My Treatment Approach: Pancreatic Cysts

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Abstract

Our treatment approach for either symptomatic or incidentally found pancreatic cysts continues to improve. The true incidence of pancreatic cysts is not known, and pancreatic cystic neoplasms, especially intraductal papillary mucinous neoplasms, are currently most commonly diagnosed and resected. This is a result of increasing awareness, widespread availability of imaging, and better understanding of the nature of pancreatic cysts as well. Recent studies on molecular analysis and devices such as microbiopsy forceps help us better define and select the treatment approach to alleviate symptoms and to prevent malignant tumors while avoiding unnecessary surgery.

Pancreatic cysts are found with increasing frequency, especially in asymptomatic and elderly patients, because of increasing awareness and widespread use of high-resolution cross-sectional imaging. The incidence of pancreatic cysts in the US population is estimated to be between 3% and 15%; however, the true incidences of these lesions are not known because most results are based on surgical series or image-based studies. In an autopsy series, pancreatic cysts were found in 24.3% of autopsy cases (73 of 300). Pancreatic cysts were incidentally detected in 3% of computed tomography (CT) scans and 20% of magnetic resonance imaging (MRI) scans. The prevalence increases with advancing age, up to 10% to 40% over 80 years. A nationwide Korean survey reported that intraductal papillary mucinous neoplasms (IPMNs) account for 41%, mucinous cystic neoplasms (MCNs) for 25.2%, solid pseudopapillary neoplasms (SPNs) for 18.3%, serous cystic neoplasms (SCNs) for 15.2%, and others for 0.3% of the pancreatic cysts. The current identification of smaller cysts reported to have a malignant potential creates anxiety and the need for further medical evaluation. Patients with pancreatic cysts have an observed incidence of pancreatic cancer 22.5 times higher (99.5% CI, 11.0-45.3) than that of the expected mortality from pancreatic cancer in the general Japanese population. In contrast, the 2015 American Gastroenterological Association (AGA) technical review on asymptomatic neoplastic pancreatic cysts reported an estimated incident risk of malignant tumor of incidental pancreatic cysts at 0.24% per year and with a prevalent malignant risk of 0.25% at the time of diagnosis. These data indicate that although pancreatic cysts can be asymptomatic at the initial presentation, they may develop into cancer, and malignant tumor risk is higher in patients with pancreatic cysts than in the healthy population without pancreatic cysts.

Pancreatic cysts can be broadly classified as either nonneoplastic or neoplastic cysts (current name is pancreatic cystic neoplasms [PCNs]) (Table 1). Histologically, nonneoplastic pancreatic cysts are better categorized as nonepithelial (pancreatic pseudocyst [PP] is the most common) and epithelial (retention cyst is the most common) cysts. In contrast, PCNs are mainly divided into mucinous and nonmucinous cystic lesions.

This review article discusses the clinically common and important types of pancreatic cysts, their diagnostic strategies, and treatment options. The distinction between PCNs and nonneoplastic cysts are also discussed in our management approach, because PCNs carry a current or future malignant tumor risk.

NONNEOPLASTIC CYSTS

Nonneoplastic cysts of the pancreas are benign lesions without malignant potential, but they are sometimes indistinguishable from PCNs. Although they are rare, the recognition of these cysts is important to avoid an unnecessary pancreatic resection. Nonepithelial cysts include PPs and infection-related cysts.
whereas epithelial cysts include retention cysts, squamoid cysts, lymphoepithelial cysts, enterogenous cysts, mucinous nonneoplastic cysts, endometrial cysts, and para-ampullary duodenal cysts. There is an uncertainty whether simple congenital cysts occur in the pancreas; however, these cysts are rare. Patients with cystic fibrosis may present with simple cysts within a diffuse atrophic fatty pancreatic parenchyma, and patients with autosomal dominant polycystic renal disease and medullary cystic disease may have cystic transformation of the pancreas.

Pancreatic Pseudocysts

The Atlanta classification of acute pancreatitis was revised in 2013, and the terminology to define inflammatory pancreatic fluid collections was updated and improved. According to the revised criteria, inflammatory pancreatic fluid collections were categorized as acute peripancreatic fluid collections, PPs, acute necrotic collections, and walled-off necrosis. Pancreatic pseudocysts are often the result of an acute pancreatitis, and 10% of patients with acute pancreatitis develop a PP. Chronic pancreatitis, penetrating trauma, and blunt trauma are other etiologies.

Pancreatic pseudocysts are mature fluid collections outside the pancreas, which develop 4 weeks after the onset of nonnecrotizing acute pancreatitis. Pancreatic pseudocysts have an enhancing capsule that does not contain an “epithelial lining” and the fluid inside the cyst is opaque, dark, and low viscosity without solid material. Pancreatic pseudocysts are usually unilocular solitary cysts ranging from 2 to 20 cm in size. They are generally sterile fluid collections but may become infected or hemorrhagic. The most common symptoms are abdominal pain, early satiety, and weight loss. A PP is suspected when abdominal pain continues or serum levels of amylase remain elevated after the clinical remission of pancreatitis.

