The role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature from January 1990 to September 2015 was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When limited or no data existed from well-designed prospective trials, emphasis was given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines were drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient’s condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines. This guideline supplements and replaces our previous document on the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas.

CYSTIC LESIONS AND FLUID COLLECTIONS OF THE PANCREAS

Cystic lesions and fluid collections of the pancreas often present a diagnostic and therapeutic challenge. Their pathology ranges from pseudocysts and pancreatic necrosis to benign and malignant neoplasms. Pancreatic cystic lesions may be encountered during the evaluation of a patient with pancreatitis or abdominal pain. However, these lesions are found incidentally in 2.5% of patients undergoing abdominal imaging performed for unrelated reasons, and their frequency increases with age to 10% in those aged ≥70 years. In the absence of characteristic radiographic features and clinical detail, pancreatic cystic neoplasms can be misclassified as pseudocysts, which are inflammatory pancreatic fluid collections that lack a true epithelial lining. This guideline will discuss the role of GI endoscopy in the evaluation and treatment of cystic pancreatic neoplasms. The role of endoscopy in the management of inflammatory fluid collections of the pancreas is addressed in another ASGE guideline.

CYSTIC LESIONS OF THE PANCREAS

Cystic lesions of the pancreas consist of nonneoplastic cysts and cystic neoplasms, the latter of which include serous cystic neoplasms, mucinous cystic neoplasms, and intraductal papillary mucinous neoplasms (IPMNs) in ductal adenocarcinomas. Recently, several
Diagnosis by EUS

EUS morphology

Several EUS findings have been evaluated as diagnostic criteria for pancreatic cystic lesions. When surgical histology is used as a reference standard, the diagnostic accuracy of EUS imaging ranges from 40% to 96%. A single prospective study demonstrated that the sensitivity (56%) and specificity (45%) of EUS morphology alone for differentiating mucinous cysts (mucinous cystic neoplasms and IPMNs) from nonmucinous cysts were low, resulting in poor overall accuracy (51%). In a study among experienced endonsonographers, the agreement of whether a cyst was neoplastic versus nonneoplastic by EUS morphologic criteria was fair ($K = 0.24$), with moderate agreement for serous cystic neoplasms ($K = 0.46$) and for solid components ($K = 0.43$).

Small cyst size alone does not exclude malignancy. One series of patients referred to a tertiary-care surgical practice reported that 20% of lesions <2 cm were malignant, and an additional 45% of lesions had malignant potential. However, only 1 of 28 (3.5%) asymptomatic lesions <2 cm was malignant. Certain EUS features are more predictive of particular types of cystic lesions. Multiple small (<5 mm) compartments within a cystic lesion (also called a microcystic lesion), suggest a serous cystic neoplasm with an accuracy of 92% to 96%, and this feature is not seen in mucinous cystic neoplasms.

A cystic lesion without septations or solid components within a pancreas having parenchymal features suggestive of pancreatitis (defined as calcifications, atrophy, or a change in echo texture) indicates a pseudocyst with a sensitivity of 94% and a specificity of 85%.

EUS imaging cannot reliably distinguish benign from malignant IPMNs. Furthermore, it is unclear whether imaging features of mucinous lesions with increased malignant potential are sufficiently predictive to influence clinical management. A meta-analysis of 23 studies with 1373 patients found that a mural nodule, main pancreatic duct dilation, thickened septal walls, and cyst size >3 cm on radiologic or EUS imaging were independent predictors of malignant branch-duct IPMN. Similarly, a recent international consensus guideline identified a main pancreatic duct (MPD) size ≥10 mm or the presence of an enhancing solid component on radiologic imaging as high-risk stigmata. Lower risk findings, categorized as worrisome features, included a cyst size of ≥3 cm, thickened enhancing cyst walls, nonenhancing mural nodules, MPD size of 5 to 9 mm, an abrupt change in the MPD caliber with upstream pancreatic atrophy, or the presence of peripancreatic lymphadenopathy.

