Cystic tumors (neoplasms) of the pancreas are far more common than once thought, developing in up to 10% of the general population. Many cystic pancreatic tumors are benign; however, some (particularly mucinous tumors) have distinct malignant potential. Unfortunately, no ideal method currently exists to predict the presence of invasive cancer in an existing cystic tumor or the risk of developing malignancy if not present already. This fact makes surgical patient selection challenging. In addition, widespread use of abdominal cross-sectional imaging has increasingly identified asymptomatic patients with “incidental” pancreatic cysts. For all of the reasons outlined above, diagnosis and treatment of cystic pancreatic tumors represent one of the most exciting and dynamic topics in pancreatic surgery today.

This chapter reviews the pathology, diagnosis, and treatment of the most common pancreatic cystic tumors, with special emphasis on the management of intraductal papillary mucinous neoplasm (IPMN), as well as the evaluation of incidentally discovered pancreatic cysts—a field in active evolution.

Epidemiology and General Considerations

Epidemiology

The true incidence of pancreatic cysts in the general population is difficult to estimate but likely approximates 2%. Radiologic studies estimate that the prevalence of pancreatic cysts ranges from 1.2 to 19.6% in asymptomatic individuals undergoing cross-sectional imaging, including magnetic resonance imaging (MRI) and computed tomography (CT).3–5 Most of these studies confirm an increasing prevalence with age—up to approximately 10% by age 70. Patients with a strong family history of pancreatic cancer who themselves are at high risk for developing pancreatic adenocarcinoma were found to have a significantly increased incidence of pancreatic cysts (39%) when surveyed with an aggressive screening program.4 One widely quoted autopsy series found pancreatic cysts in a remarkably high number, 24%, although this high incidence has yet to be validated.5

Pathology

The most common neoplastic pancreatic cysts are serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), and IPMNs. Table 1 lists all pancreatic cystic lesions, including less common pancreatic cystic tumors and lesions mimicking pancreatic cysts [see Table 1]. Pancreatic cysts can be classified into those that are benign (little to no malignant potential) and those with malignant potential. In general, potentially malignant cysts include mucin-containing pancreatic cysts (IPMNs and MCNs) and, to a lesser extent, solid and cystic papillary tumors and cystic islet cell tumors.

Table 1

<table>
<thead>
<tr>
<th>Cyst Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (little or no malignant potential)</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>Acinar cell cystadenoma</td>
</tr>
<tr>
<td>Simple (congenital) cyst</td>
</tr>
<tr>
<td>Pseudocyst</td>
</tr>
<tr>
<td>Cysts with malignant potential</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm (MCN)</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
</tr>
<tr>
<td>Solid and cystic pseudopapillary tumor</td>
</tr>
<tr>
<td>Cystic neuroendocrine tumor</td>
</tr>
<tr>
<td>Lesions mimicking pancreatic cysts</td>
</tr>
<tr>
<td>Lymphoepithelial cyst</td>
</tr>
<tr>
<td>Cystic paranganglionoma</td>
</tr>
<tr>
<td>Dermoid inclusion cyst</td>
</tr>
<tr>
<td>Intestinal duplication cyst</td>
</tr>
<tr>
<td>Accessory spleen</td>
</tr>
</tbody>
</table>

Diagnosis

Due to an increase in the use of cross-sectional abdominal imaging, many pancreatic cysts are found incidentally on cross-sectional imaging performed for a separate indication (i.e., kidney stone, abdominal pain, trauma evaluation, etc.). Abdominal CT is prevalent and relatively inexpensive and provides good detail of surrounding structures. MRI with magnetic resonance cholangiopancreatography (MRCP) provides similar detail of surrounding anatomic structures. The advantage of MRI/MRCP is more detailed information about pancreatic ductal anatomy (particularly communication with the cyst), cyst wall, and lumen (i.e., mural nodules or septations), and MRI/MRCP is more sensitive than CT in terms of detecting smaller pancreatic cysts [see Figure 1]. In addition, MRI does not expose the patient to ionizing radiation and thus may be a better (albeit more expensive) cross-sectional imaging choice for longitudinal surveillance (i.e., in the case of IPMN). Transabdominal ultrasonography (US) has the advantages of completely avoiding radiation exposure and being the least expensive imaging modality. However, transabdominal US is operator dependent and provides limited anatomic detail, and its resolution is limited by patient body habitus and the presence of overlying viscera. More invasive imaging includes endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). Each of these specialized tests offers unique advantages: EUS offers the ability for US-directed aspiration of cyst fluid and cyst wall structures [see Figure 2], whereas ERCP may identify the characteristic “fish mouth” papilla–disgorging mucin often seen in patients with IPMN [see Figure 3]. Intraoperative US is an important addition to the surgeon’s approach to pancreatic cysts, particularly when the cysts are treated laparoscopically. Finally, fluorodeoxyglucose positron emission tomography (FDG-PET) scanning may provide information about cysts’ metabolic activity and as such (at least theoretically) may help identify malignant cysts [see Figure 4]. The use of FDG-PET scanning is currently investigational.6
**Cyst Fluid Evaluation**

Evaluation of pancreatic cyst fluid is an area of enthusiastic active investigation. Currently, cyst concentrations of amylase and carcinoembryonic antigen (CEA) are the most useful indices applied to clinical use. A cyst fluid CEA concentration greater than 192 ng/mL is consistent with a mucinous cyst with reasonable sensitivity (positive predictive value > 90%), although the accuracy of this test is only about 80%. Importantly, increasing concentrations of cyst CEA have not correlated with increased risk of malignancy.