Cross-sectional imaging reveals a well-circumscribed fluid collection, which is usually round or oval. The fluid collection is completely encapsulated with a well-defined thick wall that is typically extrapancreatic; the fluid does not contain solid components and has a homogeneous fluid density. Cross-sectional imaging may also reveal signs of pancreatic parenchymal inflammation due to pancreatitis. Endoscopic ultrasonography (EUS) reveals a hypoechoic fluid collection surrounded by a thick rim (Figure 1). When the cyst is aspirated with EUS-guided fine needle aspiration (EUS-FNA), the cyst fluid is high in amylase, low in carcinoembryonic antigen (CEA), and free of epithelial cells; however, histiocytes and inflammatory cells may be present.

Most PPs resolve spontaneously; however, endoscopic and percutaneous drainage are the choices of treatment in large symptomatic PPs. Currently, EUS-guided transgastric or transduodenal endoscopic drainage is the most preferred treatment, and surgical drainage is not preferred except in the case of endoscopic drainage failure. Although percutaneous drainage under ultrasonography/CT guidance has high short-term success, it has 29% risk of complications with marked discomfort to the patient. Endoscopic drainage is generally preferred.

Retention Cysts

Retention cysts form as a result of cystic dilation of the pancreatic duct; they are usually found incidentally and have little clinical significance. Retention cysts can be either congenital or secondary to ductal obstruction.

<table>
<thead>
<tr>
<th>TABLE 1. Common Types of Pancreatic Cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Nonneoplastic pancreatic cysts</strong></td>
</tr>
<tr>
<td>1. Nonepithelial</td>
</tr>
<tr>
<td>• Pancreatic pseudocysts</td>
</tr>
<tr>
<td>• Infection-related cysts</td>
</tr>
<tr>
<td>2. Epithelial</td>
</tr>
<tr>
<td>• Retention cysts</td>
</tr>
<tr>
<td>• Squamoid cysts</td>
</tr>
<tr>
<td>• Lymphoepithelial cysts</td>
</tr>
<tr>
<td>• Enterogenous cysts</td>
</tr>
<tr>
<td>• Mucinous nonneoplastic cysts</td>
</tr>
<tr>
<td>• Endometrial cysts</td>
</tr>
<tr>
<td>• Para-ampullary duodenal cysts</td>
</tr>
<tr>
<td><strong>B. Neoplastic pancreatic cysts</strong></td>
</tr>
<tr>
<td>1. Mucinous cystic lesions</td>
</tr>
<tr>
<td>• Intraductal papillary mucinous neoplasms</td>
</tr>
<tr>
<td>• Mucinous cystic neoplasms</td>
</tr>
<tr>
<td>2. Nonmucinous cystic lesions</td>
</tr>
<tr>
<td>• Serous cystic neoplasms</td>
</tr>
<tr>
<td>• Solid pseudopapillary neoplasms</td>
</tr>
<tr>
<td>• Pancreatic neuroendocrine tumors</td>
</tr>
</tbody>
</table>

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with mucin, with calculi, or due to pancreatic adenocarcinoma or chronic pancreatitis. These cysts are usually small in size, and their wall is covered with normal ductal epithelium, which is similar to mucinous cysts. Furthermore, communication with the main pancreatic duct (MPD) may be observed, which makes the differentiation from an IPMN difficult. Although patients with ductal retention cysts usually undergo resection because they cannot be distinguished from IPMNs, no treatment is necessary.

**PANCREATIC CYSTIC NEOPLASMS**

Pancreatic cystic neoplasms are generally classified as mucinous and nonmucinous cystic lesions according to the epithelial lining of the cyst. Mucinous cystic lesions include IPMNs and MCNs; they are often called mucin-producing neoplasms or mucinous neoplasms because they both produce mucin and both have malignant potential (Figure 2). Nonmucinous lesions include SCNs, SPNs, and cystic pancreatic neuroendocrine tumors (cPNETs). Intraductal papillary mucinous neoplasms account for 27% to 48%, MCNs for 11% to 23%, SCNs for 13% to 23%, cPNETs for 4% to 7%, and SPNs for 2% to 5% in resected PCN series. The frequency of MCNs and SCNs has decreased over the past several decades, and the most common pathological diagnosis has been IPMN. Furthermore, more than two-thirds of PCNs are diagnosed incidentally and PCNs are more frequently diagnosed at smaller sizes. These improvements are mostly due to increased awareness of cystic tumors of the pancreas and also due to the advances and widespread availability of cross-sectional imaging techniques.

