Pancreatic Cystic Neoplasms: Management and Unanswered Questions

James J. Farrell1
Carlos Fernández-del Castillo2

1Yale Pancreas Center and Interventional Endoscopy, Yale School of Medicine, New Haven, Connecticut; and 2Pancreas and Biliary Surgery Program, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Approximately 10% of persons 70 years old or older are now diagnosed with pancreatic cysts, but it is not clear which ones require additional analysis, interventions, or follow-up. Primary care doctors rely on gastroenterologists for direction because no one wants to miss a diagnosis of pancreatic cancer, but meanwhile there is pressure to limit use of diagnostic tests and limit costs. We review the different cystic neoplasms of the pancreas and diagnostic strategies based on clinical features and imaging data. We discuss surgical and nonsurgical management of the most common cystic neoplasms, based on the recently revised Sendai guidelines. Intraductal papillary mucinous neoplasm (particularly the branch duct variant) is the lesion most frequently identified incidentally. We report what is known about its pathology, its risk of developing into pancreatic ductal adenocarcinoma, the pros and cons of current guidelines for management, and the potential role of endoscopic ultrasound in determining cancer risk. We also review surgical treatment and strategies for surveillance of pancreatic cysts.

Keywords: IPMN; Cyst Fluid; Surveillance, EUS.

Few topics in medicine are as controversial as the evaluation and management of patients with cystic neoplasms of the pancreas. The topic itself is relatively new—it was only in the late 1970s that a distinction was made between serous and mucinous pancreatic cystic neoplasms, and it has been barely 20 years since intraductal papillary mucinous neoplasms (IPMNs) became part of the gastroenterologist’s vocabulary. Before that, cystic tumors of the pancreas were considered extremely rare (many textbooks perpetuated the notion that most cystic lesions of the pancreas were pseudocysts and that <10% were neoplasms) and, in fact, were often the subject of case reports.

There has recently been a large increase in the number of patients with IPMNs, partially because of increased awareness of their existence but mostly because of increased use of cross-sectional imaging technologies, which led to the incidental discovery of many pancreatic cysts. Computed tomography (CT) and magnetic resonance imaging (MRI) studies have shown that the prevalence of pancreatic cysts (in individuals without history of symptoms of pancreatic disease) is about 2.5%1,2 and that this increases with age, to the point that 10% of persons 70 years or older have a pancreatic cyst.1 It is believed that most of these are small, branch duct IPMNs (BD-IPMNs), but there is no firm pathology data to support this. Regardless, because of the malignant potential of BD-IPMNs, their identification generates anxiety, subsequent imaging analyses, and sometimes invasive tests or surgery. We do not have a clear picture of how BD-IPMNs progress, so management recommendations are in a state of flux.

We review our knowledge of cystic neoplasms of the pancreas (CNPs), discussing the most common types, management strategies, and important areas for future study. We focus separately on BD-IPMNs, which are likely to be the majority of CNPs, and the role of endoscopic ultrasound (EUS) in the diagnosis and management of patients with incidentally discovered pancreatic cysts.

Abbreviations used in this paper: BD-IPMN, branch duct intraductal papillary mucinous neoplasm; CEA, carcinoembryonic antigen; CNP, cystic neoplasm of the pancreas; CPN, cystic pancreatic endocrine neoplasm; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; M-IPMN, main duct intraductal papillary mucinous neoplasm; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma; SCA, serous cystadenoma; SPN, solid pseudopapillary neoplasm.

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Presentation, Radiologic Features, Progression, and Management

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) are relatively uncommon tumors that comprise about 25% of all resected cystic neoplasms of the pancreas, based on data from a large surgical series. They occur most frequently in women (>95%), in the distal pancreas (>95%), and, unlike BD-IPMNs, are always a single lesion. They are characterized by a dense, ovarian-like stroma that surrounds the tumor, and an inner-epithelial layer with tall, mucin-producing cells. This layer can exhibit various degrees of atypia, from adenoma to invasive carcinoma, which frequently coexist. Median age of diagnosis was reported to be 45 and 48 years (range, 16 – 84 years) in 2 large series studies; most patients presented either incidentally or with vague symptoms, although about 10% have presented with acute pancreatitis and 12% with a palpable mass. The typical radiologic presentation is that of a thick-walled single cyst located in the neck, body, or tail of the pancreas, often with septations, and occasionally with nodules or calcifications. The risk of malignancy is 17.5% and in 1 series all malignant tumors had either nodules or were >4 cm. Because malignant MCNs are significantly larger (8.2 cm vs 4.5 cm) and are diagnosed in older patients (49.5 years vs 44 years), they are presumed to grow slowly over time. However, the relatively low frequency of cancer in patients with MCNs indicates that not all progress; identifying patients whose MCNs are at risk greatest risk of progressing could spare many patients from surgery.