Distinguishing cyst wall nodules that are epithelial (neoplastic) from those that are mucinous (nonneoplastic) is critical to properly risk stratify pancreatic cystic neoplasms. A recent blinded interobserver study found that EUS imaging of intracystic mucus appears as a smooth, well-defined hyperechoic rim with a hypoechoic center compared with the surrounding parenchyma. This feature serves to distinguish mucus from true epithelial nodules, which have ill-defined borders and a hyperechoic center. Specific adjuncts to standard EUS may further aid in distinguishing between these 2 entities. Intraductal US may identify malignant IPMN by the presence of protruding lesions ≥4 mm. Contrast-enhanced EUS, which uses a contrast agent to assess the vascularity of lesions, may aid in distinguishing inflammatory cysts from cystic pancreatic neoplasms and vascular epithelial mural nodules from nonvascular mucous in IPMNs.
FNA

Cytology

Tumor markers

Cyst fluid DNA and molecular analysis

Endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms
TABLE 2. Characteristics of pancreatic cystic lesions

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Pseudocyst</th>
<th>IPMN</th>
<th>Mucinous cystic neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of moderate to severe pancreatitis</td>
<td>History of pancreatitis, abdominal pain, or found incidentally</td>
<td>Usually found incidentally but can cause abdominal pain and a palpable mass if large</td>
<td></td>
</tr>
</tbody>
</table>

| Morphology/ EUS findings | Anechoic, thick-walled, rare septations, regional inflammatory nodes may be seen | Dilated main pancreatic duct or side branches; may appear as a separted cyst; may have a solid component | Macrocytic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant |

<table>
<thead>
<tr>
<th>Fluid characteristics</th>
<th>Thin, muddy-brown</th>
<th>Viscous or stringy, clear</th>
<th>Viscous or stringy, clear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Fluid chemistries</th>
<th>Elevated amylase, low CEA</th>
<th>Elevated amylase and CEA</th>
<th>Elevated CEA, low amylase</th>
</tr>
</thead>
</table>

| Cytology | Neutrophils, macrophages, histiocytes; negative staining for mucin | Mucinous columnar cells with variable atypia; fluid stains positive for mucin | Mucinous columnar cells with variable atypia; fluid stains positive for mucin |

| Malignant potential | None | Yes | Yes |

Data from references 9 and 12.

IPMN, Intraductal papillary mucinous neoplasm; CEA, carcinoembryonic antigen.

Cyst fluid CEA levels and molecular analysis in diagnosing mucinous cysts, with comparable sensitivities and diagnostic accuracies. The combination of CEA and DNA molecular analysis improved diagnostic accuracy compared to either test alone. A more recent study demonstrated that integrated molecular analysis of cyst fluid (ie, combining molecular analysis with results of imaging and clinical features) was able to better characterize the malignant potential of pancreatic cysts compared to consensus guidelines for the management of mucinous cysts. In addition to acquisition of cyst fluid via EUS-FNA, duodenal collection of pancreatic juice for DNA analysis via an echoendoscope after secretin stimulation found GNAS mutations in 64.1% of 78 patients with IPMN compared with none of the 57 control patients. Molecular analysis (which requires only 200 μL of fluid) may be most useful in small cysts with nondiagnostic cytology, equivocal cyst fluid CEA results, or when insufficient fluid is present for CEA testing. Additional research is needed to determine the precise role molecular analysis of cyst fluid will play in evaluating pancreatic cystic lesions.

Emerging techniques for cystic evaluation

Recently, direct optical and endomicroscopic examination of pancreatic cysts has become feasible. Intracystic visualization and direct intracystic biopsy specimens through a 19-gauge needle can be obtained with either a reusable 0.9-mm fiberoptic probe or via a dedicated system primarily indicated for single-operator cholangioscopy and pancreatography (SpyGlass; Boston Scientific, Natick, Mass). Real-time in vivo microscopic imaging via needle-based confocal laser endomicroscopy after intravenous administration of fluorescein (CellVizio; Mauna Kea Technologies, Paris, France) has also been reported. A study of 66 patients that used confocal laser endomicroscopy found that the presence of epithelial villous structures had a sensitivity of 59% and a specificity of 100% for IPMN, mucinous cystic neoplasm, or adenocarcinoma. Another study of 31 patients used this device to identify a superficial vascular network pattern seen only in serous cystic neoplasms. This resulted in an overall accuracy in identifying serous cystic neoplasms of 87%, with a high rate of interobserver agreement ($\kappa = 0.77$). The combined findings of mucin (by transneedle cystoscopy), papillary projections, and dark rings on confocal laser endomicroscopy improved diagnostic accuracy compared with either technique alone.