**Intraductal Papillary Mucinous Cystic Neoplasms**

Currently, IPMNs are the most commonly diagnosed and resected type of PCNs. Intraductal papillary mucinous neoplasms are characterizedly lined with an intraductal papillary mucin producing neoplastic epithelium. They may arise from the MPD (so-called main duct intraductal papillary mucinous neoplasm [MD-IPMN]), which is characterized by segmental or diffuse dilation of the MPD, the side branches of the pancreatic duct (branch duct intraductal papillary mucinous neoplasm [BD-IPMN]), or both (mixed-type IPMN). The natural history of IPMNs is variable, ranging from slow growth to a progressive invasive carcinoma. At the time of diagnosis, given the high risk of malignant tumor (malignant tumor rate of 38%–68% in surgical series), MD-IPMNs require immediate surgery whereas BD-IPMNs...
are more likely benign lesions that can be followed up. Intraductal papillary mucinous neoplasms may occur at any age; however, the mean age at diagnosis is 65 years and both sexes are almost equally affected. Most patients with IPMNs are free of symptoms and diagnosed incidentally; however, patients may present with abdominal pain, malaise, jaundice, or acute pancreatitis.

Intraductal papillary mucinous neoplasms are frequently found in the head and uncinate process; however, they can occur throughout the pancreas. Intraductal papillary mucinous neoplasms are usually solitary cysts, but up to 40% may be multifocal. Branch duct intraductal papillary mucinous neoplasms are classically uni- or multilocular thin-walled cysts without calcification, and they usually exhibit a connection between the cyst and the MPD. Although localization of IPMNs is not helpful in the differentiation of PCNs, the multiplicity of BD-IPMNs is a typical finding (because most PCNs are solitary), and communication with the MPD helps substantiate a diagnosis.

Intraductal papillary mucinous neoplasms share similar cyst fluid features with MCNs. The higher cyst fluid levels of CEA are indicative of mucinous lesions, with a sensitivity of 64% to 100% and a specificity of 60% to 98%. The most commonly used CEA level cutoff threshold of 192 ng/mL (to convert to ug/L, multiply by 1) was reported by Brugge et al., with a sensitivity of 73%, a specificity of 84%, and an accuracy of 79%. However, the CEA level is not a marker to discriminate a malignant cyst from a benign one, but is moderately specific to differentiate a mucinous cyst from a nonmucinous cyst. The amylase level is variable in IPMN cyst fluid, reflecting communication with the pancreatic duct. The fluid may stain positive for alcian blue and mucicarmine on cytology, reflecting the presence of mucin. Usually the presence of mucin on cytology and an elevated CEA cyst fluid level are used to make the diagnosis of a mucinous cyst lesion. Cytology can detect high-grade dysplasia (HGD) and invasive adenocarcinoma, and cytology is highly specific (>90%) but 50% sensitive to diagnose a mucinous cyst. However, 60% of cases have inadequate cellularity.

Histologically, IPMNs are further classified into 4 tissue types: gastric foveolar (predominant in BD-IPMNs), intestinal (predominant in MD-IPMNs), pancreaticobiliary, and oncocytic. Histological studies found that this categorization is highly predictive of the biological behavior of IPMNs: gastric type exhibits the best prognosis and intestinal the worse. However, to date, determining the subtype preoperatively was not possible. A recently introduced device, the disposable microbiopsy forceps, passes through a 19-G needle and allows tissue sampling from a PCN. A preliminary study revealed that the microbiopsy increased the tissue yield that was diagnostic of mucinous/nonmucinous cyst from 47.6% to 61.9%, when it was compared with EUS-FNA cytology. Furthermore, the specific type of pancreatic cysts (IPMNs, MCNs, SCNs, etc) was better diagnosed with microbiopsy forceps tissue histology (33.3% [14 of 42]) than with EUS-FNA fluid cytology (4.8% [2 of 42]). The use of disposable microbiopsy forceps was not associated with any significant complications other than intracystic bleeding in 1 patient. This device not only provides epithelial tissue for a more accurate diagnosis but may also provide information about the subgroup of PCNs and the grade of dysplasia preoperatively (Figure 3). However, although the results are promising, the presenting data, which support the microbiopsy forceps, are from an abstract and no peer-reviewed article has yet been published.

The genetic sequence variations in PCNs are widely studied, and these studies reveal that both IPMNs and MCNs share sequence variations in KRAS, RNF43, and TP53 (for expansion of gene symbols, see www.genenames.org) whereas a mutation in GNAS seems specific for IPMNs, which is present in 58% of cases. Preliminary studies examining the use of a combination of molecular markers in cyst fluid to identify different types of pancreatic cysts appears promising, identifying SCAs with 100% sensitivity and 91% specificity, MCNs with 100% sensitivity and 75% specificity, and IPMNs with 76% sensitivity and 97% specificity. The presence of a mutation in GNAS or KRAS is particularly helpful in identifying a mucin-producing cyst and is found in more than 90% of IPMNs.