Patients are presently treated by surgical resection and have excellent prognoses unless invasive carcinomas with either extracapsular or diffuse intracapsular infiltration are detected. Patients with small presumed MCNs (unilocular, in pancreatic body or tail locations, in female middle-age patients, with increased levels of cyst fluid, and expression of carcinoembryonic antigen [CEA]) that are devoid of nodules can potentially be managed with observation, but lifelong close surveillance is mandatory. The high incidence of MCNs in women, their location in the body or tail of the pancreas, and the presence of ovarian-like stroma indicate that hormones such as human chorionic gonadotropin are involved in pathogenesis, and might be managed therapeutically.

Serous Cystadenomas

Serous cystadenomas (SCAs) account for about 16% of resected cystic tumors of the pancreas. SCAs are benign, slow-growing tumors that also predominantly affect women (approximately 75%). Mean age of patients who underwent surgery for SCAs was 62 years in 2 large US series and 52 and 56 years in 2 European series. The typical SCA is formed by many tiny cysts lined by a cuboidal epithelium that is glycogen rich and has a honeycomb appearance, but a variant that is oligo- or macrocystic has been described and comprises about 10% of cases. Very few cases of malignant SCA (on the basis of presence of concomitant tumors in the liver or other extrapancreatic sites) have been described; they represent <1% of cases.

SCAs can form anywhere in the pancreas and can occasionally involve the entire organ. Most are diagnosed incidentally but, depending on their location and size, they can cause jaundice, pancreatitis, abdominal pain, or present as a palpable mass. Because SCAs are benign, treatment (surgical resection) should be determined based on the presence of symptoms. Patients managed without surgery should undergo imaging analysis at periodic intervals to ensure there is no rapid growth, which increases chances for symptoms and can lead to bigger or more complex procedures. Management by observation with or without serial imaging is contingent on an accurate diagnosis. The diagnosis can be made based on the lesion’s radiologic appearance (a spongy, multilobular mass, often with a central calcifications) or by EUS-guided biopsy and analysis of fluid. Fluid from SCAs characteristically has low levels of CEA (typically <5 ng/mL) but can often be difficult to acquire from the microcystic variant compared with the oligocystic variant. The oligocystic variant is harder to diagnose because its radiologic features overlap with those of MCNs and BD-IPMNs.

Patients with von Hippel-Lindau syndrome often have multiple oligocystic SCAs, and sporadic SCAs have been shown to have genetic alterations, including those that cause overexpression of vascular endothelial growth factor, which is also associated with this syndrome. It is a challenge to predict the rate of growth of SCAs in individual patients, and nonsurgical ablative therapies, which might include vascular endothelial growth factor inhibitors, require investigation.

Solid Pseudopapillary Neoplasms

Solid pseudopapillary neoplasms (SPNs) of the pancreas are uncommon and comprise <4% of resected pancreatic cystic tumors. They also predominantly affect women (>80%) at median ages of 30 or 38 years, based on 2 recent series. SPNs can be located throughout the pancreas; they are detected as incidental findings or because they cause symptoms, such as abdominal pain, pancreatitis, jaundice, or a palpable mass. In radiology examinations, SPNs appear as a well-demarcated heterogeneous mass with solid and cystic components. They can be diagnosed using EUS-guided fine-needle aspiration (FNA) or core biopsy analysis, based on the presence of cells that form microadenoid structures and branching papillary clusters with delicate fibrovascular cores. Patients are treated by surgical resection. Most SPNs are benign; <20% have vascular or perineural invasion, and even those that spread to the lymph nodes or liver can have an indolent course. SPNs are genetically distinct from ductal adenocarcinomas and are characterized by activation of β-catenin and its target genes.
Cystic Pancreatic Endocrine Neoplasms

Cystic pancreatic endocrine neoplasms (CPENs) represent about 8% of resected cystic tumors of the pancreas and 10%–17% of resected pancreatic neuroendocrine tumors. Most of them are discovered incidentally and are nonfunctional. CPENs are more likely to develop in patients with multiple endocrine neoplasias type I. They develop equally among men and women, who are generally diagnosed when they are 60–70 years old. In radiology examinations, they appear as cystic lesions, frequently with a hypervascular rim and occasionally with septation or containing a solid component.

Fluid aspirated during EUS characteristically has low levels of CEA, and the yield of FNA is high compared with other CNPs (73% vs 20%). As for all endocrine pancreatic tumors, malignancy is difficult to predict based on biopsy alone (either cytology or core biopsy), or even by examination of the tumor during surgery. Currently, surgical resection is recommended for all patients; >85% survive long term.

Solid and cystic pancreatic endocrine tumors are discovered incidentally with increasing frequency. Although the conventional wisdom has been to resect all of these lesions, given their uncertain behavior, this approach has been challenged. However, outcomes of 77 patients with small, nonfunctioning PENs who were only observed did not differ from outcomes of patients who underwent surgery. It is not clear if this approach also applies to patients with CPEN. Ablative therapies, guided by EUS or percutaneous, could also be studied.

