tamura et al.	16	2002–2016	121	Depth of invasion >8 mm
Petrova et al.	8	1994–2015	228	Lymph node metastasis, distant metastasis, positive resection margine, high tumor grade, grade C postoperative complication
Andrianello et al.	12	1998–2014	54	Postoperative pancreatic fistula
Kiriyama et al.	9	2001–2010	370	Perineural invasion, pancreatic invasion, lymph node metastasis, positive margin
Bourgourin et al.	10	2001–2011	55	T3/4, positive margin
Chung et al.	14	1995–2011	237	CA 19-9 >35 U/L, positive margin, T3 or above, lymph node metastasis

ASA, American Society of Anesthesiologists classification; CA, carcinoembryonic antigen.

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Table 165.3 Published series of survivals after surgical resection of ampullary cancer.

Authors	Reference	Country/institution	Study period	No. of patients	Five-year survival rate	MST (months)
Nationwide study						
Ishihara et al.	6	Japan	2008–2013	2053	61.3%	ND
O'Connell et al.	24	USA	1998–2003	1301	36.8%	ND
Multiinstitutional study						
Moekotte et al.	25	Europe	2006–2017	887	52%	64
Moekotte et al.	29	Europe	2006–2017	1007	53%	66
Balci et al.	45	USA, Japan, Turkey	ND	313	49%	ND
Single-center study						
Jin et al.	27	Mayo Clinic, USA	2006–2016	121	57.9%	91.8
Feretis et al.	28	Addenbrooke's Hospital, UK	2002–2013	110	34.9%	ND
Doepker et al.	26	Moffitt Cancer Center, USA	1996–2015	106	43%	49.3
Chen et al.	46	National Yang Ming University, Taiwan	1999–2014	194	42.7%	45.1
Klein et al.	47	Charite Canpus Virchow University, Germany	1992–2007	143	40%	37
Winter et al.	48	Johns Hopkins Medical Institute, USA	1970–2007	347	45.0%	ND

MST, median survival time; ND, not determined

the incidence, treatment, and survival of ampullary cancer [23]. The median overall survival of 3840 patients with ampullary cancer was 16.1 months. Within these, most patients (87.1%) had nonmetastatic disease. This may lead to a high resection rate of this disease. The five-year survival rate of nonmetastatic disease was improved from 19.8% in 1989–1995 to 29.1% in 2010–2016. The resection rate also increased from 49.5% to 63.9% in these two periods. Meanwhile, the prognosis of 463 patients with metastatic disease did not change between the two periods (median overall survival 4.4 months in 1989–1995, 5.9 months in 2010–2016).

In the database of the Surveillance, Epidemiology, and End Results (SEER) national cancer registry from the United States, 3292 patients were registered from 1998 to 2003. The resection rate was 40% and the five-year cancer-specific survival after resection was 47.3% [24]. According to the Biliary Tract Cancer Registry in Japan [6], 2161 patients were registered from 2008 to 2013, and 2053 patients (95.0%) underwent surgical resection. This high resection rate might be because the resected cases were mainly enrolled in this registry. Based on the Japanese classification of biliary tract cancers, T2 disease was the most frequently seen (38.5%), followed by T1a (17.5%), and tumor stage was most commonly classified as Stage IA (29.1%), followed by Stage IB (27.2%). The five-year survival rate was reported to be 61.3%.

In a multicenter study from Europe, a total of 887 patients who underwent pancreaticoduodenectomy for ampullary adenocarcinoma in nine tertiary referral centers (UK, Netherlands, Italy) were included, and the median overall survival and five-year survival rate of these patients were favorable with 64 months and 52%, respectively [25]. The authors emphasized that ampullary cancers had morphologic heterogeneity based on the epithelium of origin: intestinal, pancreaticobiliary, or mixed type. The pancreaticobiliary subtype was most frequently seen (53%), followed by the intestinal subtype (39%) and mixed subtype (8%). Patients with the pancreaticobiliary subtype showed worse overall survival than the other subtypes.

In high-volume single-center series, the Moffitt Cancer Center, USA, group reported that the median overall survival and five-year survival rate was 49.3 months and 43%, respectively, in their analysis of 106 resected ampullary cancer cases between 1996 to 2015 [26]. The group from the Mayo Clinic reported a study of 121 patients who underwent pancreaticoduodenectomy for ampullary cancer between 2006 and 2016 [27]. The median overall survival time was exceptionally long at 91.8 months, and the five-year survival rate was 57.9%.

Overall, the five-year survival rate for ampullary cancer was approximately 30% in all cases and 40–60% in resected cases.

Prognostic Factors (Table 165.4)

Many reports including multivariate analysis have revealed several prognostic factors for patients who underwent surgical resection. They include age,

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Table 165.4 Published series of prognostic factors after surgical resection of ampullary region cancer.

Authors	Reference	Study period	No. of patients	Prognostic factors (multivariate)
Moekotte et al.	29	2006–2017	1007	Age, margin status, tumor differentiation, AJCC T3/4 stage, nodal involvement
Feretis et al.	28	2002–2013	110	Vascular invasion, lymph node ratio
Jin et al.	27	2006–2016	121	Performance status, adjuvant therapy, disease stage
Doepker et al.	26	1996–2015	106	Lymph node count, tumor differentiation, histologic subtype
Moekotte et al.	25	2006–2017	887	Nodal metastasis, perineural invasion, adjuvant chemotherapy
Bourgouin et al.	10	2001–2011	55	Loss of BMI ≥4%, nodal metastasis, UICC stage
Winter et al.	48	1970–2007	347	Blood transfusion, perineural invasion, nodal metastasis

AJCC, American Joint Committee on Cancer; BMI, body mass index; UICC, Union for International Cancer Control.

performance status, margin status, lymph node metastasis, lymphovascular invasion, perineural invasion, histologic grade, lymph node-positive rate, T stage, pathologic stage, and adjuvant therapy [25–30]. In most studies, lymph node metastasis has been identified as the most substantial prognostic factor, as for other types of periampullary cancers.

Moekotte et al. developed a prediction model for survival in patients with resected ampullary adenocarcinoma in their international multicenter study, including 27 centers from 10 countries. They established a nomogram, including age, margin status, tumor differentiation grade, T stage, and lymph node metastasis, by analyzing the derivation cohort consisting of 1007 patients. Four groups divided by points of this nomogram showed a stratified survival curve in the Kaplan–Meier analysis. They confirmed the prediction accuracy of this nomogram using a validation set including 462 patients [29].

The role of adjuvant therapy in the survival of patients with resected ampullary cancer remains controversial. Several studies identified adjuvant therapy as a favorable prognostic factor [25,27], while others did not [26,30]. In their international cohort study, including 887 patients, Moekotte et al. described adjuvant therapy as a favorable predictor, especially in pancreatobiliary type [25]. The Mayo Clinic group also showed that adjuvant therapy was a favorable prognostic factor only in patients with Stage IIB or above [27]. These results may indicate that adjuvant therapy can improve survival, especially in advanced-stage disease patients. Limitations of these retrospective studies were the difference in patients' backgrounds and the lack of standard protocol for adjuvant therapy due to its retrospective nature. A prospective study will reveal the effect of adjuvant therapy on ampullary cancer.

As described, several recent reports have revealed that histopathologic subtype correlated with survival. The pancreatobiliary subtype was found in about 55% of cases, while the intestinal type was found in 35–37% [29,30]. Nappo et al. reported on the influence of histologic subtypes. Pancreatobiliary subtype was correlated with advanced T stage, lymph node metastasis, and perineural and vascular invasion. The five-year survival rate of the pancreatobiliary subtype was 42.1%, while that of the intestinal subtype was 75.5% (P <0.05). However, survival of the pancreatobiliary subtype was better than that of pancreatic ductal adenocarcinoma [30].

Recurrence

A few studies have reported on cancer recurrence after surgical resection. The median time of recurrence-free survival was 27–65.5 months [26,27,31]. Most of the recurrence was distant metastasis (73.5–87.5%), while locoregional recurrence was found in 12.5–26.5% of resected cases. The liver is the most frequent site of distant metastasis.

Duodenal Cancer (Adenocarcinoma)

Overall Survival (Table 165.5)

Duodenal cancer can originate from any part of the duodenum. In most studies, therefore, duodenal cancers arising in the periampullary duodenum, which have not been clearly defined yet, and in other parts of the duodenum (extraampullary duodenum) have been grouped. These two groups, periampullary and extraampullary duodenal cancers, were reported to have similar long-term survival after resection. The group from the Mayo Clinic reported their analysis of 124 patients who had an operation for duodenal cancer [32]. Twenty-five patients had tumors originating from the periampullary duodenum while 99 patients from the extraampullary duodenum. The five-year survival rate was 37% in the extraampullary group

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Table 165.5 Published series of survivals after surgical resection of duodenal cancer.

Authors	Reference	Country/nstitution	Study period	No. of patients	Five-year survival rate	MST (months)
Nationwide study						
Jiang et al.	40	China	2006–2016	137	39%	ND
		SEER	2004–2014	698	38%	ND
Bojesen et al.	33	Denmark	1994–2010	290	16%	ND
Legue et al.	39	Netherlands	1999–2013	1026	28.1%	16.3
Multiinstitutional study						
Solaini et al.	34	UK	2000–2013	143	51.2%	84
Single-center study						
Mann et al.	37	Royal Liverpool University Hospital, UK	1997–2015	53	53% (3-year)	38
Lee et al.	35	Asan Medical Center, Korea	1999–2009	47	60.9%	25.1
Onkendi et al.	32	Mayo Clinic, USA	1994–2009	99	43%	38.4
Poultsides et al.	42	Johns Hopkins Medical Institute, USA	1984–2006	112	48%	ND
Cecchini et al.	44	Massachusetts General Hospital, USA	1982–2010	103	42%	44

MST, median survival time; ND, not determined; SEER, Surveillance, Epidemiology and End Results database.

and 38% in the periampullary group. From this report, it is reasonable to analyze both groups together.

The overall survival from database analysis showed more prolonged survival in resected than in nonresected cases. A population-based study in the Netherlands, including 1026 duodenal cancers, described that the median overall survival of all cohorts was 13–14 months, and five-year survival rate was 25%. Surgical resection was performed in 58% of these patients. The median overall survival was 25 months in patients with locoregional disease, 48 months in surgically resected cases, and 66 months in cases treated with neoadjuvant therapy and surgical resection. In comparison, that of metastatic cases was only 4–5 months.

A population-based study from Denmark also demonstrated that cases with metastasis (Stage IV) showed poor survival [33]. The median survival time of patients with Stage IV duodenal cancer was only eight months, while those of Stage I/II and III were 25 and 29 months, respectively. In a multiinstitutional study in the UK analyzing 178 cases who underwent surgical treatment, the median survival times of all cases, resected cases, and palliative treatment were 44 months, 84 months, and eight months, respectively [34]. Several single-center studies also showed the importance of surgical resection for long-term survival [35–37]. No significant improvement in survival was obtained during this decade. Recent metaanalysis including 26 studies and 6438 patients demonstrated that the five-year survival rate was 46% after curative resection, both segmentectomy and pancreaticoduodenectomy, compared with 1% in palliative treated patients [38].