Furthermore, ongoing studies to classify the noninvasive markers of high-risk IPMNs...
found that N-glycan levels were correlated with invasive IPMNs, and an allelic variant in the vascular endothelial growth factor gene was associated with malignant transformation.51 Secretin-stimulated pancreatic juice, which is collected from the duodenum, can be used for genetic testing. KRAS, GNAS, and TP53 mutations were identified as potential candidate genes in pancreatic juice.52,53 In addition, as a novel endoscopic technique, needle-based confocal endomicroscopy enables real-time optical biopsies and provides in vivo histopathological assessment during EUS-FNA. Confocal endomicroscopy of IPMNs reveals papillary projections with an epithelial border and vascular core and that of SCNs shows a typical superficial vascular network.54,55 Although these results are promising, the available evidence is still insufficient to recommend using confocal endomicroscopy in current practice for the diagnosis of pancreatic cysts.

Intraductal papillary mucinous neoplasms have the malignant potential to progress from low-grade dysplasia to HGD and invasive adenocarcinoma.56 Dysplasia in IPMNs is currently categorized as low or high.57 To date, the exact grade of dysplasia in IPMNs cannot usually be identified without histological examination of the resected specimen. Only certain imaging features are able to predict HGD or invasive carcinoma in patients with IPMNs preoperatively. These features are the presence of a solid component or mural nodule cyst greater than 3 cm in size and MPD dilation with an associated odds ratios of 7.73, 2.97, and 2.38, respectively, for HGD or invasive adenocarcinoma.58 However, although statistically nonsignificant, preliminary data revealed that the pinch biopsy specimens were diagnostic of the degree of dysplasia in 64.2% of patients (27 of 42). Furthermore, microbiopsy forceps histology again increased the detection of low-grade dysplasia in a moderate proportion of patients (from 21 to 27 of 42 patients).47

The international consensus guidelines (ICG) (updated in 2012) recommend looking for high-risk stigmata (HRSs) of malignant tumor as a first step in the evaluation of BD-IPMNs.59 According to these guidelines, HRSs, which raise concern that IPMNs may have HGD or an associated invasive adenocarcinoma, are obstructive jaundice, enhancing solid component, and dilated MPD (≥10 mm). These guidelines recommend surgery if HRSs are seen. Patients with worrisome features (cyst ≥3 cm, thickened/enhanced cyst wall, MPD 5 to 9 mm, nonenhancing mural nodule, and abrupt change in MPD caliber with distal pancreatic atrophy) should be directed to EUS to look for malignant tumors. In patients with any EUS-FNA feature including definite mural nodule, MPD feature suggestive of involvement (presence of any of the thickened walls, intraductal mucin, or mural nodules), or cytology suggestive of/positive for malignant tumor, surgical resection should be considered. Nevertheless, it should be kept in mind that ampullary adenoma, papillary stenosis, chronic pancreatitis, and a small pancreatic adenocarcinoma in the head of the pancreas are other causes of pancreatic ductal dilation. In the absence of worrisome features, a decision is based on the size of the cyst (radiological surveillance for cysts <2 cm, manage cysts 2-3 cm with EUS-FNA, and direct cysts >3 cm to surgery). In contrast, the AGA reported its guidelines in 2015 and cysts 3 cm or more in size, presence of associated solid component and dilated MPD were determined as high-risk factors (HRFs). Patients without HRFs were recommended for MRI surveillance for up to 5 years, and patients having at least 2 of these HRFs were directed to EUS-FNA. Patients without concerning EUS features were recommended for MRI surveillance. In the absence of significant change in cyst features over 5 years, the AGA guidelines recommended

![Figure 3](http://dx.doi.org/10.1016/j.mayocp.2017.06.017)
discontinuation of imaging. Patients with solid component and dilated MPD (≥5 mm on both EUS and MRI) and/or concerning features on EUS were directed to surgery. The positive and negative predictive values of high-risk patients according to the ICG were 88% and 92.5%, respectively, in a large study when comparing the cross-sectional imaging with surgical histology. The AGA guidelines were also validated by comparing EUS findings with cyst fluid analysis. Advanced neoplasia was identified with 62% sensitivity, 79% specificity, 57% positive predictive value, and 82% negative predictive value. The sensitivity and specificity of cross-sectional imaging were found to be fair to moderate in detecting a mural nodule. In low-risk patients the AGA guidelines do not recommend EUS-FNA, but instead CT/MRI. In contrast, a recent study revealed that 45% of IPMNs with HGD and adenocarcinoma were missed when AGA guidelines were applied to their cohort.

