Communication from the ASGE Standards of Practice Committee

GUIDELINE

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

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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).[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.[2]

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[3,4] 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.[5-7] 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.[8]

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) (Table 2). In addition, certain pancreatic tumors may contain cystic spaces or regions of cystic degeneration, such as solid-pseudopapillary neoplasms, cystic neuroendocrine tumors, and even ductal adenocarcinomas.[9] Recently, several

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TABLE 1. GRADE system for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕O
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕OO
Very low	Any estimate of effect is very uncertain.	⊕OOO

GRADE, Grading of Recommendations Assessment, Development and Evaluation.
Adapted from Guyatt et al.[1]

strategies and guidelines regarding the diagnosis and indications for resection or surveillance of mucinous cystic pancreatic neoplasms have been published elsewhere.[10-14] In a retrospective series of 851 individuals undergoing resection of pancreatic cystic neoplasms over 33 years, the most common pathologic diagnoses were IPMNs (38%), mucinous cystic neoplasms (23%), serous cystic neoplasms (16%), and cystic neuroendocrine neoplasms (7%).[15] Lesions that were identified incidentally accounted for an increasing proportion of resections over time (22% from 1978-1989 to 50% from 2005-2011). Symptomatic cystic neoplasms in this series typically presented with abdominal pain, pancreatitis, jaundice, weight loss, malabsorption, nausea, vomiting, early satiety, or a palpable abdominal mass.

DIAGNOSIS BY EUS

EUS morphology

Several EUS findings have been evaluated as diagnostic criteria for pancreatic cystic lesions.[16-27] 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%).[26] In a study among experienced endosonographers, 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 ($K = 0.43$).[28]

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 or smaller were malignant, and an additional 45% of lesions had malignant potential.[6] However, only 1 of 28 (3.5%) asymptomatic lesions <2 cm was malignant.[6] Certain EUS features are more predictive of particular types of cystic lesions. Multiple small (<3 mm) compartments within a cystic lesion (also called a microcystic lesion), suggest a serous cystic neoplasm with an accuracy of 92% to 96%,[23] and this feature is not seen in mucinous cystic neoplasms.[29] 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%.[24]

EUS imaging cannot reliably distinguish benign from malignant IPMNs.[20,24,25,30] 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.[31] 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.[10] 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.[10]

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.[32] 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.[33] 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.[34-36]

FNA

Cyst fluid sampled by EUS-guided-FNA (EUS-FNA) may be analyzed for cytologic, chemical, and/or molecular studies. Any solid component associated with a cystic lesion or regional lymph nodes can be aspirated for cytology or histology. A prospective multicenter study demonstrated a higher diagnostic yield when a solid component was present on EUS (odds ratio 2.48; $P = .028$; 95% confidence interval [CI], 1.1-5.6).[37] A dilated pancreatic duct also can be safely targeted for FNA when IPMN is suspected.[19,38] There is no standardized method for EUS-FNA of a cystic lesion, and any available gauge needle can be used. However, viscous mucinous fluid may be difficult to aspirate with smaller needles. Although it has been recommended to completely drain aspirated cystic lesions to potentially avoid infection, it is unclear if this practice is beneficial.[39] FNA of the cyst wall may provide additional cytologic material and can increase the diagnostic yield for mucinous lesions by as much as 37%.[40] Although the use of a core-biopsy needle for histology has shown utility in confirming a diagnosis of microcystic serous neoplasms,[41] this practice is rarely required because imaging alone is often diagnostic for these tumors. A recent study demonstrated that the addition of EUS-FNA to CT and magnetic resonance imaging increased the overall accuracy for diagnosing cystic pancreatic neoplasms by 36% and 54%, respectively.[42] However, given the suboptimal performance characteristics of cytology and carcinoembryonic antigen (CEA) and the very low prevalence of malignancy in cystic pancreatic neoplasms, controversy exists about which cysts should undergo EUS with or without FNA. At present, the utility of FNA appears greatest in patients with cysts containing the imaging features most associated with malignancy at surgical resection, namely an epithelial nodule or mass lesion, cyst size >3 cm, or main pancreatic duct dilation.[43-50]