Prognostic Factors (Table 165.6)

Curative surgical resection is an important prognostic factor. Several reports performed a multivariate analysis of prognostic factors of overall survival after surgical resection. Recently reported prognostic factors are older age, advanced pathologic grade, TNM stage, lymph node status, pathologic perineural and lymphovascular invasion, and resection margin status, while gender and size of tumor have not been consistently associated with outcome [37,39–41]. Most of these studies demonstrated that lymph node metastasis is one of the most significant prognostic factors. The metaanalysis showed that lymph node involvement remained an independent prognostic factor in most studies after correction for other clinicopathologic factors. The pooled five-year survival rate was 65% for N0 cases, compared with 21% for N+ cases (odds ratio [OR] 0.17, 95% confidence interval [CI] 0.11–0.27, P <0.0001) [38]. It is noteworthy that there is a relationship between an increased number of involved nodes and poor survival [34,40,42].

Recently, many studies have showed the benefit of adjuvant therapy for pancreatic-biliary tumors, and it has become standard therapy, especially for pancreatic cancer. However, its usefulness is still controversial for duodenal cancer [35,36,43]. The metaanalysis also did not support its benefit. Within six studies investigating

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Table 165.6 Published series of prognostic factors after surgical resection of duodenal cancer.

Authors	Reference	Study period	No. of patients	Prognostic factors (multivariate)
Nitta et al.	41	2002–2018	86	Pancreatic invasion, lymph node status
Mann et al.	37	1997–2015	53	Resection margin status, tumor stage III or above
Legue et al.	39	1999–2013	1026	Favorable factors: locoregional disease, age < 60, low tumor stage, diagnosis in 2009–2013
Solani et al.	34	2000–2013	143	N category, lymphovascular invasion
Poultsides et al.	42	1984–2006	112	Nodal metastasis
Cecchini et al.	44	1982–2010	103	Perineural invasion

the five-year survival of patients treated with adjuvant therapy, there was no difference in the pooled five-year survival for the adjuvant therapy group and control group (48% vs 46%, respectively; OR 1.14, 95% CI 0.60–2.15, I^2 = 40%) [38]. This might be because there is no standard chemotherapy regimen for duodenal cancer. A future prospective study is required to disclose its benefit.

Recurrence

Median time from surgical resection to recurrence showed a wide variety between reports (14.5–53 months) [34,44]. The frequent form of recurrence was distant metastases, followed by locoregional recurrence. Among distant metastases, the liver is the most frequent site of recurrence [34,35].

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Section 10

Transplantation of the Pancreas

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Transplantation of Pancreatic Islets

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Introduction

Transplantation of allogeneic islets has evolved as an effective treatment for patients with difficult-to-control type 1 diabetes (T1D) [1] and is now available as a less invasive alternative to vascularized whole pancreas transplantation [2]. The first successful islet transplant in an experimental model was reported in 1972 [3] and the first transplant of deceased donor human islets was performed shortly thereafter in 1974 [4].

After decades of clinical research, health authorities in several countries have provided regulatory approval for use of transplantation of human pancreatic islets in the treatment of T1D. The current era of clinical investigation focuses on the evaluation of stem cell-derived islet products [5–7]. Here we provide an overview of approaches to human islet isolation and infusion, selection of patients with a favorable benefit/risk ratio, clinical efficacy and safety outcomes, the regulatory status of transplantation of allogeneic islets, and research priorities in islet β cell replacement.

Manufacturing, Release Testing, and Infusion of Allogeneic Human Islets

The preeminent procedures involved in transplantation of allogeneic human islets in T1D are illustrated in Figs 166.1 and 166.2. Selection of deceased pancreas donors is a critical factor in determining the yield of islets available for transplant [8]. Based on characteristics of 1235 deceased pancreas donors and islet yields obtained from their pancreases, a scoring system has been developed to predict postpurification islet yields of >400 000 islet equivalents (IEQ). Adherence to validated principles of donor pancreas procurement [9,10] and utilization of optimized enzyme blends for pancreatic tissue dissociation [11] increase the yield and transplant rate of human islet products.

To advance allogeneic islet products toward licensure in the United States, eight manufacturing facilities participating in the National Institutes of Health-sponsored Clinical Islet Transplantation (CIT) Consortium jointly developed and implemented a harmonized process for the manufacture of allogeneic purified human pancreatic islet (PHPI) product for evaluation in a phase III trial in subjects with T1D [12]. Manufacturing was controlled by a common master production batch record (MBPR), standard operating procedures (SOP) that included acceptance criteria for deceased donor organ pancreases and critical raw materials, PHPI product specifications, certificate of analysis and test methods. The process was compliant with current Good Manufacturing Practices and Good Tissue Practices.

The quality systems and regulatory and operational strategies developed by the CIT Consortium yielded product lots that met the prespecified characteristics of safety, purity, potency, and identity and were successfully transplanted into participating subjects. No adverse events attributable to the product and no cases of primary nonfunction were observed. The CIT MPBR and SOPs are publicly available (referenced in [12]). The most commonly used islet implantation site is the liver, with islets being infused intraportally. The portal vein is accessed by percutaneous transhepatic catheterization or minilaparatomy.

Progress on the manufacturing and transplantation of stem cell-derived islets is discussed below.

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Fourth Edition. Edited by Hans G. Beger, Markus W. Büchler, Ralph H. Hruban, Julia Mayerle, John P. Neoptolemos, Tooru Shimosegawa, Andrew L. Warshaw, David C. Whitcomb, and Yupei Zhao.
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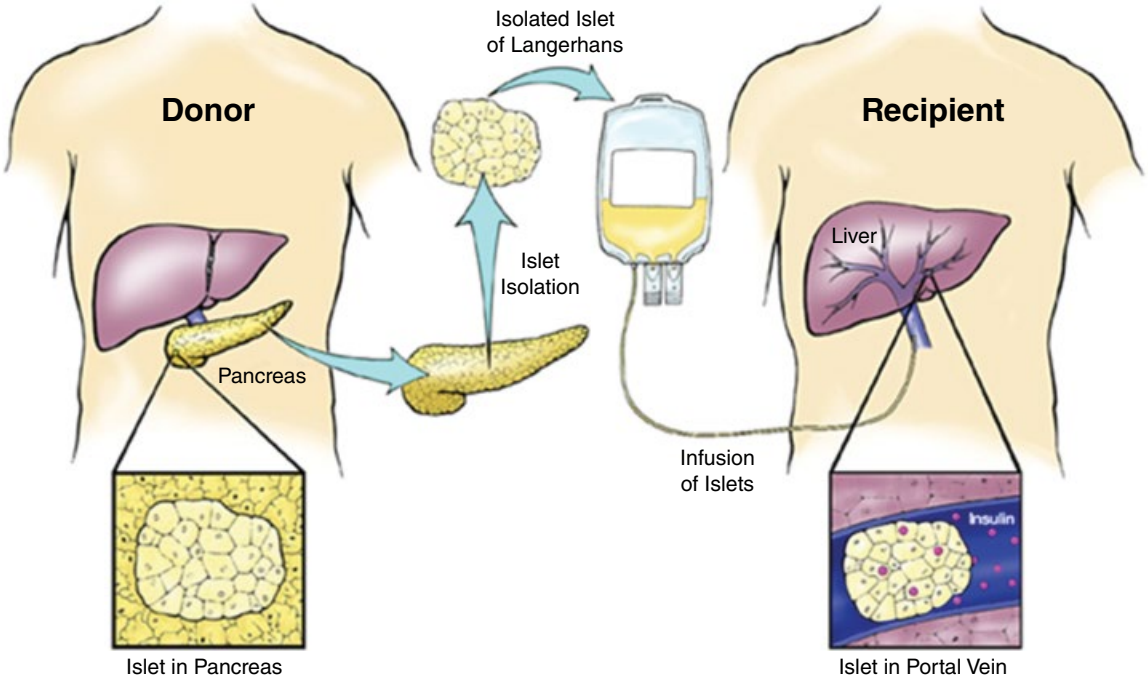


Figure 166.1 Diagram depicting the standard approach to transplantation of human allogeneic islets. A pancreas is retrieved from a suitable deceased donor. Islets are isolated from the donor pancreas, transferred to a transfusion bag, and infused through the portal vein into a type 1 diabetic recipient.

Selection of Islet Allotransplant Recipients

Allogeneic islet transplantation has been performed in patients with T1D as islet transplant alone (ITA) in nonuremic recipients, as simultaneous islet kidney (SIK) transplant in uremic recipients [13], or as islet after (previous) kidney (IAK) transplant in posturemic recipients [14].

ITA recipients are exposed to generalized immunosuppression only for the purpose of protecting the islet graft. The morbidity of diabetes complications in ITA must be perceived to be more serious than the risks associated with immunosuppression and the expectation of benefit associated with the islet graft must be high. Most ITA procedures have been performed in patients in whom T1D is complicated by impaired awareness of hypoglycemia (IAH) and recurrent severe hypoglycemic episodes (SHEs) [15]. These greatly feared acute complications require the assistance of another person for recovery [16]. IAH is found in up to one-third of adult patients with T1D and increases their risk of SHEs six-fold [17]. Recurrent hypoglycemia can have a profound impact on people's confidence, careers, and personal relationships, disrupt many everyday activities such as driving, work performance, leisure pursuits, and sleep [15], and can cause embarrassment, social ostracism, and employment discrimination [18].

Although several new educational and technologic interventions have recently been developed and should always be employed as first-line therapy in patients with SHEs, not all patients with IAH benefit from these interventions [19]. Despite accepting elevated hemoglobin A_{1c} (HbA_{1c}) targets of 8.0% and having access to behavioral therapies and sensor-augmented insulin pumps at a specialist hypoglycemia service, only 50% of patients with T1D and recurrent SHEs experienced resolution of SHEs, and 30% required pancreas or islet transplantation because of persistent SHEs [20]. Evidence-informed clinical practice recommendations identify patients in whom T1D is complicated by IAH and recurrent episodes of SHEs as candidates for islet or pancreas transplantation under the following conditions: SHEs persist after completion of a structured stepped care approach or a formalized medical optimization period that provides access to hypoglycemia-specific education including behavioral therapies, insulin analogues, and diabetes technologies under the close supervision of a specialist hypoglycemia service [19]. CIT-07 demonstrated the effectiveness of islet transplantation in restoring near normoglycemia and protection from SHEs in T1D [13].