Although the AGA guidelines do not recommend surgical resection for MD-IPMNs alone (but requires the presence of definite nodule or malignant cytology), given the high risk of malignant tumor, the ICGs recommend resection for patients with MD-IPMNs. Patients with symptomatic BD-IPMNs and BD-IPMNs with HRSs and worrisome features plus concerning EUS features (dilated MPD, mural nodule, or cyst fluid suggestive of/potential malignancy) should also be directed to surgery. For imaging of all other BD-IPMNs, surveillance is recommended on the basis of the size of the cyst. In contrast to MCNs, IPMNs can develop in the residual pancreas after resection and patients with IPMNs are also at risk for developing pancreatic adenocarcinoma in an area unrelated to a pancreatic cyst. The remnant pancreas should therefore undergo surveillance after Whipple or distal pancreatectomy. In selected patients (who are at high risk for surgery, who refuse surgery, or who have low-risk cyst), alcohol ablation or ablation with a combination of alcohol and paclitaxel are the alternative treatment options. The American Society of Gastrointestinal Endoscopy recommends cysts selected for ablation to be less than 3 to 4 cm in size, unilocular or oligolocular (<3-6 locules), and without evidence of communication with the MPD.

**Mucinous Cystic Neoplasms**

Mucinous cystic neoplasms occur almost exclusively in women (accounting for >95% of cases) at a mean age of 40 years (range, 20-82 years). Thus, “mother cysts” is a commonly used term for them. Mucinous cystic neoplasms are located in the body and tail of the pancreas in more than 97% of cases. Having some features makes MCNs easy to differentiate from other PCNs: a woman with a single cyst located at the body or tail of the pancreas usually has an MCN. Most patients (70%) are asymptomatic; however, the most common symptom is nonspecific abdominal pain.

Mucinous cystic neoplasms are well-defined thin-walled solitary cysts, which may be uni- or multilocular. The cyst wall may contain calcification at the edge of the cyst in 15% of MCNs, in contrast to SCNs, in which calcification occurs at the center. Features that help differentiate MCNs from IPMNs are based on the absence of communication with the MPD with a normal caliber and the pathognomonic ovarian-like stroma, which surrounds the inner epithelial layer of the cyst.

As described above, the cyst fluid analysis for MCNs is identical to that for IPMNs, such as variable cyst fluid amylase levels, high CEA levels, and presence of epithelial elements consisting of columnar cells with extracellular mucin on cytology. Cytology can also detect HGD or invasive adenocarcinoma.

Despite a low risk of malignant tumor in presentation (surgical series report invasive carcinoma risk of 4%-13%), MCNs carry a risk of progression to invasive adenocarcinoma. Mucinous cystic neoplasms are categorized as benign (but potentially premalignant) mucinous cystadenoma, borderline MCN, MCN with carcinoma in situ, and mucinous cystadenocarcinoma.

There is a debate about whether MCNs should be surgically resected or followed by imaging. There is an agreement about immediate resection of MCNs, causing obvious symptoms (such as pancreatitis) in patients with concerning EUS features (such as solid component or cytology positivity for HGD or invasive adenocarcinoma). However, there is a conflict about patients without these concerning features and about MCNs that are less than 3 cm in size. Some guidelines and
authors advocate surgery, because a young healthy patient may require years of radiological surveillance; MCNs do not recur in contrast to IPMNs, and the location of MCNs is technically easier to resect surgically. In contrast, others claim that preoperative differentiation of MCNs from IPMNs is not always possible, that more recent data suggest that the malignant transformation risk of MCNs is less than that of BD-IPMNs, and although distal pancreatectomy is associated with low mortality, it has approximately a 25% morbidity rate, which includes a 15% to 20% diabetes risk.12,59 Once patients with MCNs undergo surgical resection, no further surveillance imaging is needed, in contrast to IPMNs.

Serous Cystic Neoplasms
Serous cystic neoplasms are nonmucinous, predominantly benign cystic neoplasms (serous cystadenoma), and malignant cases (serous cystadenocarcinoma) are extremely rare.70 Serous cystic neoplasms are often found in women older than 60 years and therefore sometimes called “grandmother cysts.”71 They are typically benign, slow-growing cysts, which are mostly detected incidentally.1,72 Abdominal pain is the most common symptom, and less commonly patients may present with a palpable mass when the cyst attains a large size. Serous cystic neoplasms occur sporadically or in the setting of a von Hippel-Lindau (vHL) disease;73 thus, the vHL gene sequence variation plays an important role in the pathogenesis.

The more common type is the microcystic variant, in which numerous multiple cysts that are commonly less than 2 cm in size are grouped together and separated by thin septations. The cysts are lined by epithelial cells in a honeycomb or sponge-like appearance. The less common type is the oligo- or macrocystic variant, which is a solitary cyst that is difficult to differentiate from a PP, BD-IPMN, or MCN.