Cytology

Two meta-analyses have evaluated the performance characteristics of EUS-FNA to distinguish mucinous from nonmucinous pancreatic cysts. The first included 376 patients from 11 studies (all of whom had a histopathologic diagnosis) and found that cytology from EUS-FNA aspirates had a pooled sensitivity of 63% (95% CI, 56%-70%) and specificity of 88% (95% CI, 83%-93%).[51] The second study included 1438 patients from 18 studies and used surgical histology or clinical follow-up of at least 6 months as the reference standard.[52] The pooled sensitivity and specificity for cytology in this study were 54% (95% CI, 49%-59%) and 93% (95% CI, 90%-95%), respectively.

Cytologic findings suggestive of a pseudocyst include macrophages, histiocytes, and neutrophils. The presence of mucin is suggestive of a mucinous neoplasm and is seen in 35% or more of cases.[21,26] Glycogen-rich cuboidal cells indicate a serous cystic neoplasm but are present only in approximately 10% of cases.[7,21] Overall, the diagnostic accuracy of cytology from EUS-FNA for cystic lesions ranges from 54% to 97%[18,19,21,26,38,53] and may be lower in smaller cysts.[21] Malignancy within a cystic neoplasm can be identified by cytology with 83% to 99% specificity, although reported sensitivities vary from 25% to 88%.[7,19,21,38,54-56] A cytology brush (EchoBrush; Cook Endoscopy, Winston-Salem, NC) passed through a 19-gauge needle was designed to improve the diagnostic yield of cyst fluid cytology obtained from EUS-FNA. However, use has been limited because of concerns regarding its low incremental value over standard EUS-FNA and potential increased risk of adverse events.[57-60]

Chemistries and tumor markers

Because of the limited sensitivity of cytology, cyst fluid may be analyzed for levels of amylase, lipase, and tumor markers such as CEA. Unfortunately, reported sensitivities and specificities of chemical analyses have broad ranges, making interpretation difficult.[21,26,61] A pooled analysis of 12 studies including 450 patients found that amylase levels <250 U/L virtually excluded (specificity 98%) the lesion as a pseudocyst.[62] A prospective, multicenter study of 112 pancreatic cysts diagnosed by surgical resection or biopsy found an optimal CEA cutoff of 192 ng/mL for differentiating mucinous from nonmucinous cysts, providing a sensitivity of 75% and a specificity of 84%.[26] When morphologic criteria (associated hypoechoic mass and/or macrocystic septations), cytology, and CEA levels (cutoff 192 ng/mL) were taken together, EUS could differentiate mucinous from nonmucinous lesions with 91% sensitivity and 31% specificity.[26] Subsequent studies have suggested that lower CEA cut-off levels (≤30 ng/mL) have increased sensitivity for identifying mucinous cysts without sacrificing specificity.[63] Higher CEA levels increase specificity for the diagnosis of a mucinous cyst but do not correlate with malignancy.[12,26,62] Conversely, a CEA <5 ng/mL in one study was seen in only 7% of mucinous cystic neoplasms and all serous cystic neoplasms.[29] A recent meta-analysis of aspirates from EUS-FNA found CEA to have a sensitivity of 63% (95% CI, 59%-67%) and specificity of 88% (95% CI, 83%-91%) for the identification of mucinous cystic tumors.[52] Other tumor markers studied have included CA 19-9, CA 125, CA 72-4, and CA 15-3, but none of these appear accurate enough to provide a definitive diagnosis.[26]