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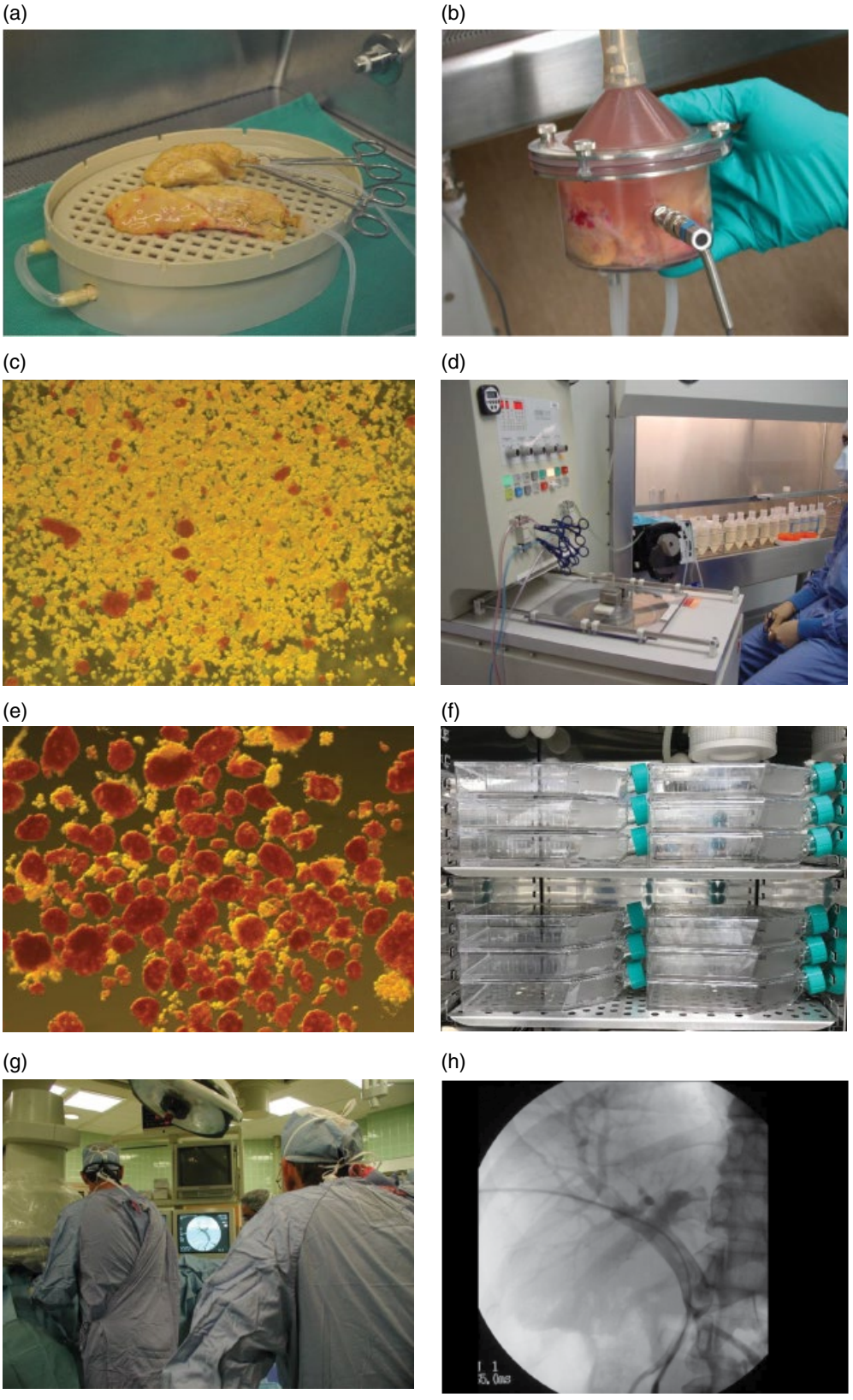


Figure 166.2 Manufacturing and transplanting allogeneic human islets. (a) Intraductal perfusion of the donor pancreas with tissue-dissociating enzymes. (b) Automated, enzyme-mediated dissociation of the distended pancreas in the Ricordi chamber. (c) Sample of tissue suspension prior to purification showing dithizone-stained, isolated human islets and nonstained acinar tissue. (d) Continuous density gradient purification of isolated islets from acinar tissue on a Cobe 2991 cell separator. (e) Sample of purified islet preparation stained with dithizone. (f) Pretransplant culture of purified human islets in T-flasks. (g) Percutaneous transhepatic catheterization of the portal vein by interventional radiologist. (h) Portal angiogram documenting the correct location of the infusion catheter in the main branch of the portal vein prior to islet infusion. *Source:* Dr A.N. Balamurugan et al. with permission from University of Louisville.

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Recent reports of multicenter trials of ITA in T1D complicated by hypoglycemia provide additional information on patient selection and eligibility [13,14,21–23]. An ideal candidate for IAK would be a patient diagnosed with T1D ≥5 years with stable kidney transplant, absent stimulated C-peptide, IAH as determined by the Clarke score, and a history of SHEs in the last one year despite medical care provided by an endocrinologist or diabetologist or patients who are unable to achieve and maintain glycemic control without hypoglycemic episodes by targeting a HbA_{1c} level above 7.5% (58.5 mmol/mol). Patients with high body mass index (BMI) (>30 kg/m^2), glomerular filtration rate (GFR) ≤40 mL/min/1.73m^2 or a history for panel reactive antibodies >50% or presence of anti-HLA antibodies against kidney donor or significant comorbidities would not be ideal candidates for islet transplant [14].

Simultaneous islet kidney and IAK recipients are already obligated to immunosuppression because of their concurrent or previous kidney transplant. The risks in ITA recipients should be minimal by following well-defined precautions (as discussed later). The risk/benefit ratio of an added islet transplant could be favorable, especially in those SIK and IAK recipients with T1D, who cannot meet clinically appropriate glycemic goals or who continue to experience SHEs after completion of a formalized medical optimization program under the guidance of an expert diabetes care team [19]. These recipients may also include patients who are not surgical candidates for or willing to accept the risks of a pancreas transplant [19,24,25].

Outcomes of Islet Allotransplantation in T1D

One- and Two-Year Metabolic Efficacy Results in ITA and IAK/SIK Recipients

The achievement of insulin independence in all of seven nonuremic ITA recipients by Shapiro et al. in Edmonton in 2000 marked a breakthrough in the clinical development of islet transplantation [26]. All patients quickly attained insulin independence after transplantation of a mean ± SD islet mass of 11 547 ± 1604 IEQ/kg. All recipients required islets from two donor pancreases, and one required a third transplant from two donors to achieve sustained insulin independence. After a median posttransplant follow-up of 11.9 months (range 4.9–14.9 months), the mean glycosylated hemoglobin values were normal, and episodes of hypoglycemic coma were avoided in all recipients. The complications were minor. The high success rate of the Edmonton protocol in restoring insulin independence has been attributed to the infusion of a high islet mass from more than one donor pancreas and the use of a glucocorticoid-free, low-dose tacrolimus and sirolimus maintenance immunosuppressive protocol, which is considerably less diabetogenic than previous protocols [27,28].

The insulin independence rate in the subsequent international multicenter trial of the Edmonton protocol for islet transplantation was 44% (16 of 36 patients) at one year post transplant [23]. The trial confirmed that persistent islet function even without insulin independence provides both protection from SHEs and improved levels of glycated hemoglobin [29]. The lower insulin independence rate compared with the initial and follow-up single-center reports by Edmonton [26,29] was in large part explained by the highly variable results achieved among the nine participating centers [23].

Consequently, and as already discussed, the manufacture of islet products for testing in the subsequent CIT trials was controlled by a harmonized process using a common batch record. Adherence to prespecified batch release criteria was demonstrated in qualification runs at each of the selected participating centers [12]. The purpose of the CIT-07 phase III trial, conducted at eight centers in North America, was to demonstrate the safety and effectiveness of transplantation of allogeneic islets in T1D complicated by SHEs [13]. Forty-eight adults with T1D for >5 years and persistent IAH and SHEs were enrolled. The primary composite endpoint of the CIT-07 trial, i.e., HbA_{1c} <7.0% at day 365 and freedom from SHEs from day 28 to day 365 after the first of up to three islet transplants, was successfully met by 87.5% of subjects. At two years, 71% of recipients met the endpoint. The median HbA_{1c} level was 5.6% at both one and two years. There were no study-related mortalities or disabilities [13]. Using the same composite endpoint as CIT-07, comparable results were reported by the Australian multicenter trial [30] and the Integrated UK Islet Transplant Program in its multicenter trial [31].

The TRIMECO multicentric randomized controlled trial assessed the efficacy and safety of islet transplantation and compared it to insulin therapies in T1D patients with severe hypoglycemia [22]. In this open label trial, T1D patients were randomly assigned in 1:1 ratio at 15 university hospitals into two groups, that received either immediate islet transplants or intensive insulin therapy followed by delayed islet transplant. The patients ranged between 18 and 65 years and suffered from SHEs or IHA or had kidney grafts with poor HbA_{1c}. Islet recipients received 11 000 IEQ/kg in 1–3 infusions. The enrolled 50 subjects were randomly assigned to the two defined groups. The median follow-up duration was six months in both groups. At six months, 64% patients in the immediate islet transplant group had a significantly higher modified β-score compared to the insulin therapy group. The authors concluded that islet transplantation effectively improves metabolic outcomes.

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The results of this first randomized controlled trial in islet transplantation showed that, compared with insulin therapy, at six months, islet transplantation was effective at achieving optimal glycemic control in patients with unstable T1D and in patients with T1D who had established kidney transplants and poor glycemic control, suggesting that islet transplantation should be integrated into the stepped care approach to treatment of these patients [22].

IAK and SIK transplantation have been studied in pilot clinical trials by single centers and the French–Swiss GRAGIL Network (Group de Recherche Rhin, Rhône-Alpes et Genève pour la Transplantation d'Ilots de Langerhans) using several immunosuppressive protocols and endpoints [1,21,25,27,28]. These studies also suggest that insulin independence and near-normoglycemia can be restored in IAK/SIK recipients at rates comparable to those for ITA recipients.

The CIT-06 trial, performed by the CIT Consortium, is the first phase III trial of transplantation of human islets in T1D patients with established kidney transplants [14]. Of the 24 participants, 62.5% achieved the primary endpoint of freedom from SHEs and HbA_{1c} ≤6.5% or a reduction in HbA_{1c} of ≥1% one year after the first islet transplant. Median HbA_{1c} declined from 8.1% before to 6.0% at one year and 6.3% at two and three years following transplant, with related improvements in hypoglycemia awareness and glucose variability. The improved metabolic control was associated with better health-related and diabetes-related quality of life. The procedure was safe and kidney allograft function remained stable after three years. The results of this phase III trial support the indication of islet transplantation in patients with T1D post kidney transplant in whom problematic hypoglycemia and poor glycemic control persist despite optimized medical therapy.

The prevalence rates for key clinical outcomes in ITA, IAK, and SIK recipients at one year after final islet transplant were analyzed by the Collaborative Islet Transplant Registry (CITR) (Table 166.1, Fig. 166.3). More detailed metabolic studies demonstrated that intraportal islet transplantation can restore partial glucagon secretion, improve epinephrine secretion, restore autonomic symptom perception, and normalize endogenous glucose production in response to insulin-induced hypoglycemia in patients with long-standing T1D and IAH enrolled in the CIT-07 protocol [32]. Minimal islet graft function is sufficient to abrogate hypoglycemia (<54 mg/dL) [33].