IPMNs

For many years, the term mucinous ductal ectasia was used to describe gross dilation of the pancreatic duct resulting from overproduction of mucus from a proliferative epithelium with papillary growth. It is not uncommon for these tumors to erode into the duodenum or bile duct, and patients often have pancreatitis-like symptoms for years. Although these tumors can become malignant, they are often confined to the duct or are minimally invasive. These tumors are now recognized as an advanced form of main duct IPMN (M-IPMN). Neoplastic proliferation can occur in either just the side branches of the pancreatic ductal system (BD-IPMN) or a combination of side branches and the main duct (mixed or combined IPMN). For a long time BD-IPMNs were confused with mucinous cystic neoplasms. They have different epidemiologic features and cancer risk than main duct or combined IPMN, based primarily on differing histologic subtypes, which can only be determined by surgical pathology.

The epithelial lining of most M-IPMNs has an intestinal phenotype and expresses typical intestinal lineage markers, such as CDX2 and MUC2. M-IPMNs have a wide degree of heterogeneity in dysplastic areas, similar to villous adenomas of the colon. The risk of harboring malignancy is high, with invasive carcinoma found in 45% of cases and high-grade dysplasia (ie, carcinoma in situ) in an additional 20%. The invasive carcinomas that arise from intestinal-type IPMN are often colloid, which have a more indolent behavior.

Most BD-IPMNs have a gastric-type epithelium: they are MUC5AC positive and MUC1 negative, with MUC2 detected in only scattered goblet cells. However, there are other histologic subtypes of BD-IPMNs, such as oncocytic, intestinal, and pancreaticobiliary. Gastric-type BD-IPMNs are typically (of) low grade; in a small percentage, a tubular-type adenocarcinoma develops, which has the same bad prognosis as conventional pancreatic ductal adenocarcinoma (PDAC). It has been proposed that pancreatic ductal glands give rise to pancreatic intraepithelial neoplasms (the precursors of PDAC) and gastric-type BD-IPMN and that they have similar biology and outcomes. This concept is supported by the increased prevalence of pancreatic cysts (presumed to be BD-IPMNs) in families at high risk for pancreatic cancer. BD-IPMN is by far the most common type of cystic neoplasm of the pancreas.

M-IPMN and combined-type IPMN occur more frequently in men worldwide, but the male-to-female ratio is highest in Asia (3:1). In one large series, the median age at diagnosis was 66 years (range, 31–87 years). The most common presenting symptom is abdominal pain (55%), followed by weight loss (45%), jaundice (17%), and acute pancreatitis (15%); in about 17% of cases the diagnosis is made incidentally. In two-thirds of cases, the tumor is located in the proximal pancreas (the head), and in 8% it affects the entire gland. Radiologic analyses have shown how the pancreatic duct is dilated by >6 mm, often extending into secondary branches. Solid components can be observed within the lumen or duct wall, as well as calcifications, and the pancreas can either be enlarged or appear atrophic. Bulging papilla-extruding mucus, which is considered pathognomonic of M-IPMN, can be seen by endoscopy in about one-third of cases. Endoscopic retrograde cholangiopancreatography can often be used to visualize the filling defects from the tumors or mucus, allow for brushings and fluid obtention, and, if pancreaticoscopy is performed, can sometimes be used to visualize the papillary or villous growths. EUS demonstrates the dilated pancreatic duct, provides morphologic detail of the solid components within it, and allows for targeted collection of biopsies.

M-IPMNs and combined-type IPMNs are treated by surgical resection. It is important to localize the tumor well before surgery, which is often difficult because the entire ductal system is dilated. Liberal use of frozen-section margins and intraoperative pancreatoscopy and/or ultrasound is recommended to ensure no tumor with high-grade dysplasia or worse is left behind. Frequently, elderly patients with this tumor have had recurrent pancreatitis for 20 years or more. For these patients, the consequences of pancreatic resection need to be weighed carefully against the potential benefits.
Figure 1. Features of the most common cystic neoplasms of the pancreas.
Figure 1. (Cont’d.)
Areas of future research in IPMN include development of more models, which include newer information on pathology subtypes, to predict which tumors are likely to become invasive and patient survival times; registries to improve our understanding of the natural history of the disease, including factors associated with postoperative recurrence; and further evaluation of intraductal ablative procedures in patients who are deemed high-surgical risk. Figure 1 summarizes the key features of the most common cystic neoplasms of the pancreas and provides radiologic, endoscopic, macroscopic, and histologic examples. Table 1 provides a comprehensive list of all pancreatic cystic neoplasms and the lesions that most commonly mimic them.

**BD-IPMNs**

BD-IPMNs account for most of the increasingly recognized, asymptomatic, incidental pancreatic cysts. They can occasionally be symptomatic, in that some patients present with pancreatitis. Their imaging features range from an isolated subcentimeter pancreatic cyst to larger multicentimeter solitary collections of pancreatic cysts. With improved imaging and pathology assessments, BD-IPMNs are now also recognized as a diffuse multifocal disease, with 21%–41% of patients having multiple BD-IPMNs (>2), of varying sizes, scattered through their pancreas. This field defect has implications not only for diagnosis, but also for postoperative surveillance; unlike MCN, surveillance of the residual pancreas after resection of a noninvasive BD-IPMN is required because of the risks of progression of residual BD-IPMNs and the development of new BD-IPMNs and concomitant PDAC.