The typical appearance of an SCN on CT/MRI is a solitary lesion anywhere in the pancreas, having a central satellite-shaped scar that is surrounded by multiple thin-walled locules. Serous cystic neoplasms classically do not communicate with the MPD, and this is best seen on magnetic resonance cholangiopancreatography. The characteristic hypervascular central region may be seen on EUS and Doppler, and the cyst fluid may be bloody because of this nature. Cytology is rarely diagnostic for SCA; however, PAS-positive small cuboidal cells (that are rich in glycogen and compose the cyst lining) are indicative of an SCN.74 The cyst fluid has low levels of amylase; the CEA level is typically less than 5 ng/mL,75 negative for both KRAS and GNAS sequence variations but positive for vHL sequence variations.76-78

The prognosis of SCNs is excellent, and given the benign nature, SCNs should be followed by surveillance imaging. Except for an uncertainty about malignant tumor, rapidly growing cysts, and patients with symptoms, surgical resection is not recommended.73 The intervals of surveillance imaging remain unclear.

Cystic Pancreatic Neuroendocrine Tumors
Cystic pancreatic neuroendocrine tumors are rare cystic variants of pancreatic neuroendocrine tumors, which are indolent tumors with a variable malignant potential. Sexes are equally affected; the mean age of presentation is 50 years; and the incidence increases with age.79-81 Most of the cPNETs are asymptomatic, nonfunctioning (no hormone overproduction–related symptoms), and often diagnosed incidentally. Most cPNETs are sporadic; however, an association with vHL syndrome, multiple endocrine neoplasia type 1, and neurofibromatosis type 1 may be seen.79,80,82,83

Imaging shows a well-circumscribed multi- or unilocular cyst surrounded by a thick fibrous capsule. The cyst does not generally communicate with the MPD. Hypervascular thickened walls can also be seen on EUS.80 The aspirated cyst fluid is usually hemorrhagic, and after aspiration, the appearance of the lesion resembles a hypoechoic mass. Cytology reveals cells with round uniform nuclei, which are stained with chromogranin and synaptophysin.81,84,85

The recommended treatment for clinically active cPNETs is complete resection; asymptomatic cPNETs below 1 cm are managed with surveillance. The prognosis is better than pancreatic adenocarcinoma; patients with resected cPNETs have an excellent prognosis.79-81
**Solid Pseudopapillary Neoplasms**

Solid pseudopapillary neoplasms are rare heterogeneous neoplasms of the pancreas, which most commonly occur in young women in their 30s. Although most patients with SPNs were symptomatic, currently SPNs are becoming more commonly detected incidentally. Solid pseudopapillary neoplasms usually reach large sizes and become symptomatic because of the mass effect (similar to that in SCNs). Abdominal pain, vomiting, and jaundice are the most common symptoms. Molecular aberrations, such as CTNNB1 sequence variations and Wnt/β-catenin pathway activations are recent findings in the pathogenesis, apart from the typical KRAS and TP53 sequence variations of pancreatic adenocarcinoma. Generally, SPNs are benign or low-grade malignant tumors. The criteria for malignant behavior, which is seen in 10% to 20% of cases, are local invasion (such as vascular invasion, perineural invasion, and adjacent tissue invasion), nodal or liver metastases, or local or distant recurrence after resection.

On CT/MRI, SPNs are well-demarcated, large, encapsulated, mixed solid, and cystic lesions without septa that can be found anywhere throughout the pancreas. The fibrous capsule, at times containing calcifications, is usually thick and encompasses the lesion. Similar findings can be seen on EUS, and EUS-FNA has increased the diagnostic yield to more than 80%. The cyst fluid is generally hemorrhagic, is highly cellular, and has a low CEA level. Furthermore, a recent retrospective study on resected SPNs revealed positive reactivity to Ki-67, which was more common in malignant tumors.

The current recommendation for the treatment of SPNs is surgical resection, because they harbor a malignant potential and because of their large sizes at presentation. The overall 5-year survival rate is 95%; however, after 5 years, SPNs can recur in approximately 10% of patients; therefore, surveillance imaging is necessary.

General features of pancreatic cysts are summarized in Table 2.

**MY TREATMENT APPROACH**

Incidentally noted cystic lesions of the pancreas are still a challenging issue for physicians, and usually a multidisciplinary approach is needed. With the advances in cross-sectional imaging, neoplastic cysts of the pancreas are more commonly diagnosed. Differentiating neoplastic pancreatic cysts

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**TABLE 2. General Features of Pancreatic Cysts**