Long-Term Metabolic Efficacy Results in ITA and IAK/SIK Recipients

A minority (~10%) of patients transplanted under the Edmonton protocol maintained insulin independence for five years post transplant. Approximately 80% showed sustained partial islet allograft function associated with HbA_{1c} levels of <7.0% and protection from SHEs for at least four years [29].

Table 166.1 One- and five-year prevalence endpoints of HbA_{1c}, severe hypoglycemic episodes (SHEs), and insulin independence for islet transport alone (ITA), islet after kidney (IAK), and simultaneous islet kidney (SIK).

Clinical endpoints	ITA (N = 877)		IAK (N = 183)		SIK (N = 24)	
	1 year	5 years	1 year	5 years	1 year	5 years[a]
HbA_{1c} <7.0	75%	61%	67%	48%	83%	80%
SHEs	94%	91%	93%	90%	100%	100%
Insulin independence	52%	25%	43%	21%	62%	33%

[a] Only 5/24 SIK recipients' endpoints have been reported at five years.
Source: Courtesy of Elizabeth Payne, PhD, and Cassandra Ballou, MS, The Emmes Company and CITR.

An analysis of CITR revealed that refined peritransplant management, including more potent induction immunosuppression, was associated with an insulin independence rate of 50% at five years after the final islet infusion [34], suggesting that a higher engrafted islet mass [35] could improve the longevity of the graft [36]. These improved results match long-term insulin independence rates after vascularized pancreas transplantation alone in nonuremic recipients [37].

The five-year outcome analysis of the French–Swiss GRAGIL Network reported sustained benefits of islet transplants [21] with 26% of recipients remaining insulin independent and 60% meeting the composite endpoint of HbA_{1c} levels of <7.0% and absence of SHEs. See Table 166.1 for prevalence rates of key clinical outcomes in ITA, IAK, and SIK recipients at five years after the final islet transplant as analyzed by CITR.

In an independent study with more than seven years of follow-up, the Zurich group also showed improved glycemic measures after SIK/IAK transplantation compared with intensified insulin therapy [38].

At the 10-year mark, in the analysis on 31 patients by the GRAGIL Network, the median HbA_{1c} was 7.2% versus 8.0% before transplantation, 74% of recipients were free of SHEs, one was insulin independent and median C-peptide was 0.6 ng/mL. The insulin requirements were significantly lower after transplantation and 51.9% had a functioning graft. These findings demonstrate that islet transplantation provided sustained improvement of glycemic control with protection from SHEs in almost 75% of the recipients for 10 years [39].

In an analysis of islet transplants performed at the University of Lille, the Kaplan–Meir estimates of patients

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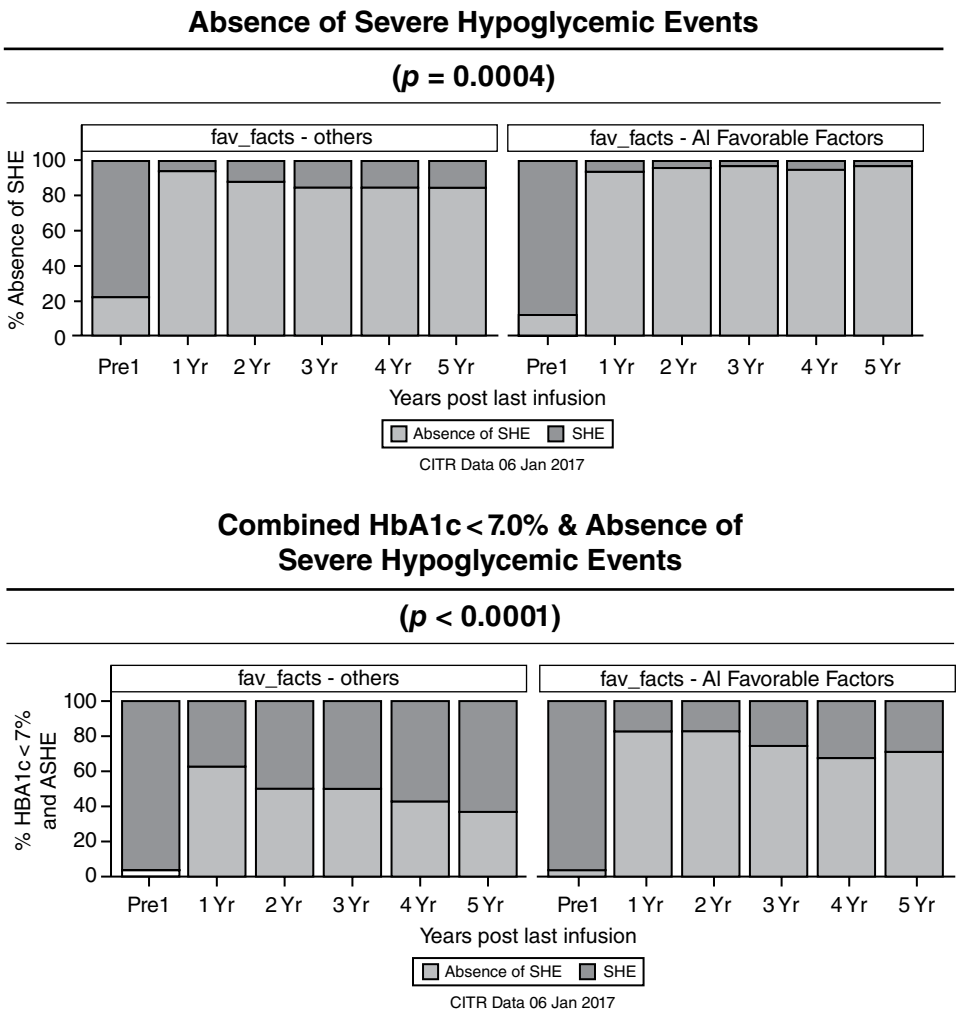


Figure 166.3 Observed prevalence rates of primary outcomes in T1D ITA recipients reported to CITR. Rates are shown according to subgroups with all four "favorable factors": (i) induction immunosuppression with T-cell depletion and/or TNF-α inhibitor, (ii) maintenance immunosuppression with mTOR inhibitor and calcineurin inhibitor, (iii) number of islet equivalents transplanted ≥325 000, and (iv) recipient age ≥35 years (left panels), and less than four favorable factors ("Rest"; right panels). Top row: proportion of recipients with absence of SHE in both subgroups prior to the first islet transplant (Pre1) and at each of the first five years after the last islet infusion. Of the 610 recipients analyzed, N = 164 met all four favorable factors, whereas N = 446 recipients met less than four of the favorable factors ("Rest"). Of those meeting all four favorable factors (N = 164), 12% (20 of 164) were free of SHE prior to transplantation, whereas 97% (67 of 69) of recipients were free of SHE at five years post last islet infusion. Bottom row: proportion of recipients meeting the composite endpoint of HbA_{1c} < 7.0% and absence of SHEs prior to the first islet transplant and at intervals post last islet infusion. Of the recipients analyzed, N = 165 met all four favorable factors, whereas N = 496 recipients met less than four of the favorable factors ("Rest"). Of those meeting all four favorable factors (N = 165), 3% (5 of 165) met the composite endpoint prior to transplantation, whereas 71% (37 of 52) of recipients met the composite endpoint at five years post last islet infusion. *Source:* Courtesy of Elizabeth Payne, PhD, and Cassandra Ballou, MS, The Emmes Company and CITR.

remaining insulin independent with $HbA1_c$ ≤6.5% were 39% at five years and 28% at 10 years [40] and the Kaplan–Meier estimates of graft survival were 82% and 78% after five and 10 years, respectively. Graft function was associated with a marked decrease of SHEs. ITA and IAK recipients had similar outcomes, and the kidney allograft function did not show a significant decline in the latter group [40].

A 12-year follow-up on seven recipients of the Edmonton protocol demonstrated sustained islet function. One subject remained insulin independent without the need for diabetic medications or supplemental transplants and another was insulin independent for more than eight years and experienced graft failure 11 years after the first islet transplant. The median $HbA1_c$ was 6.3% and no patient experienced SHEs, opportunistic

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infections or lymphoma, confirming the safety of islet transplantation in the long term [41].

Impact of Islet Transplantation on Chronic Diabetes Complications, Quality of Life, and Patient Survival

Very few studies have examined the effects of islet transplantation on chronic diabetes complications. The Milan group demonstrated in a cohort of IAK recipients followed for seven years that successful islet transplantation, when compared to controls, was associated with lower cardiovascular mortality and improved endothelial function, kidney graft function, and kidney graft survival rates [42,43]. In a prospective, crossover cohort study examining the effects of ITA and intensive medical therapy on the progression of microvascular diabetes complications, the rate of decline in GFR was slower and the rate of progression of retinopathy was lower after ITA than on medical therapy [44].

Quality of life (QOL) studies using existing questionnaires showed that islet transplants, although having no impact on overall health-related QOL, were associated with improved diabetes-specific QOL, less fear of hypoglycemia, a reduction in behaviors adopted in avoiding hypoglycemia, and attenuation in concerns about SHEs [45]. The CIT-07 subjects reported consistent, statistically significant, and clinically meaningful improvements in condition-specific health-related quality of life as well as self-assessments of overall health [46]. Similar results were observed in the CIT-06 trial; both the Diabetes Distress Scores and Hypoglycemia Fear Scores improved significantly over the three years after the islet transplant [14].

A patient survival analysis in islet transplant recipients with IAH and SHEs pretransplant showed survival of 100% at 10 years and >80% at 20 years after islet transplantation, and incidence rate of mortality was 3.28 per 1000 person-years, suggesting that islet transplantation is not associated with increased mortality regardless of the use of long-term immunosuppressive therapy [47].

Adverse Effects of Islet Transplantation and Immunosuppression

Procedure-related complications of intraportal islet infusion include portal venous thrombosis, transient increase in liver enzymes, perforation of the gallbladder, and bleeding. Portal thrombosis is a preventable complication, provided that therapeutic anticoagulation is maintained and the infused packed cell volume is limited to <5.0 mL [48]. Postprocedural bleeding can be avoided by effective obliteration of the intraparenchymal catheter tract in the liver [49,50] or by accessing a mesenteric vein via minilaparotomy for intraportal islet infusion.

Immunosuppression- and immunity-related complications in ITA recipients include nephrotoxicity and sensitization to donor human leukocyte antigen (HLA) antigens. Although the decrease in GFR is common and significant, the GFR typically remains in the normal range. The decline in GFR is explained by an acute CNI effect [51] and is possibly also associated with correction of hyperfiltration after restoration of near-normoglycemia [52,53]. Whether the decline in GFR is progressive or stable in ITA recipients, as demonstrated in kidney transplant recipients immunosuppressed with CNI [54], remains to be determined. Of note, the rate of decline in GFR was slower in CNI-treated ITA recipients than in control patients on intensive medical therapy [55]. The risk of HLA class I sensitization is significant in ITA recipients in whom immunosuppression is discontinued after complete graft loss; it can be reduced by minimizing the number of islet donors used per recipient and by repeating HLA class I mismatches with subsequent islet infusions [56,57]. In the CIT-07 phase III trial, six of 48 participants had positive panel reactive antibodies at two-year follow-up and donor-specific antibodies developed in two patients [13].