**Risk of Malignancy**

BD-IPMNs are all considered to be premalignant, but risk can vary based on size and associated features, such as nodules, multiplicity, and epithelial subtype. The mean frequency of malignancy (defined as high-grade dysplasia and invasive cancer) for surgically resected BD-IPMNs is 25.5% (range, 6.3%–46.5%), and the mean percent that become invasive is 17.7% (range, 1.4%–36.7%). However, in surveillance studies of presumed BD-IPMNs, the actuarial risk of developing cancer has been reported to be as high as 20% during a 10-year period (about 2% per year), there have been lower estimates (see Table 2). Reports that concomitant PDACs develop independently of BD-IPMNs within the pancreas have compounded the risk for cancer in certain individuals. In an analysis of 183 resected invasive IPMNs, 66% were classified as “PDAC derived from IPMN” and 17% as “PDAC concomitant with IPMN.” These findings support the concept of a pancreatic field defect that promotes development of IPMN and PDAC.

**Clinical Evaluation**

Diagnosis and cancer-risk stratification are the two main clinical challenges for BD-IPMN. Although the presence of multiple pancreatic cysts in the setting of a normal pancreatic duct strongly indicates multifocal BD-IPMN, the presence of a solitary pancreatic cyst of any size is a diagnostic challenge. Detection of a ductal communication by MRI could indicate BD-IPMN over MCN, but this is not always seen. In addition, patients with a solitary pseudocyst or BD-IPMN could each have a clinical history of pancreatitis. Although the addition of EUS and identification of ductal communication, internal significant nodules, and increased levels of CEA in cyst fluid could aid in the diagnosis, physicians are often left managing patients with presumed BD-IPMNs in the absence of definite diagnoses. This difficulty in preoperative diagnosis was highlighted in a recent study demonstrating that, even for patients who underwent surgery for presumed BD-IPMNs, many had main pancreatic duct involvement or alternate diagnoses based on pathology analysis.

**Guidelines for Management**

For patients with either a definite diagnosis or strong suspicion of BD-IPMN, the next major challenge is to determine their risk of cancer developing, which will determine whether they will undergo surgery or surveillance. The original Sendai guidelines published in 2006 recommend surgery for patients with definite or presumed BD-IPMNs, cysts >3 cm, symptomatic cysts <3 cm, a main pancreatic duct dilated >6 mm, or nodules. The remainder can be managed nonoperatively with routine surveillance. Retrospective evaluation of these guidelines using data from patients with surgically resected BD-IPMNs showed that these guidelines had a high negative predictive value (meaning no cancers were missed), but a low positive predictive value (approximately 20%); this means that that for every 5 surgical resections, only 1 patient had an advanced lesion. Therefore, the decision of whether or not a patient presumed to have an BD-IPMN should undergo surgery should consider additional factors, including the patient's age, overall medical condition, operative risk, and the location of the cyst. It has been proposed that for patients younger than 65 years old, a threshold of 2 cm be used to determine surgical resection because of the cumulative effect of cancer risk during the patients' lifetime. A BD-IPMN >3 cm is a weaker indicator of malignancy than the presence of mural nodules or positive results from cytology analysis, so a BD-IPMN >3 cm without these additional features can be observed without immediate resection—particularly in elderly patients. A Fukuoka guideline was recently published and provided more specific and updated recommendations for surgical resection and surveillance. These newer guideline's operating characteristics require prospective validation in a clinical setting.
Large surgical series have indicated that multifocal BD-IPMNs could have a lower risk for becoming malignant than solitary BD-IPMNs, and decisions about surgery and surveillance should be made for each individual cyst, rather than the collective of cysts.\textsuperscript{32,33,61,62} Partial pancreatectomy is the preferred treatment method for disease confined to just one area of the pancreas, or of the area deemed to be at highest risk for disease progression, with surveillance of the residual pancreas. Total pancreatectomy is rarely necessary.\textsuperscript{63}

**Surveillance Strategies**

With the accepted low, but persistent risk of malignancy for most BD-IPMNs, the role of surveillance in the nonoperative management of presumed BD-IPMNs has been refined. In a cumulative series of patients who underwent surveillance for presumed BD-IPMNs, the surgical intervention rate was <10% and the risk of finding an associated malignancy was <5%, indicating that the overall risks are low—even in a highly selected group of patients (Table 2).\textsuperscript{36–47} In addition to the level of anxiety this surveillance can cause patients, it also represents a huge economic cost without evidence for improved long-term outcomes or quality of life. MRI with magnetic resonance cholangiopancreatography is generally preferred over CT for surveillance because of the enhanced ability to see nodules and ductal communication, and because it does not involve radiation exposure.\textsuperscript{64}

The exact interval of surveillance is unclear. For surveillance, patients without high-risk stigmata (high-risk stigmata [Figure 2]: symptoms/signs related to IPMN, presence of mural nodules, dilation of the main pancreatic duct) and associated carcinoma have been refined. In a cumulative series of patients who underwent surveillance for presumed BD-IPMNs, the surgical intervention rate was <10% and the risk of finding an associated malignancy was <5%, indicating that the overall risks are low—even in a highly selected group of patients (Table 2).\textsuperscript{36–47} In addition to the level of anxiety this surveillance can cause patients, it also represents a huge economic cost without evidence for improved long-term outcomes or quality of life. MRI with magnetic resonance cholangiopancreatography is generally preferred over CT for surveillance because of the enhanced ability to see nodules and ductal communication, and because it does not involve radiation exposure.\textsuperscript{64}