A cyst fluid CEA concentration greater than 800 ng/mL is highly sensitive for MCN or mucinous cystadenocarcinoma and thus may influence the decision to operate. A high amylase concentration in pancreatic cyst fluid simply suggests communication with the pancreatic ductal system, as seen in pseudocyst or IPMN. A cyst fluid amylase less than 250 IU/mL is typically seen with SCN.

A great deal of investigation has focused on identifying sensitive and specific measures of malignancy in pancreatic cysts. Several studies have reported cyst fluid DNA analysis; unfortunately, none have been able to distinguish a “usable”

---

**Figure 1**  
(a) Computed tomographic scan of a patient with intra-ductal papillary mucinous neoplasm (IPMN) in the uncinate process (arrow). Note the relative lack of detail even with intravenous contrast administration.  
(b) T2-weighted magnetic resonance imaging study of the same patient with IPMN.  
(c) Magnetic resonance cholangiopancreatography imaging study of the same patient with IPMN. The dashed arrow marks the common bile duct, the solid long arrow shows the cyst, and the solid short arrows mark the main pancreatic duct.
DNA profile that successfully predicts cyst malignancy.\textsuperscript{10} Similarly, commercial assays are available to test for K-ras mutation, a very common genetic mutation seen in pancreatic adenocarcinoma. Clinical application of these tests has failed to accurately differentiate benign from malignant or mucinous and nonmucinous cysts.\textsuperscript{11} Current investigation is focused on identifying novel markers in cyst fluid, including shed proteins and microRNA.

Cytology obtained from the cyst fluid may be diagnostic; however, it has low sensitivity due to limited cell yield and potential contamination by intestinal mucosal cells.

**MANAGEMENT**

Management of the patient with a pancreatic cyst should be tailored based on how secure clinicians are with accurate diagnosis of the cyst, individual patient factors (i.e., family history of pancreatic cancer, age, general medical comorbid state, fitness for operative intervention), and patient symptoms. Ideally, pancreatic cyst patients are evaluated by a multidisciplinary group of physicians, including pancreatic surgeons, gastroenterologists, and experienced gastrointestinal/pancreatic radiologists. Many high-volume pancreatic centers have developed pancreas “cyst clinics” or tumor boards, including all of these clinicians. A general management algorithm for pancreatic cystic lesions identified on cross-sectional imaging is shown in Figure 5 [see Figure 5].

**OPERATIVE INDICATIONS**

Table 2 summarizes operative indications for patients with pancreatic cysts [see Table 2]. In general, symptomatic cysts should be resected in patients fit for surgery. Large pancreatic cysts may cause symptoms by mass effect, that is, early satiety, nausea, or vomiting from gastric or duodenal obstruction; biliary obstruction; or pain from retroperitoneal expansion. Acute pancreatitis caused by pancreatic cysts is more common than generally appreciated. As many as 33% of IPMN patients coming to resection have had at least one bout of pancreatitis.\textsuperscript{12} Finally, patient anxiety should not be overlooked as a symptomatic indication for surgery, particularly in young patients who would require long-term surveillance, as well as in those with personal experience (i.e., relatives) with pancreatic cancer. Obviously, the decision to operate for the indication of anxiety alone is complex and should be determined only after extensive counseling on the risk/benefit profile.
Figure 4  (a) Abdominal computed tomographic image of a patient with a mucinous cystic neoplasm that on final pathologic analysis proved to harbor adenocarcinoma. (b) Positron emission tomographic (PET) scan of the same cyst as in a. Arrows highlight the PET-avid portion of the cyst wall. The standard uptake value was 2.5.

Figure 5  Algorithm for general management of pancreatic cystic neoplasm. BD-IPMN = branch duct intraductal papillary mucinous neoplasm; CNEN = cystic neuroendocrine tumor of the pancreas; EUS = endoscopic ultrasonography; FNA = fine-needle aspiration; GI = gastrointestinal; MCN = mucinous cystic neoplasms; MD-IPMN = main duct intraductal papillary mucinous neoplasm; SPN = solid pseudopapillary neoplasm.
Pseudocyst

By definition, a pseudocyst has no epithelial lining. Pseudocysts form when a pancreatic duct becomes disrupted; as the leaking pancreatic digestive juice is walled off, a fibrotic capsule develops [see Figure 6]. Many older surgical textbooks identify pseudocyst as the most commonly occurring pancreatic cystic lesion. Contemporary imaging data have shown that neoplastic cysts are more common than pseudocysts.3 All patients with pancreatic cysts should be questioned specifically regarding historical symptoms of acute pancreatitis: epigastric or abdominal pain. Most patients with an episode of acute pancreatitis will seek medical attention, which almost always includes evaluation of serum amylase and lipase. However, the rare patient may experience an episode of acute pancreatitis without coming to medical attention. The diagnosis of pseudocyst is often apparent from this clinical history of acute or chronic pancreatitis. Pseudocyst fluid analysis reveals a substantially high concentration of amylase (tens to hundreds of thousands IU/mL). Detailed discussion of pseudocyst management strategy is beyond the scope of this chapter; however, a few salient points deserve mention. In general (and regardless of size), pseudocysts do not require treatment unless they become symptomatic.13 Second, treatment strategy (percutaneous aspiration versus endoscopic versus surgical) should be dictated based on the pancreatic duct anatomy.14 Lastly, if surgical drainage of a pancreatic pseudocyst is performed, the cyst wall must be biopsied to prove the absence of epithelial lining. Also noteworthy is the fact that some pseudocysts may be entirely filled with viscid, postinflammatory debris that mimics mucin on cross-sectional imaging and EUS evaluation.