A total of 51 instances of neoplasms have been reported to CITR in 34 of 1086 islet recipients who collectively represent a total of 4583 person-years of observed follow-up. Neoplasms diagnosed were basal or squamous cell carcinoma (N = 35), breast cancer (N = 4), mucinous adenocarcinoma of the appendix (N = 1), thyroid cancer (N = 4), lung cancer (N = 2), and posttransplant lymphoproliferative disorder (PTLD) (N = 2). There were 33 reports of death in 1086 recipients to the Registry for islet allograft recipients, corresponding to 3.0% crude mortality over a mean of 4.4 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up) [58].

Regulatory Status of Transplantation of Allogeneic Human Islets

Multiple countries recognize islet transplantation as standard of care or have provided regulatory approval for use, including selected provinces in Canada, the UK, several health authorities in continental Europe, Australia, and Japan [59]. The path to regulatory approval varies across the world. According to the regulatory framework in the United States, allogeneic pancreatic islets meet the definition of a biologic product and a drug

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and are considered a somatic cell therapy. As such, allogeneic islets will require approval of a Biologics License Application (BLA) before they can be marketed in the US for the treatment of patients with diabetes [60]. The National Institutes of Health sponsored the CIT-06 and CIT-07 licensure trials in the US, which demonstrated the efficacy and safety of purified human pancreatic islets in patients with T1D [13,14].

Nevertheless, and possibly related to the costly and onerous regulatory path, none of the participating academic centers have submitted a BLA since the completion of the trials. The single BLA for allogeneic islets, which has been submitted by a for-profit entity to the US Food and Drug Administration, remains under review [61]. For these reasons, the use of allogeneic islets for the treatment of T1D has remained investigational in the US. Regulatory approval of islets in additional countries including the US would facilitate patient access to β cell replacement through third-party medical reimbursement and improve outcomes through continued clinical research [62].

Research Priorities in Islet Transplantation

Optimizing donor pancreas procurement and transportation, refining islet isolation and release testing, establishing extrahepatic sites and novel islet delivery techniques for enhanced islet engraftment, developing CNI-free immunosuppressive protocols lacking islet toxicity, and incorporating islet imaging and donor-specific immune assays into monitoring will improve the outcomes and utilization of islet allotransplantation [63]. However, the three most impactful research priorities are the generation of an unlimited supply of islet cells for transplant along with effective islet banking technologies, optimization of islet delivery and implantation techniques, and the development of strategies that facilitate islet graft survival without the need for maintenance immunosuppression.

Facing the substantial shortage of suitable deceased donor pancreases, academia and industry developed an alternative, stem cell-derived source of insulin-secreting islet β cells for transplantation [64]. The recent refinements represent a monumental accomplishment, culminating in the restoration of insulin independence after intraportal infusion of what was considered a half dose of stem cell-derived islets into a type 1 diabetic recipient in a clinical trial conducted by Vertex Pharmaceuticals [7]. Progress has also been made in preclinical studies of transplantation of porcine islets as an alternative source of islets in immunosuppressed nonhuman primates [65].

Large-scale application of β cell replacement strategies in diabetes will require high-quality islets that are accessible in cell banks. Cryopreservation could solve islet supply chain challenges. The comprehensive optimization of cryoprotectant agent composition, its loading and unloading conditions, and methods for vitrification and rewarming of mouse, porcine, human, and stem cell-derived β cells allowed considerably improved transplantation outcomes [66]. Better islet delivery and implantation technologies would improve engraftment and functional survival of transplanted islets, thereby lowering the costs of curative islet products and their applicability in the treatment of diabetes.

Faleo et al. demonstrated that cotransplantation of parathyroid gland and stem cell-derived insulin-producing cells enhances graft survival through release of proangiogenic and prosurvival factors [67]. The intrahepatic milieu is considered inhospitable to transplanted islets. To promote the utilization of the subcutaneous space as an alternate, safe, and easily accessible site for islet transplantation, islets were admixed with a device-free islet viability matrix, resulting in long-term euglycemia in murine and nonhuman primate animal models and paving the way for clinical development of alternate sources of pancreatic islets [68].

Finally, strategies have been advanced for minimizing and eliminating maintenance immunosuppression in islet transplant recipients. A recent preclinical study demonstrated that two peritransplant infusions of apoptotic donor leukocytes under short-term immunosuppression with anti-CD40, rapamycin, sTNFR, and anti-IL-6R induced long-term (>1 year) immune tolerance to islet allografts in nonhuman primates [69]. Important improvements in islet micro- and macroencapsulation have been reported in the last decade. Transplanted human islets survived for more than 10 months without immunosuppression in an oxygenated and immune-isolating chamber [70]. Other refinements of the encapsulation approach include the incorporation of the chemokine CXCL12 into alginate [71], conformal coating of stem-cell derived islets [72], and a nanofibrous encapsulation device for safe delivery of insulin-producing cells [73].

Multiplex genome editing is used to mitigate the innate and adaptive immune response to stem cell-derived islet cell products with the ultimate goal of developing an immune-evasive cell replacement therapy for diabetes. Genes being targeted include the highly polymorphic HLA Class I and II, PD-L1, HLA-G, and CD47 [74]. CRISPR Therapeutics and ViaCyte, Inc. announced in February of 2022 that they have dosed their first patient in a phase I clinical trial of a novel gene-edited cell replacement strategy to treat T1D [75]. Gene editing of stem cell-derived islet products will likely become a

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focus of academic and corporate research efforts in β cell replacement for diabetes.

Conclusion

Islet allotransplantation has become a viable treatment option for patients with T1D and IAH in whom optimized medical therapy has been ineffective in preventing SHEs. Islet transplantation should also be considered in patients with T1D and end-stage renal failure who cannot meet clinically appropriate glycemic goals or in whom SHEs persist. Despite superior efficacy in restoring normoglycemia and freedom from severe hypoglycemia compared with current diabetes technologies, transplantation of allogeneic human islets has remained an underutilized treatment option, presumably largely due to concerns related to the risks associated with immunosuppression.

Considering the substantial progress made in developing limitless sources of islet cells for transplantation, improving their delivery and engraftment, and averting the need for maintenance immunosuppression, it is fair to assume that transplantation of islets will soon play an increasingly important role in the care of patients with diabetes.

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Conflict of Interest

B.J.H. has an equity interest in and serves as paid executive officer and director of Diabetes Free, Inc., an organization that may commercially benefit from this chapter. This interest has been reviewed and managed by the University of Minnesota in accordance with its conflict-of-interest policies. M.D.B. discloses research support from ViaCyte, Inc. and Dexcom, Inc. and membership on the Data Safety and Monitoring Board of Insulet Corporation. J.S.R. has no conflicts of interest to disclose.

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Transplantation of the Pancreas

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Introduction

The medical, financial, and social consequences of diabetes mellitus are a global challenge to public health. According to the World Health Organization (WHO), at least 420 million people are affected worldwide, with rising prevalence and a 5% increase in premature mortality. Diabetes is a major cause of blindness, kidney failure, heart attack, stroke, lower limb amputation, and poor quality of life. It is the ninth leading cause of death (presumably underreported) with an estimated 1.5 million deaths per year directly caused by diabetes [1,2]. In the United States alone, the annual cost of diagnosed diabetes amounts to $327 billion, a 26% increase over a five-year period [3]. Insulin-dependent, autoimmune type 1 diabetes (T1D) affects 0.1–1% of the population, dependent on the country, with its highest incidence around 10–15 years of age. The incidence has increased over time, approximately doubling over the past 2–3 decades [4].

Conservative treatment options for diabetes mellitus include a wide spectrum of modalities ranging from diet and exercise to drugs and insulin pumps. However, all of these options have resulted in suboptimal disease management and intensive insulin therapy comes at the expense of potentially life-threatening iatrogenic hypoglycemia with an estimated incidence of 2–10% per year [5,6]. Due to these deficiencies, transplantation of β cells as an organ (pancreas) or cellular preparations (islets) have been performed in increasing numbers over the past decades.

Pancreas transplants are performed in patients who require administration of insulin because of T1D, type 2 diabetes mellitus (T2D) or after a total pancreatectomy. Successful pancreas transplants have also been performed after failed islet transplants [7]. A successful pancreas transplant is the only definitive long-term treatment for patients with insulin-dependent diabetes mellitus that consistently restores glycemic control without exposing patients to the risk of severe hypoglycemia, and prevents, halts or even reverses the development or progression of secondary complications of diabetes mellitus [1,8]. Early in the history of pancreas transplantation, such transplants between identical twins contributed to our understanding of T1D as being an autoimmune disease. In patients with T1D who received a pancreas graft from their identical twin, T1D returned within weeks in the absence of immunosuppressive therapy [9].

Pancreas transplants are performed in three different categories of patients with diabetes mellitus [1]. The first and most common category includes diabetic patients with uremia who require a simultaneous pancreas and kidney transplant (SPK). The second category includes patients who are diabetic and posturemic and who undergo a pancreas after a previous (living or deceased donor) kidney transplant (PAK). The third category consists of patients with brittle diabetes mellitus without uremia who undergo a pancreas transplant alone (PTA).

The first pancreas transplant was performed on December 16, 1966, by William Kelly and Richard Lillehei at the University of Minnesota, USA [10]. Since then and as of December 31, 2020, about 35 000 pancreas transplants from the United States and almost 29 000 from outside the United States have been reported to the International Pancreas Transplant Registry (IPTR) [11]. Outcome after pancreas transplantation has significantly improved over time due to advances in surgical techniques and immunosuppressive therapy: at one year post transplant, patient survival rates are now >96% and graft survival rates are almost 86% (see below) [11].

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Evolution of Surgical Techniques

Advances in surgical techniques have been instrumental in improved outcome after pancreas transplantation. In fact, more so than with any other solid organ, the history of pancreas transplantation has predominantly revolved around the development and application of different surgical techniques. No other abdominal organ has seen such a wide variety of surgical techniques for the purpose of transplantation [12].

Since the first pancreas transplant in 1966, the surgical focus has been on determining the optimal management for drainage of pancreatic exocrine secretions and venous outflow. While enteric drainage and systemic drainage are now the two most common techniques used, portal vein and other forms of gastrointestinal drainage (via the duodenum or stomach) are viable options and are considered complementary, rather than competing, alternatives [13]. Hence, the surgical technique should be adapted to the individual circumstances of donor and recipient and to the individual surgeon's preference to achieve an optimal outcome.