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### Table 1. Classification of Cystic Neoplasms of the Pancreas

<table>
<thead>
<tr>
<th>Epithelial neoplasms</th>
<th>Nonepithelial</th>
<th>Lesions resembling pancreatic cystic neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma\textsuperscript{a}</td>
<td>Lymphangioma</td>
<td>Pseudocyst</td>
</tr>
<tr>
<td>MCNs and associated carcinomas\textsuperscript{a}</td>
<td>Epidermoid cyst in intrapancreatic spleen</td>
<td>Lymphepithelial cyst (epidermoid cyst)</td>
</tr>
<tr>
<td>IPMNs and associated carcinoma\textsuperscript{a}</td>
<td>Cystic pancreatic hamartoma</td>
<td>Mucinous non-neoplastic cyst</td>
</tr>
<tr>
<td>SPNs\textsuperscript{a}</td>
<td>Mesothelial cyst</td>
<td>Enteric duplication cysts</td>
</tr>
<tr>
<td>PDAC with cystic degeneration\textsuperscript{a}</td>
<td></td>
<td>Squamous cyst</td>
</tr>
<tr>
<td>CPENs\textsuperscript{a}</td>
<td></td>
<td>Endometrial cyst</td>
</tr>
<tr>
<td>Acinar cystadenoma and cystadenocarcinoma</td>
<td></td>
<td>Hydatid cyst</td>
</tr>
<tr>
<td>Dermoid cyst (cystic teratoma)</td>
<td></td>
<td>Retention cyst</td>
</tr>
<tr>
<td>Intraductal papillary variant of acinar cell carcinoma</td>
<td></td>
<td>Accessory splenic cyst</td>
</tr>
<tr>
<td>Intraductal tubulopapillary neoplasm</td>
<td></td>
<td>Cystic pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cystic GIST</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retention cyst</td>
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GIST, gastrointestinal stromal tumor.
\textsuperscript{a}Clinically common and important diseases.

### Table 2. Outcomes for Surveillance of Presumed BD-IPMNs

<table>
<thead>
<tr>
<th>Study, first author</th>
<th>Year</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>Imaging progression</th>
<th>Malignancy/surgery</th>
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<td>47</td>
<td>41</td>
<td>1</td>
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<td>Carbognin</td>
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<td>36</td>
<td>27</td>
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<tr>
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<td>2006</td>
<td>31</td>
<td>60</td>
<td>0</td>
<td>0/0 0</td>
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<tr>
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<td>89</td>
<td>32</td>
<td>5</td>
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<td>2007</td>
<td>45</td>
<td>27</td>
<td>10</td>
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<td>81</td>
<td>41</td>
<td>11</td>
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<td>2009</td>
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<td>41</td>
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<td>2/19 11</td>
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<td>59</td>
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<td>201</td>
<td>28</td>
<td>39</td>
<td>8/35 23</td>
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<tr>
<td>Uehara</td>
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<td>100</td>
<td>97</td>
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<td>1/1 100</td>
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<td>Khannoussi</td>
<td>2012</td>
<td>53</td>
<td>84</td>
<td>15</td>
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<tr>
<td>Maguchi</td>
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<td>44</td>
<td>62</td>
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<td>Cauley</td>
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<td>30</td>
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<tr>
<td>Bee</td>
<td>2012</td>
<td>152</td>
<td>13</td>
<td>18</td>
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<td>Total</td>
<td>2012</td>
<td>2207</td>
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NOTE. Modified with permission from Al-Haddad, et al.\textsuperscript{49}
duct by >10 mm, or positive results from cytology analysis of pancreatic juice) should be evaluated by pancreatic MRI with magnetic resonance cholangiopancreatography (or CT) every 3–6 months to establish disease stability, followed by annual surveillance.64 Concern about the development of PDAC in a pancreas with IPMN has prompted some physicians to continue surveillance at short intervals.64 However, for subcentimeter cysts, surveillance every 2–3 years seems reasonable.64 Patients with high-risk stigmata detected during surveillance should undergo surgery if they are fit enough (Figure 2). Shorter intervals of surveillance (3–9 months) should be considered for patients with progressing IPMNs and for patients who already have high-risk stigmata and, for reasons of operative risk or personal preference, have chosen heightened surveillance over resection.35 Shorter interval surveillance should also be performed for patients with IPMNs and a family history of hereditary PDAC (such as more than one first-degree relative with PDAC), although it is not clear whether these patients are susceptible to more aggressive IPMNs.65 Whether rapid growth of an IPMN increases risk of malignancy is also unclear, but closer surveillance, including use of EUS, is recommended for these patients.46 For patients undergoing surgical resection for noncancerous BD-IPMNs, the overall prognosis is excellent, but these patients are always at risk of developing significant metachronous cysts in the remaining pancreas, as well as concomitant PDAC, necessitating ongoing postoperative surveillance.17,66 There is controversy about when to stop surveillance in patients with presumed BD-IPMNs. It makes no sense to continue surveillance of patients who are not good candidates for surgery. Arbitrarily, 85 years old is used as the cutoff for surveillance, but it really should be determined by the patient’s overall medical condition. The concept of stopping surveillance of a small cyst that shows stability after 2 years, in any age group, has been also proposed by the American College of Radiology, but there are no good long-term data to support this approach.64 Recommendations to stop surveillance of BD-IPMNs are countered by anecdotal stories of patients with chronically stable presumed BD-IPMNs that grew and developed cancer after long periods of stability, and the persistent risk of development of concomitant PDAC in patients with a history of IPMN.50–53