Serous Cystadenoma

The major distinction between serous and mucinous pancreatic cysts is important because serous cystadenomas (SCAs) are predominantly benign lesions. SCAs arise mostly in women (75%) and are typically diagnosed in the sixth to seventh decade of life.15,16 These cysts may arise in any portion of the pancreas and are often large at the time of diagnosis. Patients with the von Hippel-Lindau syndrome may have multiple SCAs. Patients may be asymptomatic or may manifest symptoms related to mass effect of the cyst, including abdominal pain, early satiety, gastric outlet obstruction, or jaundice. It is extremely rare for SCA to cause acute pancreatitis.

The typical SCA is composed of multiple small cysts lined with cuboidal epithelium; these lesions are well circumscribed and may have a characteristic central “stellate”

---

Table 2  Operative Indications for Pancreatic Cysts

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Malignant potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Mucinous cysts (see above)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Solid and cystic pseudopapillary tumor</td>
</tr>
<tr>
<td>Early satiety</td>
<td>Cystic neuroendocrine tumors</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
</tbody>
</table>

---

Serous Cystadenomas (SCAs) are predominantly benign lesions. SCAs arise mostly in women (75%) and are typically diagnosed in the sixth to seventh decade of life.15,16 These cysts may arise in any portion of the pancreas and are often large at the time of diagnosis. Patients with the von Hippel-Lindau syndrome may have multiple SCAs. Patients may be asymptomatic or may manifest symptoms related to mass effect of the cyst, including abdominal pain, early satiety, gastric outlet obstruction, or jaundice. It is extremely rare for SCA to cause acute pancreatitis.

The typical SCA is composed of multiple small cysts lined with cuboidal epithelium; these lesions are well circumscribed and may have a characteristic central “stellate”

Figure 6  (a) Magnetic resonance imaging (MRI) study of a patient with a clinical history of severe acute pancreatitis. This MRI suggests both solid (solid arrow) and fluid (dashed arrow, bright in this T₂-weighted image) components in the pseudocyst. (b) Intraoperative ultrasound image of the same patient’s pseudocyst (circled), which was found to be composed entirely of amylase-rich fluid.
fibrous scar that lends itself to a secure radiologic diagnosis [see Figure 7]. These lesions may also demonstrate calcification of the cyst wall. On the other hand, “oligocystic” (i.e., < 5 cysts) or “macrocystic” SCAs are less common but may be confused with mucinous cystic lesions. Cyst fluid analysis generally reveals low (< 5 ng/mL) CEA concentration and variable amylase concentration; cytology is usually non-diagnostic. Because SCAs are mostly benign, operative management should be dictated by the presence of symptoms. The SCA patient managed expectantly should be surveyed at an interval to exclude rapid cyst growth. The natural history of SCA is unknown, although some authorities have suggested that cysts greater than 5 cm in size may have increased growth rate and thus that this size in itself may represent an operative indication.16

Although rare, malignant degeneration of SCA to serous cystadenocarcinoma does occur. In the largest single-institution series of resected SCA, 1.3% of patients had malignant transformation.15 This number is likely artificially elevated because many patients with SCA never come to operation; that is, the true denominator of SCA patients is not known. In fact, to date, an aggregate of only 26 patients with serous cystadenocarcinoma has been reported in the English literature.15-17 These patients with malignant transformation clearly have larger cysts (10.1 cm) and had a median survival of 36 months after resection. Clinicians should have an elevated index of suspicion for malignant transformation of SCA if new or worsening symptoms develop or if rapid cyst enlargement is observed.

### Mucinous Tumors

The recent Fukuoka working group consensus guidelines on mucinous cyst (including IPMN and MCN) management delineate operative indications for patients with mucinous pancreatic cysts.18 Fit patients with a secure diagnosis of MCN should undergo resection. Similarly, fit patients with main duct (MD) IPMN should undergo resection. The decision for surgery in patients with branch duct (BD) IPMN is more complex. Previous recommendations suggested operative resection for fit patients with BD-IPMN greater than 3 cm.19 The more current consensus guidelines no longer recommend operation based on size alone and focus on those cysts with “ worrisome features” of greater than 3 cm.

![Figure 7](image-url) (a) Abdominal computed tomographic scan showing serous cystadenoma with typical characteristics: note the central “stel- late” fibrous scar. (b and c) T1- and T2-weighted abdominal magnetic resonance image showing multiple small cysts of serous cystadenoma in the pancreatic tail.
a thickened cyst wall, main pancreatic duct (MPD) size of 5 to 9 mm, nonenhancing mural nodules, abrupt change in MPD caliber with distal pancreas atrophy, and lymphadenopathy. Additional “high-risk stigmata” of jaundice, an enhanced solid component, and MPD greater than 10 mm are also indications for resection based on the current Fukuoka guidelines [see Figure 8].

**Mucinous Cystic Neoplasms: Mucinous Cystadenoma and Mucinous Cystadenocarcinoma**

MCNs represent one of two mucin-secreting pancreatic cysts (IPMN is discussed below); it bears repeating that all mucinous pancreatic neoplasms have malignant potential. MCNs arise most commonly in women (95%) at a mean age of 48 years. Most MCNs are located in the pancreatic body or tail. The clinical presentation of MCN ranges from the asymptomatic incidental finding to significant abdominal pain or mass effect from the cyst. Up to 10% of MCN patients may present with acute pancreatitis. Radiologically, MCNs are characteristically thick walled and typically appear as a single cyst with internal septation [see Figure 9].

Some MCNs appear radiologically similar to pseudocysts; however, the pancreatic parenchyma adjacent to (particularly upstream from) MCN does not typically manifest chronic pancreatitis features such as calcification and atrophy. Fluid analysis from MCN commonly reveals elevated CEA; the cyst amylase concentration is variable but is typically low as the vast majority of MCNs do not communicate with the pancreatic ductal system.