A multitude of surgical techniques for diverting exocrine pancreatic secretions have been reported over time: enteric drainage (used in the first pancreas transplant) (Figs 167.1 and 167.2), cutaneous graft duodenostomy, open intraperitoneal duct drainage, duct ligation, duct injection, gastric drainage, ureteral drainage, bladder drainage, and duodenal drainage (in chronological order) [11–13]. Of those, enteric and bladder drainage have been the most common techniques. Bladder drainage was the most popular technique until the 1990s for two reasons. First, it enables timely diagnosis and treatment of rejection [14]. Since rejection of the exocrine pancreas precedes rejection of the endocrine pancreas by 5–7 days, a drop in urinary amylase indicates rejection and treatment can be successfully implemented when the recipient is hypoamylasuric but still normoglycemic. More than 90% of pancreas rejection episodes are reversible in the absence of hyperglycemia [14]. Second, bladder drainage avoids morbidity and mortality of bacterial contamination that occurs with enteric drainage leaks. However, bladder drainage is associated with unique metabolic and urologic complications, including hyperchloremic metabolic acidosis (secondary to bicarbonate loss through the urine), dehydration, recurrent urinary tract infections, dysuria, hematuria, and/or graft pancreatitis secondary to reflux of urine into the ductal system of the graft [12–14].

The introduction of tacrolimus (Tac) and mycophenolate mofetil (MMF) in the mid-1990s resulted in a significant reduction in pancreas rejection rates and led to a major change in the management of pancreatic exocrine



Figure 167.1 Whole-organ transplant with systemic vein and enteric exocrine drainage (caudad position): side-to-side two-layer duodenojejunostomy. The pancreas with its vascular anastomoses (donor Y-graft to recipient common iliac artery, donor portal vein to recipient common iliac vein) is implanted in the standard fashion on the right side of the pelvis. The arterial anastomosis is medial and proximal to the venous anastomosis. *Source:* [13]/Springer Nature.

secretions in that enteric drainage became the predominantly used technique worldwide in about 95% of transplants. For enteric drainage, the pancreas graft can be placed in either a caudad (see Fig. 167.1) or a cephalad (see Fig. 167.2) position. Enteric drainage has seen several modifications. Construction of a Roux-en-Y loop is rarely performed (in about 15% of all transplants) and has been all but abandoned in favor of a direct donor duodenum-to-recipient jejunum anastomosis. The anastomosis itself is usually hand-sewn rather than stapled.

Duodenal and gastric (rather than jejunal) drainage are being used at some centers because they afford direct access to the allograft duodenum and pancreas for biopsy and for surveillance endoscopies, including graft endoscopic retrograde cholangiopancreatography (ERCP). The main disadvantage of duodenal drainage is the surgical management of eventual leaks or graft pancreatectomies: closure of the native duodenum can be very challenging and is associated with morbidity and mortality. Enteric drainage into the recipient jejunum remains the most commonly used exocrine drainage technique [11,12].

Venous drainage of the pancreas graft into the systemic circulation, bypassing the liver, is less physiologic than venous drainage into the portal circulation (Fig. 167.3).

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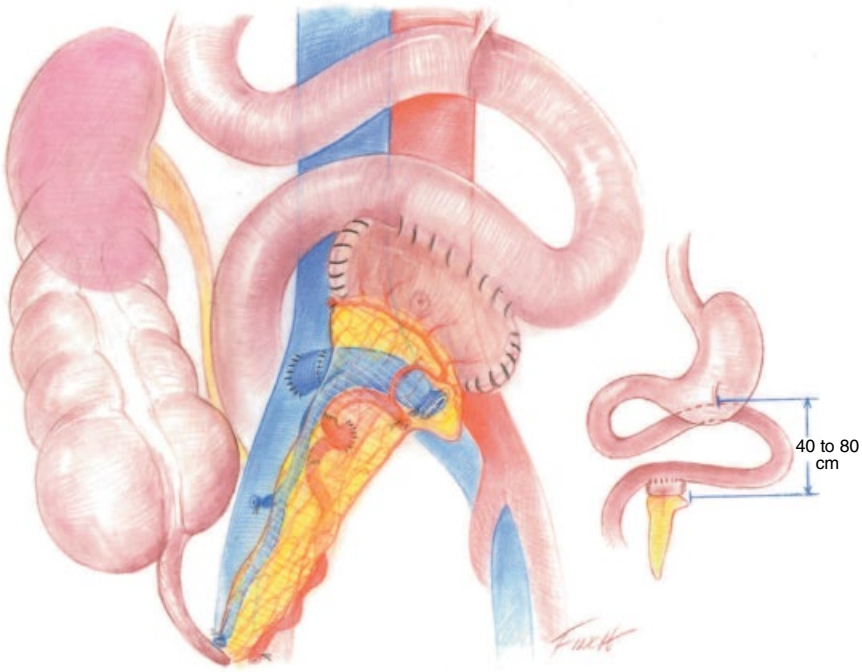


Figure 167.2 Whole-organ transplant with systemic vein and enteric exocrine drainage (cephalad position). The donor portal vein (in this case with an extension graft) is anastomosed end-to-side to the recipient common iliac vein or infrarenal cava. The donor Y-graft is anastomosed to the recipient common iliac artery. A two-layer side-to-side duodenojejunostomy is constructed about 40–80 cm distal to the ligament of Treitz (inset). The arterial anastomosis is medial and distal to the venous anastomosis. *Source:* [13]/Springer Nature.

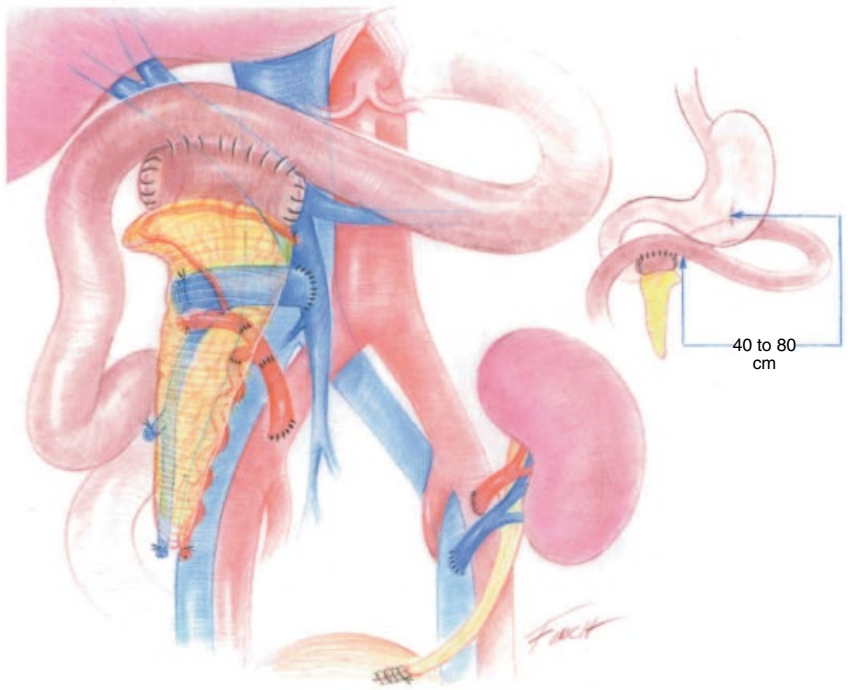


Figure 167.3 Whole-organ transplant with portal vein and enteric exocrine drainage using the intraperitoneal approach. The pancreas graft overlies the root of the small bowel mesentery, with the duodenal segment below the transverse colon. The donor portal vein is anastomosed end-to-side to the recipient superior mesenteric vein. The donor Y-graft (with an extension graft) is anastomosed to the recipient common iliac artery through a mesenteric tunnel. A two-layer side-to-side duodenojejunostomy is constructed about 40–80 cm distal to the ligament of Treitz. In the final position, the jejunal limb usually lies anterior to the donor duodenum. The simultaneously transplanted kidney is anastomosed to the recipient external iliac artery and vein. The ureter is implanted into the bladder using the extravesical ureteroneocystostomy (Lich) technique. *Source:* [13]/Springer Nature.

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Systemic drainage was used in the first pancreas transplant due to its technical ease and has prevailed since. Portoenteric drainage was most popular in the 1990s [11–13]. Although systemic venous drainage causes peripheral hyperinsulinemia and portal hypoinsulinemia, serious metabolic consequences have not been reported. In fact, comparable metabolic control and graft outcome is achieved with portal vein and systemic vein drainage. As with enteric and bladder drainage, portal and systemic vein drainage should not be considered competing, but rather complementary, techniques. Obesity, thickened mesentery, and small mesenteric veins favor systemic vein drainage, whereas previous pelvic transplants or operations, severe iliac atherosclerosis, and short arterial grafts favor portal vein drainage. Systemic venous drainage is used in about 90% of all pancreas transplants [11–13].

Other, initially controversial technical issues have been resolved. They included pancreatic mass (whole organ is preferred over segmental transplant) and graft placement (intraperitoneal is preferred over extraperitoneal position); in SPK, bilateral is preferred over ipsilateral graft positioning.

According to the IPTR, an intraabdominal whole-organ pancreas transplant with enteric and systemic venous drainage (see Figs 167.1 and 167.2) is now the preferred technique worldwide [11]. However, the surgical technique may need to be adapted to the individual circumstances of donor and recipient to optimize outcome.

Lastly, from both a historical as well as a technical perspective, the pancreas was the first extrarenal organ to be successfully transplanted using a living donor and the first dual-organ transplant (SPK) from a living donor [15,16]. The (distal) pancreas was also the first extrarenal solid organ that was successfully procured, with spleen preservation ("Sutherland" technique), from a living donor using the minimally invasive (laparoscopic) technique [17].

In the United States, favorable changes in organ allocation policies have resulted in an adequate number of deceased donor pancreases in recent years. For that reason, a living donor pancreas transplant is rarely indicated (except for a highly sensitized patient, avoidance of high-dose immunosuppression or availability of a nondiabetic identical twin or a 6-antigen-matched sibling). In contrast, living donor pancreas transplants continue to be performed in moderate numbers in Asian countries (China, Japan, Korea) due to the lack of organ donation for cultural and religious reasons [18]. The evolution of strict metabolic criteria has diminished the risk for the donor to develop diabetes post donation [19]. Outcome after living donor pancreas transplantation is at least as favorable as for deceased donor transplantation [20].

Substantial improvements in immunosuppressive therapy and antimicrobial prophylaxis and therapy have added extra safety nets to the various surgical techniques and contributed to a significant decrease in technical complications and failures. From a technical perspective, pancreas transplants can be quite demanding and require solid skills in general and vascular surgery; graft pancreatectomies, pancreas retransplants, pancreas transplants after native pancreatectomy, living donor and split pancreas transplants, and pancreas transplants in combination with other extrarenal organs such as the liver or lung can be extremely challenging [11,21,22].

The evolution of pancreas transplantation with its many technical facets, including the introduction of robotic surgery for selected pancreas transplant recipients, has also greatly advanced the field of pancreatic surgery at large [23],

IPTR: Transplant Demographics

Between December 17, 1966, and December 31, 2020, a total of 63 871 pancreas transplants were reported to the IPTR; this total includes about 35 000 pancreas transplants from the US and almost 29 000 from outside the US [11,24]. The overall development of reported cases over the years for US and non-US cases is shown in Figure 167.4. The decrease in numbers in 2020 is due to the COVID-19 pandemic which impacted all pancreas transplant centers worldwide [11,24].