**Role for EUS in Diagnosis and Treatment**

Before evaluating a CNP by EUS, EUS with FNA, and cyst fluid aspiration, the likely effects on diagnosis, management, and patient outcomes should be determined. This is best done in a multidisciplinary setting after discussion of

![Figure 2. The Fukuoka guidelines for managing patients presumed to have BD-IPMN and MCN.](image-url)
the patient’s presentation and operative risk, as well as expert review of high-quality CT or MRI data.67

CT and MRI alone can be used in the diagnosis and management of CNP when certain features are present. For example, a microcystic pancreatic lesion with a central stellate calcification detected by CT imaging is pathognomonic of a benign serous cystadenoma; a tortuous, dilated, main pancreatic duct with associated cysts indicates an M-IPMN; and multiple diffuse pancreatic cysts associated with a normal caliber main pancreatic duct are likely to be multifocal BD-IPMN.

**EUS Imaging**

Not all CNPs can be completely evaluated by CT or MRI—often the diagnosis and risk of malignancy are unclear. For example, a multiple macrocystic lesion in the body and tail of the pancreas could be a benign macrocystic serous cystadenoma or a premalignant mucinous lesion, such as an MCN or a BD-IPMN.68 In fact, a single pancreatic cyst of any size, detected by CT or MRI, is the most challenging clinical problem, especially in the absence of pancreatitis; it could be a BD-IPMN, a benign pseudocyst, or, more wrongly, a degeneration of a solid neoplasm, such as a PDAC or an endocrine neoplasm. Studies have shown the difficulties in using high-quality CT or MRI analyses to distinguish mucinous from nonmucinous pancreas lesions.1,69 Although EUS is an operator-dependent invasive imaging modality, its advantages over CT or MRI include superior, higher-resolution imaging of the pancreas (to detect ductal communication, additional cyst, nodules, and associated masses), and its ability to sample the cyst fluid contents for cytology and tumor markers.

EUS of the pancreas can often detect a communication between a pancreatic cyst and a normal main pancreatic duct, indicating a BD-IPMN, although this communication is not always found and can occur in patients with pseudocyst. When EUS was compared with high-quality MRI of the pancreas and magnetic resonance cholangiopancreatography in a prospective study, however, EUS and MRI were equivalent at detecting pancreatic cyst–main duct communications.70 Sometimes MRI or CT images raise concern about involvement of the main pancreatic duct in the CNP, which could indicate a mixed or main duct IPMN rather than a BD-IPMN. This important difference can be clarified using EUS rather than a diagnostic endoscopic retrograde cholangiopancreatography pancreateogram, which is not routinely recommended for evaluation of CNPs.

Detection of multiple pancreatic cysts by CT or MRI supports a diagnosis of a multifocal-type BD-IPMN. The superior imaging abilities of EUS allow it to detect smaller cysts throughout the pancreas, such as those associated with multifocal-type BD-IPMN. However, in prospective studies comparing high-quality CT, MRI, and linear and radial EUS for the identification of pancreatic cysts, MRI and EUS are equivalent and much better than CT in detecting smaller additional cysts.30,32,33,71,72

The presence of nodules on surgically resected BD-IPMNs is associated with increased risk of advanced pathology (high-grade dysplasia or invasive cancer). Only 3% of BD-IPMNs with low- or intermediate-grade dysplasia were found to have a nodule during pathology analysis, compared with 60% of BD-IPMNs with high-grade dysplasia or carcinoma.53 Interestingly, none of the patients with low-grade dysplasia had evidence of a nodule from pathology examination and, on occasion, the significant advanced pathology finding of either high-grade dysplasia or invasive cancer was remote from the nodule in the cyst. In addition, not all the nodules found were even precancerous. For example, the nodules seen in lymphoepithelial cysts are keratinizing squamous pearls, and mucin globules account for a large percentage of nodules seen during imaging of IPMN cysts.