Pathologic analysis of MCN reveals the pathognomonic feature of “ovarian stroma”: a hypercellular stromal layer lying beneath columnar mucinous epithelium [see Figure 10]. This ovarian stroma expresses estrogen and progesterone receptors (detectable by immunohistochemistry) and distinguishes these cysts from others, especially IPMN. The vast majority of MCNs do not communicate with the pancreatic ductal system.

Between 10 and 20% of MCNs in surgical series demonstrate malignant changes; some authorities have suggested that most MCNs greater than 4 cm in size harbor malignant change. Patients with mucinous cystadenocarcinoma generally have larger cysts and are older. Patients managed with a strategy of watchful observation (i.e., those reluctant

---

**Figure 8** Algorithm for managing patients with branch duct intraductal papillary mucinous neoplasm based on recent Fukuoka guidelines. "Worrisome features" include cyst size greater than 3 cm, a thickened cyst wall, main pancreatic duct (MPD) size of 5 to 9 mm, nonenhancing mural nodules, abrupt change in MPD caliber with distal pancreas atrophy, and lymphadenopathy. "High-risk stigmata" include jaundice, an enhanced solid component, and main pancreatic duct size greater than 10 mm. CT = computed tomography; EUS = endoscopic ultrasonography; MRI = magnetic resonance imaging.
to have operation, those in whom the diagnosis is not completely secure) should have routine and lifelong surveillance. The ideal surveillance interval and modality remain a point of debate. On the other hand, patients with resected MCNs that have no evidence of malignant degeneration do not need routine follow-up.\textsuperscript{18}

Intraductal Papillary Mucinous Neoplasm

In 1982, Ohhashi and colleagues presented what is felt to be the first report of what is now understood to be IPMN.\textsuperscript{22}

These authors described a “new” type of mucinous pancreatic cyst that they termed “mucin-secreting pancreatic cancer.” Of course, the pathologic process of IPMN is not new—that is to say that human beings did not start developing IPMNs in the 1980s. A formal pathologic review of all resected pancreatic cancers at the Mayo Clinic between 1960 and 1980 documented much earlier cases of what is now recognized as IPMN.\textsuperscript{23} It is now recognized that IPMN is the most common cystic pancreatic neoplasm. This unique pancreatic cyst is interesting for a number of reasons. First, IPMN harbors the most significant malignant potential of any pancreatic cyst. Although most IPMN patients will not develop malignant degeneration, all IPMNs must be considered a “premalignant” condition as malignant changes are observed in as many as half of all resected IPMNs.\textsuperscript{24} Second, IPMNs may develop in the MPD (MD-IPMN), branch ducts (BD-IPMN), or both main and branch ducts in a mixed type [see Figure 11]. Third, as many as 40% of patients with IPMN have multiple cysts in multiple locations in the pancreas, making operative planning a major challenge. The latter facts are of particular interest considering the development and natural history of IPMN, raising the intriguing theory of a “field genetic defect” in the pancreatic parenchyma.\textsuperscript{18,24} The fact that IPMN patients may develop progressive or recurrent cysts in the pancreatic remnant after resection lends credence to this field defect theory, makes operative decision making more difficult, and highlights the need for lifelong surveillance in these patients.

Both MD-IPMN and mixed-type IPMN occur more commonly in men than in women and are diagnosed at a mean age of 66 years.\textsuperscript{24,25} Patients with IPMN present with complaints similar to those with other pancreatic cysts: abdominal pain (50%), weight loss (40%), jaundice (15%),

---

**Figure 9** (a) Coronal computed tomographic scan showing a large mucinous cystadenoma in the pancreatic tail. (b) Magnetic resonance image of the same patient’s mucinous cystadenoma demonstrating a thick-walled single cyst with septations (arrow).

**Figure 10** Histologic image of mucinous cystic neoplasm “ovarian stroma” architecture detailing a hypercellular stroma layer (solid arrows) lying beneath columnar mucinous epithelium (dashed arrows).
and other obstructive symptoms, such as nausea, vomiting, and early satiety. In contrast to other cyst types, as many as 15 to 30% of IPMN patients may experience acute pancreatitis. In most large IPMN series, 15 to 20% of patients are discovered incidentally.

Both CT and MRI are useful imaging modalities in IPMN. The advantages of CT include its widespread availability, ease of tolerance for patients, lower cost, and reasonably standardized acquisition protocols. On the other hand, CT exposes patients to ionizing radiation; even the reduced radiation dose of contemporary CT scanning protocols must be considered in IPMN patients, who will most often require lifelong surveillance. In contrast to CT, MRI is more expensive and requires longer scanning times in a confined tube, which may not be tolerated by some patients. However, no ionizing radiation exposure is required with MRI. Perhaps the most significant advantage of MRI lies in the improved visualization of internal cyst architecture: septae, mural nodularity, and pancreatic duct–cyst communication. Secretin administration stimulates pancreatic exocrine secretion, which distends the pancreatic ducts. Imaging features that raise concern for malignancy include cyst wall thickening, the presence of cyst wall nodules [as illustrated in Figure 2], and solid components. Invasion into surrounding structures is an ominous sign. Pancreatic parenchymal atrophy is commonly seen in patients with MD-IPMN, sometimes making this lesion difficult to distinguish from chronic pancreatitis.