The following transplant demographics focus on the United States experience where reporting is mandatory. Of 34 998 US pancreas transplants, 96% were performed for diabetes mellitus and 4% as part of multivisceral transplants for technical reasons (i.e., elimination of a separate bile duct anastomosis).

Of all US pancreas transplants in patients with diabetes mellitus, 76.6% were in the SPK category, 15.2%, in the PAK category, and 8.2%, in the PTA category. Of those, 94% were primary transplants and 6% were retransplants. Until the late 1980s, pancreas transplants were performed almost exclusively in recipients with T1D. Between 1996 and 2000, only 4.6% of all recipients were reported to have T2D; the overall rate increased to 18.4% between 2016 and 2020. Most T2D recipients required an SPK transplant because of end-stage renal disease. About 60% of pancreas transplant recipients in the SPK and PAK categories were male, but in the PTA category more women (60%) were transplanted.

Pancreas transplants from donation after circulatory death (DCD) and living donors are rare. In the US, in contrast to many European countries, DCD donors were utilized in only 3% of all transplants, but the trend is slightly

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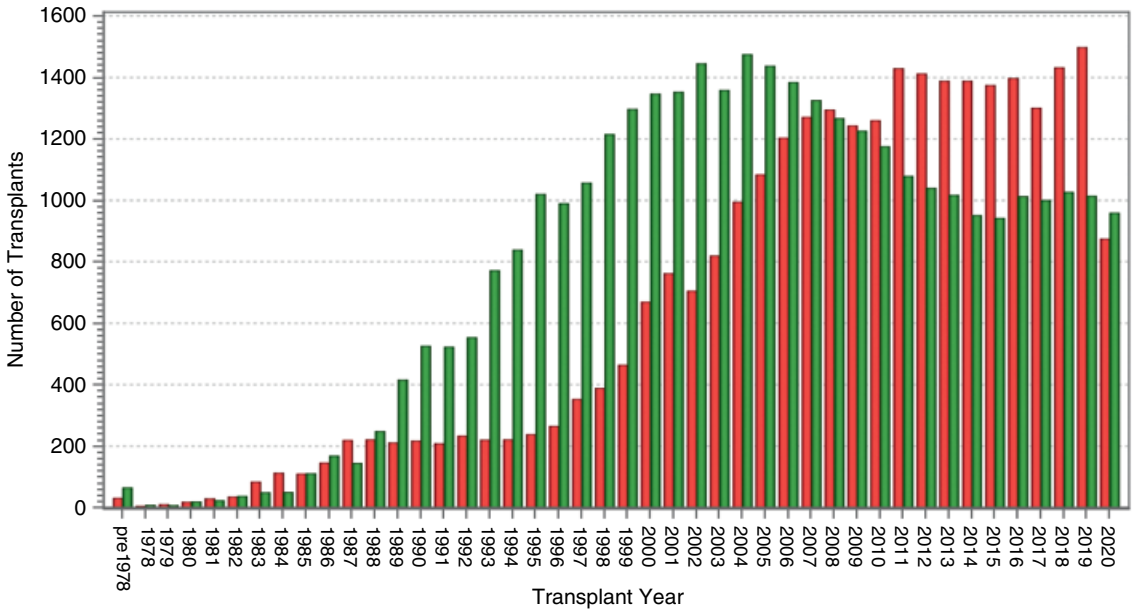


Figure 167.4 Annual number of US and non-US pancreas transplants reported to the IPTR between 12/17/1966 and 12/31/2020.

increasing. Living donor pancreas transplants account for less than 1% of all transplants in the United States.

Over time, the overall median recipient age for primary deceased donor pancreas transplants has significantly increased, from 32 (range 15–54) years in 1966–1985 to 42 (12–75) years in 2016–2020. In contrast, the median pancreas donor age has significantly decreased from 27 (range 4–62) years in 1986–1990 to 22 (4–53) years in 2016–2020. The most common cause of donor death was trauma and most deceased donors were of male gender. Preservation time of deceased donor pancreas also decreased significantly over time from 13.2 (1.5–50) hours in 1991-1995 for SPKs to 9.4 (1–46) hours in 2016-2020.

Little consideration is given any more to good HLA matching due to improvements in immunosuppressive therapy. In the SPK category, the median number of mismatches increased to five (out of a maximum of six) in 2016–2020; in the more immunogenic PAK and PTA categories, better HLA matching was achieved and "only" 57% of transplants were performed with a 5- or 6-antigen mismatch. Enteric and systemic vein drainage are the most commonly used surgical techniques (Fig. 167.5).

The mid-1990s saw a major change in immunosuppressive therapy after pancreas transplantation and led to significantly improved outcomes (see below). First, over 90% of recipients are now receiving induction therapy, in most cases with depleting antibodies. Second, the TAC-MMF combination is the most frequently used maintenance regimen, accounting for >80% in all three recipient categories. Third, the trend away from steroid avoidance and withdrawal continues; such protocols accounted for only 30% in all three categories for the 2016–2020 time period.

IPTR: Outcome

From 1966 through 2020, pancreas transplant outcomes in all three recipient categories improved significantly. The advancements were mainly due to better donor and recipient selection criteria as well as technical and immunosuppressive improvements which in turn resulted in a significant decrease in the rates of technical failures and immunologic graft losses [11,24].

The patient survival rate at one year for SPK recipients was 97% in 2016–2020 vs 58% in 1966–1985; for PAK recipients, 96% vs 81%; and for PTA recipients, 99% vs 75%. Long-term patient survival rates have paralleled short-term outcomes: five-year patient survival rate for 2016–2020 was >90% and the 10-year survival rate >70% in all three recipient categories.

Pancreas graft survival rates have even more impressively improved over time in all three recipient categories. The IPTR has always defined pancreas graft function as insulin independence. The pancreas graft survival rate at one year for SPK recipients was 91% in 2016–2020 vs 33% in 1966–1985 (Fig. 167.6); for PAK recipients, 86% vs 22%; and for PTA recipients, 87% vs 19% (Fig. 167.7). These pancreas graft survival rates are comparable to kidney graft survival rates. Long-term pancreas graft survival rates have paralleled short-term outcomes: five- and 10-year pancreas graft survival rates for 2016–2020

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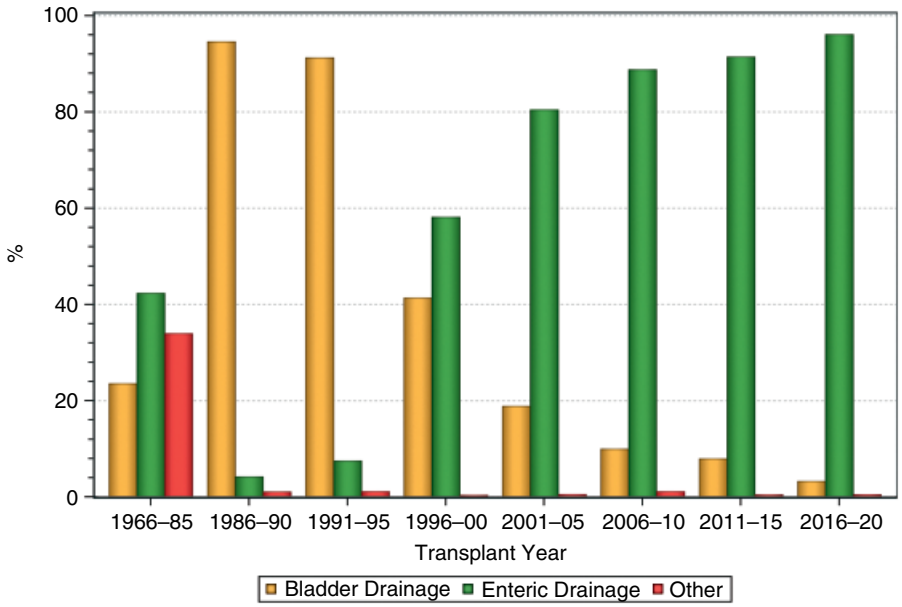


Figure 167.5 US duct management techniques in primary deceased donor pancreas transplants performed between 12/17/1966 and 12/31/2020.

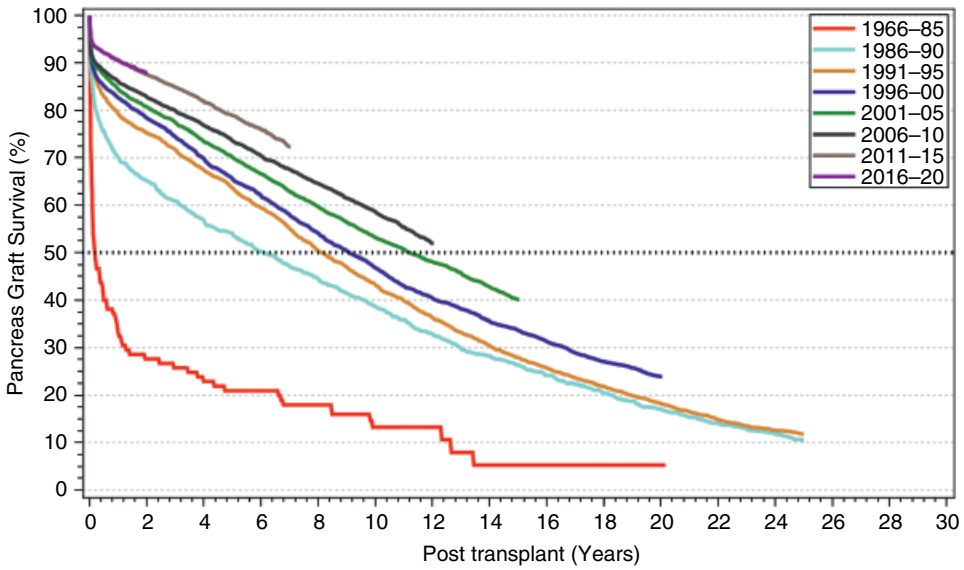


Figure 167.6 US pancreas graft survival by era after primary deceased donor simultaneous pancreas/kidney transplantation (SPK) performed between 12/17/1966 and 12/31/2020.

were 73% and 56% for SPK recipients; 64% and 38%, for PAK recipients; and 53% and 36%, for PTA recipients. Long-term graft survival paralleled improvement in short-term outcome. The half-life (50% graft function) for a SPK pancreas (kidney) graft increased from 73 months in 1986–1990 to 134 months in 2001–2005. Since 2005, more than 50% of all grafts are still functioning and therefore the half-life could not be computed (Table 167.1).