<table>
<thead>
<tr>
<th>Feature</th>
<th>PP</th>
<th>IPMN</th>
<th>MCN</th>
<th>SCN</th>
<th>cPNET</th>
<th>SPN</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>M/F</td>
<td>M/F</td>
<td>F</td>
<td>F</td>
<td>M/F</td>
<td>F</td>
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<td>Median age (y)</td>
<td>60</td>
<td>65</td>
<td>40</td>
<td>60</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Localization</td>
<td>Entire pancreas</td>
<td>Head</td>
<td>Body and tail</td>
<td>Entire pancreas</td>
<td>Entire pancreas</td>
<td>Body and tail</td>
</tr>
<tr>
<td>Morphology</td>
<td>Unilocular</td>
<td>Unilocular; septated, dilated MPD</td>
<td>Unilocular</td>
<td>Microcystic</td>
<td>Associated mass</td>
<td>Mixed solid and cystic</td>
</tr>
<tr>
<td>Number of cysts</td>
<td>Multiple</td>
<td>Multiple (40%)</td>
<td>Solitary</td>
<td>Solitary</td>
<td>Solitary</td>
<td>Solitary</td>
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<tr>
<td>Epithelium type</td>
<td>No epithelial lining</td>
<td>Papillary mucinous</td>
<td>Mucinous</td>
<td>Serous (PAS+ for glycogen)</td>
<td>Endocrine</td>
<td>Endocrine-like</td>
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<tr>
<td>Communication with the MPD</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Risk of malignant tumor</td>
<td>No risk</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Genetic sequence variations</td>
<td>No sequence variation</td>
<td>KRAS, GNAS, RNF43, CTNNB1</td>
<td>KRAS, RNF43</td>
<td>vHL</td>
<td>Mostly sporadic CTNNB1</td>
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<td>Cyst fluid viscosity</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Cyst fluid amylase level</td>
<td>High</td>
<td>Variable, high</td>
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<td>Cyst fluid CEA level</td>
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</tr>
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</table>

*CEA = carcinoembryonic antigen; cPNET = cystic pancreatic neuroendocrine tumor; F = female; IPMN = intraductal papillary mucinous neoplasm; m = male; MCN = mucinous cystic neoplasm; MPD = main pancreatic duct; PP = pancreatic pseudocyst; SCN = serous cystic neoplasm; SPN = solid pseudopapillary neoplasm.

In sporadic cases, mutated genes mostly appear to be involved in the remodeling of chromatin. An association with von Hippel-Lindau syndrome, multiple endocrine neoplasia type 1, and neurofibromatosis type 1 may also be seen.
from nonneoplastic cysts is the most important concern in the management of these patients. Patients with PPs usually present with clinical pancreatitis, may have a history of pancreatitis, or present with evidence of pancreatitis on cross-sectional imaging. However, some patients may present with mild pancreatitis, which may not be clinically overt. In addition, patients with PCNs may present with pancreatitis. In a patient with a known history of pancreatitis without an associated solid mass in the pancreas, a PP should be suspected rather than a PCN. In contrast, a PCN has to be strongly considered in patients presenting with pancreatitis for the first time without a known etiology. We suggest reviewing previous imaging, especially a CT scan, in such patients to search for evidence of pancreatitis.

In patients with a history of pancreatitis, an oval or round, well-circumscribed, fluid-filled lesion surrounded by a thick, dense wall adjacent to the pancreas on abdominal CT is almost diagnostic for a PP. Except for PPs and IPMNs, most of the pancreatic cysts are solitary, which needs to be remembered in the differential diagnosis. Evaluating the adjacent tissue for pancreatitis and searching the mediastinum, mesentery, and pelvis, in which large PPs may be seen, are the additive advantages of CT. In patients with an indication of a neoplastic cyst, EUS should be performed. On EUS, PPs are anechoic fluid-filled lesions surrounded by a thick hyperechoic rim. The cyst wall of a PP does not contain calcification, which would be highly suggestive of a cystadenoma. Multiple prominent vessels, including paragastric varices, are suggestive of a PP with splenic vein thrombosis.

Cyst fluid analysis is the next step in the differential diagnosis, where there is a concern about diagnosis. A fairly high amylase level, which is a strong predictor of communication with the pancreatic duct, helps confirm the diagnosis of a PP. In contrast, BD-IPMNs may also communicate with the pancreatic duct, but MCNs generally do not. Intraductal papillary mucinous neoplasms may have variable amylase levels, but not as high as do PPs; however, these levels are generally low in patients with MCNs. In addition, relatively low cyst fluid CEA levels help distinguish a PP from a mucinous cyst. Epithelial cells seen in cytological analysis should raise the suspicion of a PCN rather than a PP. Histiocytes, inflammatory cells, and degenerative debris are supportive of PPs.

Differentiating epithelial nonneoplastic cysts (retention cysts are more common) is also a challenging problem, because IPMNs and retention cysts both may communicate with the MPD and both contain ductal epithelium. Although it is not typical and common, proximal ductal dilation seen in retention cysts may help differentiate between them. However, sharing similar features, most ductal retention cysts generally undergo resection.