Malignant IPMNs manifest differential histopathology, which has been defined by immunohistochemical staining (particularly CDX2 and MUC2) and correlates with outcomes. Colloid carcinomas have intestinal-type differentiation and a better relative prognosis than tubular carcinomas. Similarly, different cell lineage has been identified in the papillary components of IPMN. Gastric, intestinal, pancreaticobiliary, and oncocytic types have all been defined.
Most BD-IPMNs have gastric-type histology, in which only a small percentage will develop malignant degeneration. Management strategies differ based on the presence of main duct versus side branch types of IPMN; a recent expert consensus conference held in Fukuoka, Japan, has detailed guidelines for the clinical approach to IPMN patients.

**Main Duct IPMN**

For the sake of management decisions, MD-IPMN and mixed-type IPMN are considered together. The incidence of malignant transformation seen in MD-IPMN is high; nearly half of resected MD-IPMNs will demonstrate invasive carcinoma and an additional 20% will have high-grade dysplasia or carcinoma in situ. The majority (66%) of MD-IPMNs are found in the pancreatic head, whereas up to 10% of these lesions affect the entire pancreatic duct. Cross-sectional imaging typically identifies MPD dilation greater than 6 mm.[24,25] The majority (66%) of MPD is greater than 2 cm and MPD size change with distal pancreatic atrophy, and peripancreatic lymphadenopathy to be more important than size alone. Younger patients with cysts greater than 2 cm may be candidates for operation due to the long length of potential follow-up necessary.[21] Figure 8 illustrates a decision-making algorithm for IPMN patients based on the most current Fukuoka guidelines.[26]

Patients with multifocal BD-IPMN should have decision making regarding operation or surveillance based on individual cysts rather than the collection of cysts. That is to say, it may be appropriate to resect one cyst with higher-risk features while leaving other cysts in situ with plans for longer-term surveillance.[25,32,33]

**Therapeutic Considerations in IPMN**

**Intraoperative Margin Analysis**

A major surgical challenge in IPMN patients lies in determining the extent of resection. This challenge is particularly apparent in patients with MD-IPMN. The high incidence of malignant degeneration, differential risk based on morphology (i.e., main duct versus branch duct lesions), the presence of “skip” lesions or a field defect, and the known difficulty in accurately identifying dysplasia in the setting of inflammation are all important factors for the surgeon to balance during the intraoperative decision-making process. Frozen-section analysis of IPMN is extremely difficult even for the most experienced pancreatic pathologist.[24] MPD epithelium may be eroded, leading to a missed diagnosis of dysplasia. Increased cellular atypia present in severe inflammation may mimic dysplasia. Chronic pancreatic duct obstruction or chronic pancreatitis may also mimic malignant change on frozen-section analysis. The most concerning limitation of frozen-section analysis is the known presence of “skip” or discontinuous lesions, which have been documented in up to 20% of surgical series.[34,35]

Intraoperative decision making must take into account the limitations of frozen-section analysis and understanding of underlying pathology (i.e., single cyst, multifocal disease) but also, importantly, general patient considerations such as age and comorbid medical status. In general, if clear high-grade dysplasia or invasive carcinoma is present at the margin frozen-section analysis, further resection should be performed.[35] On the other hand, low-grade or moderate dysplasia may not require further treatment. Thus, preoperative patient counseling should include discussion with the patient about the potential need for TP. Prudent pancreatic surgeons also consult their experienced pancreatic surgical pathologists preoperatively to “warn” them of an upcoming challenging IPMN case.

**Indications for Total Pancreatectomy**

Consideration of TP arises in patients with MD-IPMN and in those with multiple, multifocal BD-IPMNs. MD-IPMN

[Scientific American Surgery]

12/13
clearly has a significant risk of malignant change, although the “main” tumor focus may be quite difficult to identify even with the most sophisticated imaging techniques (both preoperative and intraoperative US). As noted above, intraoperative frozen-section analysis of the cut pancreatic duct margin is not completely accurate even in the most experienced hands. Perhaps most concerning in the context of the IPMN patient’s global management strategy is the real concern for cyst recurrence and subsequent cancer development in the postsurgical pancreatic remnant.\textsuperscript{35,36}

The intuitively attractive concept of removing all “at-risk” pancreatic parenchyma must be carefully balanced with the physiologic consequences imposed on TP patients.

The clinician must consider whether patients have adequate psychological, social, and financial support to survive with reasonable quality of life in an apancreatic state. Pancreatic exocrine insufficiency is relatively straightforward to treat, although exocrine enzymatic replacement is expensive. Pancreatic endocrine insufficiency, on the other hand, remains a significant challenge for patients with TP. Even with the better balance of contemporary insulin preparations, TP patients may experience relatively brittle diabetes mellitus. Often the hypoglycemic episodes are more concerning and challenging to the patient than either short-term (diabetic ketoacidosis) or longer-term complications of hyperglycemia. Some contemporary literature suggests that TP patients have quality of life similar to that of those undergoing segmental pancreatectomy.\textsuperscript{57} In clinical practice, the challenges of brittle diabetes should not be underestimated.

One potential avenue to avoid brittle diabetes in patients undergoing planned TP involves autologous islet cell transplantation. Experience has grown nationally with total pancreatectomy–islet autotransplantation (TP-IAT) for chronic pancreatitis patients.\textsuperscript{38} Although most TP-IAT patients immediately or eventually require some insulin replacement, their glucose control seems to be much more easily managed than that of patients with TP alone. The concept of TP-IAT for IPMN patients is provocative; however, the specter of reimplanting potentially malignant cells looms large in IPMN patients, and, to date, TP-IAP has not been applied in IPMN.