Cyst fluid DNA and molecular analysis

Analysis of molecular markers in pancreatic cyst fluid has been proposed to improve on the limitations in diagnostic accuracy by using cytology and chemical and/or tumor marker analysis alone. An initial study evaluated the role of molecular analysis in 113 patients and found that detection of a K-*ras* mutation was strongly associated with mucinous cysts and that a combined K-*ras* and allelic loss showed a specificity of 96% for malignancy.[64,65] Subsequent studies, however, found poor agreement between

TABLE 2. Characteristics of pancreatic cystic lesions

	Pseudocyst	IPMN	Mucinous cystic neoplasm
Clinical features	History of moderate to severe pancreatitis	History of pancreatitis, abdominal pain, or found incidentally	Usually found incidentally but can cause abdominal pain and a palpable mass if large
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 septated cyst; may have a solid component	Macrocystic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant
Fluid characteristics	Thin, muddy-brown	Viscous or stringy, clear	Viscous or stringy, clear
Fluid chemistries	Elevated amylase, low CEA	Elevated amylase and CEA	Elevated CEA, low amylase
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,[66] with comparable sensitivities and diagnostic accuracies.[66,67] The combination of CEA and DNA molecular analysis improved diagnostic accuracy compared to either test alone.[66,67] 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.[68] 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.[69] 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.[67] However, additional research is needed to determine the precise role molecular analysis of cyst fluid will play in evaluating pancreatic cystic lesions.

Emerging techniques for cyst 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).[70,71] 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.[72] Another study of 31 patients used this device to identify a superficial vascular network pattern seen only in serous cystic neoplasms.[73] This resulted in an overall accuracy in identifying serous cystic neoplasms of 87%, with a high rate of interobserver agreement (κ = 0.77).[73] 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.[74]

Adverse events from EUS

A recent ASGE guideline addresses adverse events associated with EUS and EUS -FNA.[75] In a systematic review of 51 studies, adverse events specific to EUS-FNA of pancreatic cystic lesions occurred in 2.7% of 909 patients.[76] 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.[77] The most common adverse events include abdominal pain,[77-79] pancreatitis,[76,77,79] and intracystic hemorrhage.[80,81] 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,[55] another retrospective study found only a single infection in 603 patients undergoing EUS-FNA of pancreatic cysts, including no infections in 60 patients who did not receive

TABLE 2. Continued

Serous cystic neoplasm	Cystic endocrine neoplasm	Solid pseudopapillary neoplasm	Ductal adenocarcinoma with cystic degeneration
Usually found incidentally but can cause abdominal pain and a palpable mass if large	May have clinical features of solid pancreatic endocrine neoplasm	Usually found incidentally; rarely causes abdominal discomfort	Presents with painless jaundice, abdominal/back pain or rarely pancreatitis
Microcystic with a "honeycomb" appearance; rarely has a macrocystic component; central calcification	Unilocular cyst occupies most of neoplasm	Solid and cystic components	Primarily solid mass with cystic spaces
Thin, clear to serosanguineous	Thin, clear	Bloody + necrotic debris	Bloody ± debris
Low CEA and amylase	Variable	Variable	Variable
Cuboidal epithelium that stains positive for glycogen	Monomorphic endocrine tumor cells; stains positive for chromagranin and synaptophysin	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin and a-1-antitrypsin	Malignant adenocarcinoma may be seen, but varying degrees of atypia may be present in the specimen
Almost none (rare reports)	Yes	Yes	Already present

antibiotic prophylaxis.[77] 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.[39] Nevertheless, current ASGE guidelines suggest administration of antibiotics for 3 to 5 days after EUS-FNA of a pancreatic cystic lesion.[82]

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.[83] 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.[33,54,83,84] A pancreaticoduodenal fistula extruding mucous is seen in up to 2% of IPMN cases and suggests malignant invasion.[85]

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.[85] 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.[85]

Pancreatoscopy 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%.[33] 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.[86] 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.[54] 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%).[87] Several reports have described pancreatoscopy by using a videoscope with narrow-band imaging or via a fiberoptic probe to obtain tissue or cytology.[88-91] 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.[95-97] 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

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

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