Therefore, the importance of finding and characterizing CNP mural nodules during preoperative imaging is clear. Although the definitions of the various mural nodules detected by CT, MRI, and EUS have not been standardized, a meta-analysis associated detection of mural nodules (by CT or MRI of presumed BD-IPMNs) with a 9-fold increase in risk for advanced pathology (high-grade dysplasia or invasive pathology). However, detection of mural nodules by only EUS was associated with a 3-fold increase in risk for advanced pathology; the difference is likely related to the overdiagnosis of nonpathologic mucin globules by EUS.60,73–76

In EUS analysis, mucin globules are hypechoic, have smooth edges and hyperechoic rims, and move when patients are repositioned or during FNA. A recent study that used pathology results as the standard and trained endosonographers to distinguish mucin globules from real nodules found that EUS was more sensitive than CT in detecting significant cystic nodules.74 Although it has been proposed that detection of pathologic nodules in cysts during EUS indicates the need for surgical management, it is unclear if there is a nodule size threshold below which surgery could be avoided. Data support surveillance of patients with large presumed BD-IPMNs (>3 cm) who do not have nodules.82 It has also been suggested that presumed small MCNs (unilocular, in the pancreatic body or tail, in middle-aged women, with increased fluid levels of CEA) without nodules (based on EUS) can be monitored closely, without surgery.

**Analysis of Pancreatic Cyst Fluid**

Another strength of EUS for evaluation of CNP compared with CT or MRI is the ability to safely aspirate cyst fluid and use cytology analysis to assess tumor markers.77 Although this approach identifies tumors with close to 100% specificity, it has a low level of sensitivity (detects only 30%–50% of mucinous cysts and 20% of malignant mucinous cysts). The low-sensitivity results from factors such as the low yield of lesion cells from the aspirate, insufficient sample volume, and contamination of samples with gastrointestinal wall cells.78–80 Although a variety of strategies have been used to improve sensitivity, including targeted FNA biopsies, the use of brush cytology, different preparation techniques...
for samples, and inclusion of cytopathology expertise, the results remain poor. One additional strategy has been to lower the bar and include detection of high-grade atypical epithelial cells as criteria for diagnosis of malignant CNP, recognizing that epithelial cells with cellular atypia are quantitatively and qualitatively insufficient to support a diagnosis of cancer. When detection of high-grade atypical epithelial cells are included in the diagnostic criteria, the accuracy of cyst fluid analysis increases to 85%.80

The roles of existing and newer markers of cancer from pancreatic cyst fluid continue to be evaluated. The real benefit of measuring cyst fluid levels of CEA is to differentiate mucinous from nonmucinous pancreatic cysts. For example, a low level of CEA (<5 ng/mL) indicates the presence of a serous cystadenoma or pseudocyst (vs a mucinous CNP) with a positive predictive value of 94% and 70% accuracy. Similarly a high level of CEA (>800 ng/mL) indicates the presence of a mucinous CNP (vs a serous cystadenoma or a pseudocyst) with a positive predictive value of 94% and 79% accuracy.81 The exact cutoff value at which the pancreatic cyst fluid level of CEA level distinguishes mucinous from nonmucinous lesions is unclear. In the prospective pancreatic cyst cooperative study, a cutoff of 192 ng/mL distinguished mucinous from nonmucinous cysts with 80% accuracy—the best operating characteristic of any fluid marker or cytology tested in the study.79 More importantly, the pancreatic cyst fluid level of CEA does not correlate with the risk of malignancy. Even though one study reported extremely high levels of CEA (>6000 ng/mL) in cysts from patients with malignant mucinous lesions, the absolute level of CEA was not a better predictor of which patients would develop cancer.80 Pancreatic cyst fluid level of CEA can therefore be helpful in evaluating macrocystic lesions of the pancreas when trying to distinguish among benign macrocystic serous cystadenoma (low levels of CEA and associated satellite microcysts), precancerous mucinous cystic neoplasm (high levels of CEA, unicocular cyst in body tail of the pancreas with internal septations), or a precancerous BD-IPMN (high level of CEA, communication with the main pancreatic duct).68

DNA in pancreatic cyst fluid can also be analyzed using commercially available assays. However, a multi-institutional prospective study (the Pancreatic Cyst DNA Analysis [PANDA] study) and several retrospective, single-institution studies, were not able to establish their optimal clinical indication.82–86 Assays to detect mutations in KRAS or other genetic features associated with cancer, used alone or in combination with assays to measure CEA levels, do not accurately differentiate between mucinous and nonmucinous cysts, or between benign or malignant pancreatic cysts; they have poor operating characteristic values and detect cancer with low levels of sensitivity and specificity.82–86

In addition, it is not clear if studies that measure levels of CEA in pancreatic cyst fluid or analyze genetic features produce results that are applicable to clinical practice. In the Pancreatic Cyst Cooperative Study and the PANDA study, 35%–43% of the patients were ultimately diagnosed with a malignant cyst—much higher than expected in the regular patient population. The types of pancreatic cysts that gastroenterologists need the most help assessing were not well represented in these studies. For example, the number of patients with cysts <2 cm ranged from 27% to 40% of the entire study group, and of those with a final mucinous pathology, only 29%–40% were <2 cm in size. The operating characteristic values of pancreatic tumor markers therefore require re-evaluation in the population of patients that gastroenterologists and surgeons typically treat and have the greatest difficulty managing.79,82 Additional studies of newer markers in pancreatic cyst fluid, such as variants of GNAs or microRNAs, could improve diagnosis and cancer risk determination, and also be used to refine stratification strategies for patients in pancreatic cyst surveillance programs.87,88