**EXTRAPANCREATIC MALIGNANCY AND IPMN**

Numerous investigators have documented a significant incidence of extrapancreatic malignancy in IPMN patients.\textsuperscript{39,40} Overall, between 10 and 50% of IPMN patients will be diagnosed with a malignant neoplasm outside the pancreas. The majority of these neoplasms involve the gastrointestinal tract; colon polyps and adenocarcinoma are most common in Western countries, whereas gastric adenocarcinoma is most common in Asia. Most extrapancreatic neoplasms are diagnosed before or at the time of IPMN diagnosis. This observation informs the IPMN patient’s evaluation: in the West, colonoscopy is indicated during evaluation of newly diagnosed IPMN, whereas Asian IPMN patients should also have screening upper endoscopy. Screening for other common malignant tumors (i.e., breast, uterine cervix, prostate, etc.) should be carried out as recommended for the general public.

**INTERVAL, TYPE, AND DURATION OF SURVEILLANCE**

The interval, type, and duration of surveillance are points of ongoing controversy in IPMN patients. The controversy revolves around the interval and type of surveillance, either in patients with primary cysts managed nonoperatively or surveillance of the pancreatic remnant after resection. The economic implications of long-term (in many cases, lifetime) surveillance are significant and are felt at both the societal and the individual patient level. Not to be overlooked is the anxiety experienced by a patient who has a “tumor” in his or her pancreas.

Patients managed nonoperatively who do not have “high-risk stigmata” of jaundice, an enhancing solid component, or an MPD greater than 10 mm should have initial short-term (3 to 6 months) CT or MRI to establish cyst stability. After this point, these patients should undergo an annual history/physical examination, a blood tumor marker evaluation, and cross-sectional imaging by CT or MRI/MRCP. Patients whose cysts develop high-risk stigmata and those who have a family history of hereditary pancreatic cancer (i.e., two or more affected first-degree relatives) should have shorter interval surveillance of 3 to 9 months. Patients who develop “worrisome features” (i.e., thickened cyst walls, a cyst greater than 3 cm or rapid cyst growth, nonenhancing mural nodules, MPD size greater than 5 mm, abrupt MPD size change with distal pancreatic atrophy, or peripancreatic lymphadenopathy) should be offered surgical resection if physically fit.

Patients with a strong familial pancreatic cancer history represent a population with a significantly elevated risk of developing pancreatic cancer. These patients also develop pancreatic cysts at a higher rate than the general public.\textsuperscript{41} This group of patients should undergo short-interval surveillance with CT or MRI/MRCP and EUS every 3 months. If no change is seen in the cyst over a 2-year period, the surveillance interval may be lengthened to every 6 months.

Screening after resection should be based on the pathologic analysis of the resected specimen and the presence of other known cysts in the pancreatic remnant. Patients with noninvasive MCN require no further screening. Patients with resected noninvasive IPMN and no residual lesions should have screening of the pancreatic remnant; however, imaging at 2- to 3-year intervals seems adequate. Patients with low- or moderate-grade dysplasia in the resected cyst should have interval follow-up physical examination, tumor marker evaluation, and imaging on a 6-month schedule. Patients with invasive IPMN should have follow-up on the same schedule as those with resected pancreatic ductal adenocarcinoma.

**ROLE OF ABLATION IN IPMN AND OTHER Pancreatic CYSTS**

The fact that the majority of patients with pancreatic cysts do not harbor malignant potential has led some investigators to propose more minimally invasive treatment, such as cyst ablation.\textsuperscript{41} Clinical experience with cyst ablation is limited, and all patients have been extremely carefully selected (i.e., single cyst, size < 4 cm, etc.). The cysts are visualized by EUS, mucin is aspirated (as completely as possible), and then ethanol ± a chemotherapeutic agent (paclitaxel) is
instilled into the cyst. The goal of this procedure is to chemically ablate (sclerose) all of the cyst epithelial lining. Short-term complications of this procedure occur infrequently but include potentially severe bleeding and pancreatitis. In the largest series of these patients reported to date, 169 patients have had a relatively short median follow-up of 29 months; 52% of patients were seen to have a complete cyst response with 4% recurrence.42 This modality is intuitively attractive for patients with comorbid conditions that make operation prohibitively risky, such as patients with portal vein thrombosis and cavernous transformation [see Figure 12] or those with hepatic cirrhosis. Currently, however, cyst ablation should be considered experimental. Critics of cyst ablation correctly point out three facts. First, the diagnosis of many pancreatic cysts is relatively inaccurate without completely resecting the cyst. Second, the technique of intraluminal sclerosant does not effectively destroy all of the at-risk epithelium. Finally, cyst manipulation hampers the ability to interpret subsequent radiologic follow-up studies. Further research under controlled conditions with adequate long-term follow-up will be necessary before cyst ablation becomes part of routine clinical practice.

Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasms (SPNs) are rare, accounting for less than 5% of resected pancreatic cysts in most large series. These tumors almost universally occur in young women (mean age 22 years) and are typically quite large (10+ cm) at the time of diagnosis.43,44 A variety of names have been applied to this rare tumor: solid and cystic tumor, papillary cystic tumor, solid and papillary tumor, Frantz tumor, and Hamoudi tumor (the latter two eponyms recognize the pathologists who first described the tumor). Radiologically, these tumors are predominantly solid, with characteristic cystic areas related to tumor necrosis or hemorrhage [see Figure 13]. The fact that these lesions are predominantly solid distinguishes them from postinflammatory collections (i.e., walled-off pancreatic necrosis). The cyst wall may contain calcium.

Not surprisingly given the typically large size at diagnosis, most patients present with symptoms related to the cyst’s mass effect [see Figure 14]. Biopsy of SPN is not usually necessary as most patients will come to resection; however, biopsy (either fine-needle aspiration or core-needle biopsy) reveals microadenoid cells with pseudopapillae branching around a central vascular core.