After excluding the nonneoplastic cysts, the next step is to define whether the cyst is a mucin-producing cyst. In a middle-aged woman, a solitary cyst located in the body or tail of the pancreas strongly suggests an MCN. In contrast to other cysts, BD-IPMNs may be multiple. Mucinous cystic neoplasms generally do not communicate with the MPD, and the MPD is of normal diameter. When a dilated duct is found in a patient with a pancreatic cyst, it is important to exclude other etiologies such as a small adenocarcinoma in the head of the pancreas, chronic pancreatitis, ampullary adenoma, and papillary stenosis. In the absence of these causes, an MD-IPMN or a mixed type IPMN should be considered. On imaging, although rare, calcification in the cyst wall suggests an MCN, in contrast to stellate-shaped central calcifications of an SCN. The classical microcystic variant of an SCN, which can be found anywhere in the pancreas, is usually easy to diagnose because of its appearance on imaging. However, the oligocystic variant is sometimes indistinguishable from a PP, MCN, and BD-IPMN. A key diagnostic factor for an SPN is the presence of a fibrous capsule that surrounds and encompasses the lesion. A thick fibrous capsule usually surrounds a well-circumscribed multi- or unilocular cyst in cPNETs as well.

Endoscopic ultrasonography—guided fine needle aspiration can be performed in cases in which clinical and imaging features are indeterminate. However, EUS-FNA may not be always feasible in pancreatic cysts when they are small in size or because of their
location. We suggest performing EUS in patients with worrisome features (cyst ≥3 cm, thickened/enhanced cyst wall, MPD 5 to 9 mm, nonenhancing mural nodule, and abrupt change in MPD caliber with distal pancreatic atrophy) to look for malignant tumors. When performed, the cyst fluid is viscous in mucin-producing neoplasms and nonviscous in SCNs. The fluid is generally bloody in SPNs and cPNETs. Cyst fluid CEA levels greater than 192 ng/mL favor a diagnosis of a mucinous cyst rather than of an SCN, and levels less than 5 ng/mL are suggestive of an SCN. Although variable, the cyst fluid amylase level is generally high in patients with IPMNs and low in patients with MCNs and SCNs. The presence of mucin on cytology with a high cyst fluid CEA level is nearly diagnostic for a mucin-producing neoplasm. If present, PAS-positive cuboidal cells are diagnostic for an SCN. Cytology is positive for chromogranin- and synaptophysin-stained cells for cPNETs. The positivity of both cyst fluid KRAS and GNAS sequence variations strongly suggests an IPMN, and MCNs are negative for GNAS sequence variations. In the absence of both KRAS and GNAS sequence variations, vHL sequence variations should be searched for SCNs and CTNNB1 sequence variations for SPNs.

**RECOMMENDATIONS**

In both symptomatic patients and those with incidentally diagnosed pancreatic cysts, we evaluate the demographic characteristics (most PCNs occur in women predominantly; however, SPNs affect younger, MCNs middle-aged, and SCAs older women), clinical features (symptoms, physical examination findings, pancreatitis history, family history of pancreatic adenocarcinoma, or genetic syndromes), and imaging features carefully. The first step is to rule out a PP. If there is a question regarding a PCN or when the above features are indeterminate or worrisome on cross-sectional imaging, we advise the performance of EUS-FNA to aid in the diagnosis. We suggest aspirating at least 1 mL of cyst fluid (when possible) to send for biochemical, cytological, and molecular analysis. We also suggest obtaining biopsies from the cyst epithelium and septations with the microbiopsy forceps, which seems to help differentiate PCNs and the grade of dysplasia. We recommend surgical resection for patients with MCNs, MD-IPMNs, mixed IPMNs, SPNs, clinically active cPNETs, and pancreatic cysts causing symptoms. The remaining BD-IPMNs should be managed on the basis of the presence of HRSs or cytology results. We advise resection for patients with BD-IPMNs having any of the HRSs (enhancing nodule, MPD ≥10 mm, and obstructive jaundice) or cytology suggestive of/positive for malignant tumor or a young surgically fit patient having a cyst greater than 3 cm in size. Patients with BD-IPMNs with worrisome features are directed to EUS-FNA. Except for symptomatic cysts and when there is an uncertainty about malignant tumor, SCAs should be followed clinically as needed.

Abbreviations and Acronyms: AGA = American Gastroenterological Association; BD-IPMN = branch duct intraductal papillary mucinous neoplasm; cPNET = cystic pancreatic neuroendocrine tumor; CEA = carcinoembryonic antigen; CT = computed tomography; EUS = endoscopic ultrasonography; EUS-FNA = endoscopic ultrasonography-guided fine needle aspiration; HGD = high-grade dysplasia; HRF = high-risk factor; HRS = high-risk stigmata; ICC = international consensus guidelines; IPMN = intraductal papillary mucinous neoplasm; MD-IPMN = main duct intraductal papillary mucinous neoplasm; MRI = magnetic resonance imaging; PCN = pancreatic cyst; PP = pancreatic pseudocyst; SCN = serous cystic neoplasm; SPN = solid pseudopapillary neoplasm; vHL = von Hippel-Lindau

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