The most critical time period after a pancreas transplant remains the first year due to the risk of technical and immunologic complications. Not surprisingly, for grafts that survived the first year after transplantation, long-term outcome was significantly better. For SPK transplants which did not fail during the first year post transplant, pancreas (kidney) half-lives increased from 134 months (133 months) in 1986–1990 to 170 months (175 months) in 2001–2005 (see Table 167.1). SPK

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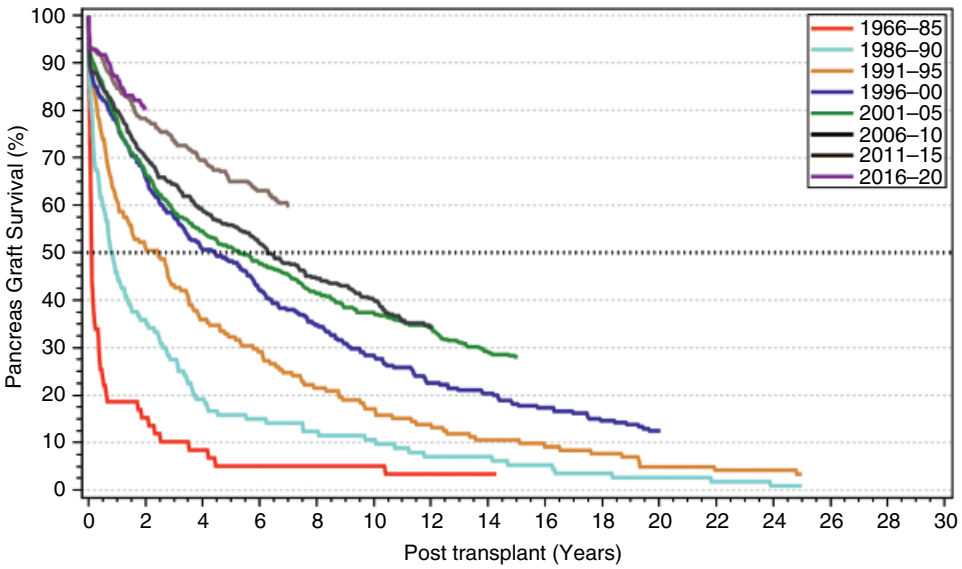


Figure 167.7 US pancreas graft survival by era after primary deceased donor pancreas transplantation alone (PTA) performed between 12/17/1966 and 12/31/2020.

Table 167.1 Pancreas and pancreas/kidney transplant half-lives for transplants performed between 1/1/1986 and 12/31/2005.

	SPK			
Transplant year	**Pancreas**	**Kidney**	**PAK**	**PTA**
1986–1990	73 (134)	92 (133)	6 (61)	10 (42)
1991–1995	98 (132)	115 (141)	23 (79)	29 64)
1996–2000	109 (140)	144 (163)	56 (89)	53 (80)
2001–2005	134 (170)	161 (175)	70 (113)	64 (107)

Brackets show conditional half-lives for txs that reached the one-year mark with functioning graft.
SPK, simultaneous pancreas and kidney transplant; PAK, pancreas after kidney; PTA, pancreas transplantation alone.

transplants performed after 2005 will have an even longer half-life. Similar improvements have been seen in the solitary transplant categories although not quite as marked, with half-lives of 113 months for PAK and 107 months for PTA recipients in 2001–2005 (Table 167.1).

At the time of this writing (January 2022), 7068 SPK pancreas transplants had reached the 10-year follow-up mark, and 1227 transplants the 20-year mark with a functioning pancreas. Important factors influencing long-term function were those that described the quality of the deceased donor. Pancreas transplants in younger, high panel reactive antibody (PRA) or black recipients showed an increased risk of early graft failure. Induction therapy with depleting antibodies had a significant positive impact on long-term survival.

Table 167.2 Early technical failures in enteric-drained primary deceased donor pancreas transplants performed in adult recipients between 1/1/2016 and 12/31/2020.

	SPK	**PAK**	**PTA**	**P**
N	**3397**	**194**	**234**	
Technical failure rate (%)	**5.5**	**6.2**	**6.4**	**0.79**
Graft thrombosis (%)	3.7	4.1	5.9	
Infection (%)	0.5	0.5	0.0	
Pancreatitis (%)	0.2	0.5	0.0	
Anastomotic leak (%)	0.4	0.0	0.2	
Bleeding (%)	0.3	0.5	0.0	
Technical/other (%)	0.4	0.6	0.3	

SPK, simultaneous pancreas and kidney transplant; PAK, pancreas after kidney; PTA, pancreas transplantation alone.

The rates of graft losses from technical and immunologic causes have significantly decreased over time in all three recipient categories. Technical failures (Table 167.2) include graft thrombosis (4%), infection (<1%), pancreatitis (<1%), anastomotic leakage (<1%), and bleeding (<1%); at one year, the overall technical failure rate in 2016–2020 was about 6% in all recipient categories vs 25% in 1966–1985. The rate of graft losses for immunologic reasons (mainly rejection; rarely, recurrent autoimmune disease) at one year was about 2% in the SPK category and about 5% in the PTA and PAK categories. Very few fields in all of solid organ transplantation have seen such improvement in reducing graft losses from

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rejection: for solitary pancreas transplants (PAK, PTA) from 65% in 1966–1985 to 5% in 2016–2020. However, the long-term graft loss rates from rejection still remain higher in the solitary recipient categories (PTA and PAK) than in the SPK category; the transplanted kidney (serum creatinine levels) of SPK recipients frequently serves as an effective harbinger for the early diagnosis of rejection. Graft loss from rejection is also higher for younger (<30 years of age) vs older recipients and in nonuremic vs uremic patients.

Pancreas graft survival has not been different for T1D vs T2D recipients.

Multivariate analyses have provided further insight into outcome after pancreas transplantation. The factors with the highest impact on patient survival were functioning pancreas and kidney grafts. The loss of either organ increased the relative risk (RR) of death significantly (RR 15.98 for kidney graft loss, RR 3.3 for pancreas graft loss in the SPK category). Hence, maintenance of stable graft function is pivotal to patient survival. In the SPK category, recipients who were on dialysis before transplant had a higher risk of death, as well as patients over the age of 45; in the PAK category, recipients who had received a deceased donor kidney showed a higher RR of death compared to recipients of a living donor kidney.

The factors with the highest impact on patient survival were donor selection factors. Donor age >30 years of age and cold preservation time >12 hours significantly increased the risk of losing the pancreas graft. Older recipient age showed a slightly higher risk of pancreas graft loss in SPK recipients, but the risk was decreased in PTA recipients. A sensitization rate >60% increased the RR of graft failure. The COVID-19 pandemic has negatively impacted both pancreas and kidney graft survival [11,24].

IPTR: Survival Benefit

For a long time, the perception had persisted that a pancreas transplant is simply an alternative to insulin replacement therapy, despite evidence in the literature to the contrary [25,26]. Unlike liver and heart transplants, pancreas transplants are usually not immediately life-saving procedures. However, their life-saving nature becomes evident within several months post transplant by decreasing the recipients' risk of death from hypoglycemic unawareness, cardiocerebrovascular events, and other secondary diabetic complications.

Over a 21-year time period, from January 1, 2000, to May 31, 2021, the IPTR/UNOS collected information about listing and transplant outcome of diabetic patients. To determine the survival benefit of pancreas transplantation, patient survival on the waiting list versus after transplantation was defined as the primary outcome. Over the 21-year time period, pancreas and/or kidney transplantation in all four diabetic recipient categories saved a total of 273 843 life-years. On average, 11.7 life-years per patient were saved in the SPK category, 6.4 life-years in the PTA category, 6.3 life-years in the PAK category, and 6.6 life-years in the KTA category [8]. The survival benefit of pancreas and/or kidney transplant recipients in all three categories was highly significant compared to diabetic patients still waiting for transplantation (SPK category) [8,27]. The survival benefit was higher for patients with T1D vs T2D. The significant survival benefit of PTA recipients versus patients on the waiting list justifies the argument for preemptive pancreas transplantation, i.e., before the development of end-stage renal disease.

Given the survival benefit as evidenced by 273 843 life-years saved, pancreas transplantation should be more widely applied, specifically in the PTA category, and pancreas donation encouraged [8,28].

Impact on Secondary Diabetic Complications

A large body of literature clearly demonstrates the positive impact of pancreas transplantation on secondary diabetic complications in that a successful pancreas transplant can prevent, halt or even reverse the development and progression of these debilitating complications across many organ systems [29]. Primarily after SPK transplantation, functional improvements have been reported in diabetic nephropathy, neuropathy (autonomic and peripheral), gastroparesis, retinopathy, microvascular and macrovascular disease (including cerebral vasculopathy and morphology), cardiac function, and sexual function. In PAK recipients, improvements in graft function of a previously transplanted kidney have been demonstrated [30]. In PTA recipients, prevention or reduction in the progression of secondary complications have been reported despite the paucity of pretransplant symptoms in this category. This is most evident by the observation that long-term normoglycemia had reversed glomerular and cortical lesions of diabetic nephropathy with return to normal glomerular structure at 10 years post transplant [31]. Nevertheless, life-long exposure to calcineurin inhibitors and dehydration can still result in impaired kidney function.

Polyneuropathy also improved in recipients who achieved a normoglycemic state after a successful pancreas transplant, in contrast to the progression observed in the control group that was treated with insulin. Improvement was maintained over 10-year follow-up,

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contributed to a higher level in general life activities, and correlated with a significant reduction in mortality in transplant recipients [32].

The positive impact of pancreas transplantation on secondary diabetic complications is primarily based on complete freedom from insulin and establishment of normoglycemia. A successful pancreas transplant completely normalizes and more effectively lowers the levels of HbA_{1c} when compared to intensive insulin therapy. Even 10 years post transplant, a successful pancreas transplant preserves almost normal insulin secretion and provides excellent glycemic control. Thus, restoration of β-cell secretory capacity, normalization in glucose counterregulation, and return to hypoglycaemia awareness are all achieved with a successful pancreas transplant [33].

Quality of Life After Pancreas Transplantation

One of the most pivotal factors in assessing quality of life issues after pancreas transplantation is graft function. In all three recipient categories, graft loss results in a marked reduction in quality of life whereas stable graft function significantly increases quality of life [34].

As the majority of pancreas transplants is performed in the SPK category, most available literature focuses on this population. Compared to remaining on the waiting list, SPK leads to greater improvements in general health and vitality, physical and mental health functions, social functioning and diabetes-related issues. Long-term follow-up studies clearly demonstrate that benefits to health and quality of life are not only present in the first year post transplant but are maintained and continue to increase in following years for as long as the graft functions. From the perspective of allocating healthcare resources, SPK provides a significantly greater number of quality-adjusted life-years than kidney transplants alone or dialysis. SPK is the therapy of choice for an increasing number of eligible diabetic patients.

As the number of SPK recipients with functioning grafts increases, more attention is now being placed on quantifying other quality of life issues such as the impact of psychologic and social support before and after surgery and in underrepresented groups. Due to the severity of established medical and psychologic impairment at the time of transplant, SPK does not fully return patients to the level seen in the general population. The impact of early referral for pancreas transplantation prior to end-stage organ damage is obvious and enforces the need for increasing the number of transplants in the PTA category.

There is a relative dearth of studies examining the impact on quality of life in the PAK and PTA categories due to the much smaller numbers of recipients. However, most recipients of these two categories find it easier to manage their immunosuppression on a daily basis than their diabetes mellitus. Future multicenter studies may better assess the impact of solitary pancreas transplants on patients' quality of life outcomes. Consistent with studies of heart, lung, kidney, and liver transplantation, pancreas transplantation clearly has a positive effect on quality of life [1,34].

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