---

**Figure 12** Coronal computed tomographic scan of a patient with prohibitively complex anatomy. This man suffered an episode of necrotizing pancreatitis that resulted in portal vein thrombosis and cavernous venous transformation in the porta hepatis (solid arrows). He has a high-risk main duct intraductal papillary mucinous neoplasm in the pancreatic head/uncinate process (dashed arrow) that is being treated by chemotherapy and ethanol ablation. Note that this treatment strategy is not the standard of care.

**Figure 13** (a) T₁-weighted magnetic resonance image (MRI) of a solid pseudopapillary neoplasm. This large size is typical. (b) T₂-weighted MRI of the same tumor.
Although SPNs are typically thought of as benign, recent relatively large single-institution series suggest that as many as 20 to 25% of these tumors manifest malignant potential, including lymphatic and distant (usually hepatic) spread. Treatment of SPN is by resection. Recently, some pancreatic surgeons have embraced enucleation of specific lesions as a measure of pancreatic parenchymal preservation (see below). It is noteworthy, however, that SPNs typically have a pseudocapsule; thus, even the most enthusiastic enucleators do not recommend enucleating SPNs for fear of leaving behind potentially malignant cells.

Cystic Neuroendocrine Tumors

Pancreatic cystic neuroendocrine tumors (CNETs) are rare, accounting for only 1.2% of all pancreatic resections and 8% of all resected cystic pancreatic lesions in two large series. These cysts occur with equal frequency in men and women, are generally diagnosed in the fifth to sixth decade of life, and are almost uniformly discovered incidentally. Patients with multiple endocrine neoplasia syndrome type I may have an increased risk of developing CNET.

The diagnosis of pancreatic CNET may be suspected on CT or MRI cross-sectional imaging if the cyst wall demonstrates early (arterial phase) hyperenhancement, although not all CNETs have this feature and may be indistinguishable from BD-IPMNs. EUS-directed fine-needle aspiration for fluid analysis may help secure the diagnosis; most CNETs will have cells with positive immunostaining for the neuroendocrine markers synaptophysin and chromogranin A.

The vast majority of CNETs are nonfunctional, although patients with an appropriate clinical picture should have biochemical evaluation; a few cystic insulinomas have been reported. The majority of CNETs are benign, although all of the relatively large CNET reports document approximately 15% malignant potential (either lymph node or distant metastases). An area of current controversy in pancreatic surgery revolves around appropriate management of patients with nonfunctional solid small (< 2 cm) pancreatic neuroendocrine tumor. Some authorities have suggested a strategy of observation with serial imaging for these patients; this argument has been proposed by some experts to extend to patients with CNET. Fine-needle or core-needle biopsy of the cyst wall may inform this discussion; high-grade CNET (i.e., more than 5 mitoses per high-power field), regardless of size, may be more likely to metastasize. If patients elect observation, serial cross-sectional imaging is a mandatory part of the follow-up.

Acinar Cell Cystadenoma/Cystadenocarcinoma

Acinar cell cystadenomas (ACAs) are rare cysts that may be unilocular or multilocular. These cysts arise more commonly in females (2:1) and are almost universally benign, although the entity of acinar cell cystadenocarcinoma has been reported. Radiologically, pancreatic ACAs resemble SCA. Biochemically, many ACAs have increased CEA. Histologically, these cysts resemble acinar cells both morphologically and immunohistochemically. Patients with ACA may come to resection because of symptoms (pain, mass effect) or size increase during serial observation.

Simple Cyst

Simple pancreatic cysts are uncommon cysts that are lined by plain cuboidal epithelium. These cysts are usually fairly small and are universally benign. Simple pancreatic cysts rarely cause symptoms, although some patients with large simple cysts may come to resection for the typical spectrum of indications.

Mimickers of Cystic Pancreatic Tumors

A number of different benign cystic lesions may mimic pancreatic serous or mucinous cysts. Most of these cysts are diagnosed at the time of pathologic analysis.
Lymphoepithelial cysts may occur in any portion of the pancreas and are usually (but not always) peripancreatic as opposed to intrapancreatic. These cysts are more common in men. Pathologically, lymphoepithelial cysts are lined by squamous cells, which are surrounded by a rim of lymphoid tissue. The diagnosis is fairly straightforward on frozen-section analysis; thus, these cysts may be amenable to enucleation.

Dermoid cysts resemble lymphoepithelial cysts grossly and radiologically; however, they do not have the surrounding layer of lymphoid tissue on microscopic analysis. These cysts may be filled with sebaceous glands or other skin elements.

Lymphangiomas are also similar to lymphoepithelial cysts, having endothelial lining surrounded by lymphoid tissue. These cysts are found predominantly in young women.

Hemangiomas and cystic paraganglioniomas adjacent to the pancreas are extremely unusual.

Various intestinal duplication cysts may be located adjacent to the pancreas or even within the pancreatic parenchyma. These cysts are lined by respiratory, intestinal, squamous, or transitional epithelium.

Accessory spleens are common (incidence 10 to 15%); these lesions may masquerade as a pancreatic cyst and on very rare occasions may even be located within pancreatic parenchyma. Accessory spleens are usually recognized as solid lesions on cross-sectional imaging.