Adverse events from EUS

A recent ASGE guideline addresses adverse events associated with EUS and EUS-FNA. In a systematic review of 51 studies, adverse events specific to EUS-FNA of pancreatic cystic lesions occurred in 2.7% of 909 patients. This number increased to 5% when data were prospectively collected. No patient-specific or cyst-specific characteristics appear to predict the development of an adverse event. The most common adverse events include abdominal pain, pancreatitis, and intracystic hemorrhage. Data regarding the use of prophylactic antibiotics in pancreatic cysts after EUS-FNA are equivocal. Although a cyst infection rate of 14% was reported in an initial series of 22 patients undergoing cyst FNA, another retrospective study found only a single infection in 605 patients undergoing EUS-FNA of pancreatic cysts, including no infections in 60 patients who did not receive...
antibiotic prophylaxis. A recent retrospective cohort study of antibiotic prophylaxis for EUS-FNA of pancreatic cysts identified 1 possible infection each in 88 patients treated with antibiotics and 178 patients given no antibiotics. Nevertheless, current ASGE guidelines suggest administration of antibiotics for 3 to 5 days after EUS-FNA of a pancreatic cystic lesion.

**Diagnosis by ERCP**

ERCP is rarely indicated for the evaluation of pancreatic cystic lesions. In main-duct IPMN, duodenoscopy may reveal the highly specific finding of mucus extruding from a patulous pancreatic orifice. This pathognomonic finding is seen in 20% to 55% of patients with main-duct IPMN and was seen more frequently in malignant disease in some, but not all, studies. A pancreaticoduodenal fistula extruding mucus is seen in up to 2% of IPMN cases and suggests malignant invasion.

Pancreatography has limited utility in the assessment of cystic neoplasms. In the absence of other risk factors for ductal stenosis, such as chronic pancreatitis or pancreatic trauma, a narrowed pancreatic duct suggests malignancy. Communication with the MPD suggests either a pseudocyst or an IPMN and is rare in mucinous or serous cystic neoplasms. Pancreatographic findings of chronic pancreatitis, such as ectatic or blunted side branches favor the diagnosis of pseudocyst, but can be seen in IPMN as well. Other features of IPMN include segmental or diffuse dilatation of the MPD or focal side-branch dilatation. Filling defects in the MPD caused by mucus may be distinguished from stones by their transient nature and movement when passed with contrast material injection, a catheter, or a guidewire. Persistent filling defects that represent polypoid lesions also may be seen.

Pancreatocstopy in IPMN may be facilitated by an enlarged papillary opening and provides direct visualization of mucus, stones, or a tumor. Direct examination of the main duct may determine the extent of disease and guide biopsy specimens. One study found the combination of pancreatoscopy, and intraductal US was capable of distinguishing benign from malignant IPMNs with an accuracy of 88%. Another study of 44 patients undergoing single-operator pancreatoscopy when radiologic imaging suggested IPMN found 76% and 78% of surgically confirmed main duct and side-branch IPMNs were correctly identified by pancreatoscopy. Furthermore, the pancreatoscopy results impacted clinical decision making in 76% of cases.

ERCP-directed tissue sampling of main duct IPMNs includes the evaluation of aspirated mucus, brush cytology, biopsy specimens of fixed filling defects or strictures, and random biopsy specimens of dilated duct walls. In 1 study, transpapillary biopsy with standard or pediatric-sized forceps yielded a histopathologic diagnosis of IPMN in 11 of 13 patients. However, in general, ERCP tissue sampling has a relatively low diagnostic yield. A systematic review of 13 studies totaling 483 patients with IPMN found a pooled sensitivity of 35.1% and a specificity of 97.2% for ERCP-based cytology, with lavage cytology showing minimal improved sensitivity (45.8%) compared with fluid aspiration (41.5%) but increased sensitivity compared with brushings (20.9%). Several reports have described pancreatoscopy by using a videoscope with narrow-band imaging or via a fiberoptic probe to obtain tissue or cytology. Its use has been shown to result in an
absolute increase in the sensitivity of lavage cytology for malignancy in main duct IPMN by 24% compared with fluid aspiration with a catheter. 88