**Therapeutic EUS**

Researchers have tested EUS-guided ablation of pancreatic cysts with either ethanol or ethanol followed by administration of paclitaxel to large unicocular cyst without obvious ductal communication or to high-risk pancreatic cysts in patients that refuse or are not able to undergo surgery.89,90 Although this approach can cause complications such as pancreatitis, abdominal pain, and splenic vein obliteration, it does resolve cysts, based on CT analysis.81 However, this approach is still considered experimental and should be performed under a research protocol because of concerns about incomplete destruction of premalignant tissue, uncertainty about its effects on progression of CNPs, persistent risk of concomitant PDAC, and lack of data on long-term outcomes.

**Which Patients With CNP Benefit From EUS?**

After experts from multiple disciplines discuss clinical features of patients with CNPs and review their CT or MRI data, can they determine which are most likely to benefit from additional EUS evaluation? Patients with single or multiple subcentimeter pancreatic cysts, but a normal pancreatic duct, are unlikely to benefit from additional EUS evaluation—they are likely to have BD-IPMN and a low chance of developing cancer or invasive cancer before their next screening examination.**92,93** For patients whose lesions have radiologic features of a microcystic serous cystadenoma, including a central stellate scar, EUS analysis rarely alters their diagnosis, management, or outcomes. On rare occasions, CT, MRI, and even EUS images of a microcystic serous cystadenoma can be mistaken for a solid pancreatic endocrine neoplasm.84,85 This can be a good indication for an EUS-guided core biopsy to confirm the diagnosis.85

EUS has select benefits for other patients with CNPs. As previously mentioned, if the clinical presentation and imaging results raise concerns about differentiating between a macrocystic serous cystadenoma and a mucinous neoplasm (MCN or BD-IPMN), then EUS and cyst fluid aspiration could be helpful. When multidisciplinary evaluation and expert review of high-quality CT and MRI data raise the possibility of a solid component or focal or
diffuse main duct involvement of a solitary cyst, then EUS can help clarify these finding and support the diagnosis. This can be especially important for patients with chronic pancreatitis or recurrent acute pancreatitis, in whom focal or diffuse main-duct abnormalities can be features of M-IPMN rather than chronic pancreatitis.

EUS could also be useful in the evaluation of patients with presumed BD-IPMNs >3 cm. Although current guidelines support surgical therapy based on size alone for patients who are elderly, poor candidates for surgery, or just reluctant to undergo surgery in the absence of a more definite diagnosis (of high-grade dysplasia or invasive cancer), the lack of nodules on EUS in cysts >3 cm can help identify patients with presumed BD-IPMNs who are suitable for close surveillance rather than surgery.

EUS has a definite role for patients with solitary or multifocal cysts, from 1 to 3 cm—especially those that do not have high-risk stigmata based on CT or MRI analysis. However, the most recent Fukuoka guidelines question the value of EUS for cysts <2 cm without these high-risk stigmata. Most of these are presumed to be single or multifocal BD-IPMNs, which are typically managed by surveillance. Before initiating a noninvasive surveillance strategy, which could include MRI or CT assessment every 1–2 years, a single EUS helps rule out associated masses (eg, CPEN), identify internal nodules, collect cyst fluid samples for cytology analysis and CEA measurement, and confirm the suspicion of a mucinous cyst. In a surveillance program, EUS imaging might be used to follow cysts that are increasing in size to rule out malignancy.9,46 Although data are limited, rapid increase in cyst size has been associated with increased risk of advanced pathology. It is important to remember that benign serous cystadenomas also tend to increase in size, so EUS might be able to differentiate these entities.9,46

Surgery

Surgical resection is the treatment of choice for symptomatic patients with cystic neoplasms of the pancreas and for those with incidentally discovered tumors that have a high likelihood of malignancy, such as mucinous cystic neoplasms, CPENs, SPNs, and main and combined duct IPMNs. The type of resection depends on the location of the lesion. In a recent series composed of 851 resected cystic tumors, 44% required distal pancreatectomy, 43% required pancreatoduodenectomy (Whipple procedure), and 7% required middle pancreatectomy (where the end of the pancreas toward the duodenum is closed, and the end coming from the tail is anastomosed to either the stomach or jejunum). The remaining tumors were treated by enucleation (usually reserved for small lesions with low risk of malignancy), other atypical pancreatic resections, or total pancreatectomies.3 This study found that operative mortality, when these operations are performed at specialty centers, can be kept at <1%, but that complications still occur in >40% of patients.3,96

In many centers, laparoscopic resections, particularly distal pancreatectomies, are being used increasingly for cystic neoplasms of the pancreas. In addition to the morbidity of the operation, long-term sequelae of the loss of pancreatic parenchyma (such as diabetes, exocrine insufficiency, and their effects on quality of life) need to be carefully considered. Research is needed to determine the risks and benefits of pancreatic resection for cystic neoplasms, along with cost analyses of the long-term surveillance strategies recommended by the most recent guidelines.

References