Approach to the Patient with Incidental Pancreatic Cyst

Patients with incidentally discovered pancreatic cysts are common in contemporary practice. A careful history and physical examination are the initial important step in the evaluation of these patients. Symptoms of pain should be characterized carefully; initiation (i.e., suddenly versus gradual onset), duration, severity (with changes, i.e., escalation with time), and location are all important. Cysts in the pancreatic head may cause right upper quadrant, back, or shoulder pain, whereas those in the tail may localize pain predominantly to the left side and left shoulder. Symptoms of mass effect may be subtle and include early satiety and reflux. All patients should be questioned about a history of pancreatitis; the diagnosis of pseudocyst is supported by a historical episode of acute pancreatitis or in a patient with known chronic pancreatitis. On the other hand, many pancreatic cysts (especially MCN and IPMN) can cause acute pancreatitis; although the natural history of this situation is not entirely clear, many pancreatic surgeons consider an episode of acute pancreatitis to be an operative indication. Also important historically is any family history of pancreatic malignancy. The patient’s age and general medical condition are major factors in treatment planning. For example, a prudent approach to an asymptomatic 85-year-old patient with major cardiopulmonary comorbidities and a small cyst (< 3 cm) may be no further follow-up specific to the cyst as the patient’s overall life span is unlikely to be affected by the cyst. On the other end of the spectrum is a young, healthy person with an intermediate-sized cyst; even with a secure diagnosis of benign cyst, consideration must be given to extended follow-up, imaging, and even resection.

Specific physical examination findings to be sought include the presence of supraclavicular (Virchow) or umbilical (Sister Mary Joseph) lymphadenopathy or the rare finding of migratory thrombophlebitis (Trousseau syndrome) seen with pancreatic malignancy. Subtle findings of mass effect include tympany or succession splash over the partially obstructed stomach or scleral or buccal jaundice.

The surgeon should review all imaging studies for type and quality and question the role for supplemental/additional images. For example, would a dedicated pancreatic MRI/MRCP with secretin stimulation provide more information about cyst communication with the pancreatic duct or mural nodularity in a patient with suspected IPMN? Does the cyst location correspond with symptoms? Is the cyst associated with peripancreatic inflammation, upstream parenchymal atrophy, or pancreatic duct dilation? Is the cyst amenable to the laparoscopic approach or a parenchymal-sparing operation (enucleation)?

Figure 16  (a) Computed tomographic scan and (b) T1-weighted magnetic resonance image of a patient with intrapancreatic lymphoepithelial cyst in the pancreatic tail.
Finally, laboratory chemistry studies should include a complete blood count, a comprehensive metabolic panel (to evaluate jaundice and nutritional status), and the tumor marker CA 19-9.

Ideally, a pancreas cyst patient will be managed cooperatively in conjunction with experienced pancreatic surgeons, gastroenterologists, radiologists, and pathologists. One physician should assume responsibility for coordinating follow-up management. Figure 5 shows a general algorithm for management of pancreatic cysts [see Figure 5].

**Special Operative Considerations**

As greater experience with pancreatic surgery has accrued over the past several decades, the postoperative consequences of pancreatic surgery (i.e., exocrine and endocrine insufficiency) have become clearer. Efforts toward pancreatic parenchymal preservation include tailoring pancreatectomy to include resecting the minimal amount of pancreatic parenchyma possible. These operations include central or “middle segment” pancreatectomy and enucleation [see Figure 17].

Pancreatic cysts, particularly those that are most likely benign, represent an excellent pathology to which to apply these operations.

A few caveats deserve consideration. First, no operation should spare parenchyma at the cost of an oncologically unsound procedure. Frozen-section analysis should be performed on all lesions resected with central pancreatectomy or enucleation; if malignancy is suspected or diagnosed at intraoperative pathology analysis, these operations should be converted to a traditional procedure (i.e., pancreatoduodenectomy or left-sided pancreatectomy) that permits adequate margin and nodal harvest. Obviously, this plan demands thorough preoperative discussion with both the patient and the pathologist. Second, most pancreatic surgeons accept the fact that central pancreatectomy and enucleation are accompanied by a higher incidence of pancreatic fistula than traditional pancreatectomy (in general, pancreatoduodenectomy 15%, distal/left pancreatectomy 25%, and enucleation and central pancreatectomy 33%).

Preoperative patient counseling should explain this fact and discuss fistula management strategy. Most pancreatic “enucleators” are willing to accept the short-term consequence of a relatively higher fistula rate (most of which do not significantly impact the patient’s perioperative course) for the tradeoff of longer-term preservation of exocrine and endocrine function. Finally, the importance of intraoperative US cannot be overstated. The relationship of cysts to the main pancreatic duct should be closely interrogated with intraoperative US; lesions that are close to or involve the MPD are not amenable to enucleation. MPD disruption creates high-volume pancreatic fistulas that rarely (if ever) heal with nonoperative management.

---

**Figure 17** Central pancreatectomy (a) resection and (b) reconstruction.
Conclusion

Pancreatic cystic tumors are common and are becoming more frequently identified with today’s widespread application of cross-sectional imaging. Knowledge of specific pancreatic cyst biology (especially IPMN) is evolving, making this field dynamic. Understanding the typical pancreatic cyst pathobiology and diagnosis is crucial to inform the individual patient management strategy.

Financial Disclosures: Nicholas J. Zyromski, MD, has no relevant financial relationships to disclose.

References


31. Weinberg BM, Spiegel BM, Tomlinson JS, et al. Asymptomatic pancreatic cystic neoplasms: maximizing survival and

Acknowledgments

Figure 2 Courtesy of Gregory A. Coté, MD
Figure 3 Courtesy of Stuart Sherman, MD
Figures 7 and 9 Courtesy of Temel Terkes, MD
Figures 11 and 16 Courtesy of C. Max Schmidt, MD, PhD
Figure 17 Revised and updated by Christine Kenney

Scientific American Surgery