**Endoscopic treatment of cystic lesions**

Recently, endoscopic cyst ablation with ethanol alone or in combination with paclitaxel for suspected pancreatic cystic neoplasms has been proposed as an alternative to surgery. 92-95 Cysts selected for ablation have typically been less than 3 to 4 cm in size, unilocular or oligolocular (<3-6 locules), and without evidence of communication with the MPD. A randomized trial showed that ethanol is superior to saline solution for pancreatic cyst ablation. 92-96 The chemotherapeutic agent paclitaxel has been added in more recent studies to standard ethanol lavage to potentially improve response rates. The hydrophobic nature of paclitaxel is believed to foster its retention in the cyst and minimize peri-cystic leakage. Overall reported rates of cyst resolution range from 33% to 79%, with increased efficacy observed with smaller initial cyst volumes, multiple ethanol ablations, or ethanol and/or paclitaxel combination therapy.92-94 Adverse events have been reported in approximately 12% of cases and include abdominal pain, focal peritonitis, pancreatitis, fever, pericystic spillage, splenic vein obliteration, and portal venous thrombosis. 96,98 Uncertainties remain regarding the durability of the technique,99 whether complete epithelial ablation has been achieved in radiographically resolved cysts and the impact on the malignant potential of these cysts.100 A recent study demonstrated that EUS-guided cyst ablation may eliminate mutant DNA in neoplastic pancreatic cysts.101 However, patients achieving cyst ablation are thought to be at continued risk of developing ductal adenocarcinoma and should undergo continued surveillance imaging.102 Given these limitations, EUS-guided cyst ablation is performed only at select centers and might be considered for patients who refuse or are not candidates for surgery.

**Recommendations**

1. We recommend EUS-FNA of any pancreatic cystic lesion over 3 cm in diameter or when cross-sectional or EUS imaging confirms an epithelial nodule, dilated main pancreatic duct, or suspicious mass lesion. ☑

2. We suggest that EUS-FNA is optional in asymptomatic patients in whom cross-sectional imaging demonstrates a cyst <3 cm and without either a mass and/or epithelial nodule or associated dilated main pancreatic duct. ☑

3. We recommend initial testing of aspirated pancreatic cyst fluid for CEA, amylase, and cytology. ☑

4. We suggest that molecular testing of the cyst be considered when initial ancillary testing of cytology and CEA is inconclusive and when test results may alter management. ☑

5. We suggest administration of prophylactic antibiotics for patients undergoing EUS-FNA for the evaluation of cystic pancreatic neoplasms. ☑

6. We suggest that ERCP, pancreatoscopy, and intraductal US may be helpful in the diagnosis and characterization of suspected main duct IPMNs. ☑

**DISCLOSURES**

M. Khashab is a consultant for Boston Scientific and Xlumena. V. Muthusamy is a consultant for Boston Scientific. He also received honoraria and research support from Medtronic. K. Chaibabi is a consultant for Boston Scientific. All other authors disclosed no financial relationships relevant to this publication.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CEA, carcinoembryonic antigen; EUS-FNA, EUS-guided FNA; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.

**REFERENCES**

13. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management


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1. On imaging, which of the following features suggest a high likelihood of malignant IPMN
   a. pancreatic duct stricture
   b. pancreatic duct size > 10 mm
   c. solid enhancing component in the cyst
   d. thickened septal walls

2. Pancreatic cysts that should be targeted for EUS and diagnostic aspiration are those with one or more of the following features
   a. Size >3 cm
   b. Pancreatic tail location
   c. Epithelial nodule or mass lesion
   d. Main pancreatic duct dilation

True or False

3. Antibiotic therapy in not necessary when sampling pancreatic cysts <3cm in diameter.

4. All pancreatic cysts, regardless of size should be evaluated with EUS + aspiration

5. The presence of macrophages and histiocytes in a cystic lesion suggests a serous cyst neoplasm

6. High CEA levels increase the diagnostic likelihood of a malignant mucinous cyst

7. ERCP sampling for cytology has a higher yield than EUS sampling, but higher complication rate

8. Mucus in mucinous cysts can mimic cyst wall nodules that can be seen in malignant cysts, a hypoechoic center favors mucus over true epithelial nodules

9. Cytology is an insensitive way of diagnosing malignancy in cystic lesions of the pancreas

10. A 2cm cyst with a pancreatic duct of 1.2cm should undergo EUS and aspiration for analysis

11. Successful cyst ablation with ethanol and paclitaxel eliminates the risk of ductal adenocarcinoma.