

## ASGE guideline: the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas

*This is one of a series of statements discussing the utilization of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy prepared this text. In preparing this guideline, a MEDLINE literature search was performed and additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts.*

*Guidelines for appropriate utilization of endoscopy are based on a critical review of the available data and expert consensus. Further controlled clinical studies are needed to clarify aspects of this statement, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations*

### INTRODUCTION

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; but often these lesions are found incidentally during abdominal imaging performed for unrelated reasons. Because of their radiographic appearance, pancreatic cystic neoplasms frequently are misclassified as pseudocysts.<sup>1,2,3</sup> Inflammatory pancreatic fluid collections (PFC), such as pseudocysts and pancreatic abscesses, arise as a complication of acute and chronic pancreatitis or pancreatic trauma, and may be amenable to endoscopic therapy. This guideline will discuss the role of EUS and ERCP in the evaluation and the management of cystic lesions and fluid collections of the pancreas.

### CYSTIC LESIONS OF THE PANCREAS

Cystic lesions of the pancreas consist of pseudocysts, congenital cysts (sometimes called simple cysts) and cystic neoplasms including serous cystadenomas, mucinous cystadenomas and cystadenocarcinomas, and intraductal papillary mucinous neoplasm (IPMN) (Table 1). Other pancreatic tumors may contain cystic spaces or regions of cystic degeneration, such as solid-pseudopapillary neoplasms, cystic endocrine tumors, and even ductal adenocarcinomas.<sup>4</sup> In a retrospective series of 212 cases, 63% had their cystic lesions identified during evaluation of signs and symptoms, whereas the remainder had their cysts found incidentally.<sup>2</sup> The most common symptoms and signs were abdominal pain, weight loss, back pain, jaundice, pancreatitis, a palpable mass, and postprandial fullness.<sup>2</sup> Even among asymptomatic patients, 17% had in situ or invasive cancer and 42% had a lesion with malignant potential.<sup>2</sup>

### DIAGNOSIS BY EUS

#### EUS morphology

Several EUS findings have been evaluated to diagnose pancreatic cystic lesions.<sup>5-14</sup> Small cyst size does not exclude malignancy; one series reported 20% of lesions 2 cm or smaller were malignant and 45% had malignant potential.<sup>2</sup> However, only one of 28 (3.5%) asymptomatic lesions smaller than 2 cm were malignant.<sup>2</sup> Certain features do appear to be more predictive in diagnosing particular types of cystic lesions. The finding of multiple small (<3 mm) compartments within a cystic lesion, also called a microcystic lesion, is suggestive of a serous cystadenoma, with an accuracy of 92% to 96%,<sup>12</sup> and is not seen in mucinous cystadenomas.<sup>15</sup> A cystic lesion without septations or solid components and seen within a pancreas having parenchymal abnormalities suggests a pseudocyst with a sensitivity of 94% and a specificity of 85%.<sup>13</sup>

A hypoechoic mass associated with a cyst was 83% sensitive and 95% specific for adenocarcinoma in one study, but this was less reliable in the presence of a diffusely dilated pancreatic duct, as is often seen in IPMN (sensitivity of 47% and specificity of 78%).<sup>8</sup> EUS

**TABLE 1. Characteristics of pancreatic cystic lesions**

	<b>Pseudocyst</b>	<b>IPMN</b>	<b>Mucinous cystadenoma</b>
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	Macrocytic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant
Fluid characteristics	Thin, muddy-brown	Viscous or stringy, clear	Viscous or stringy, clear
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 4 and 10.

IPMN, Intraductal papillary mucinous tumor.

cannot accurately determine the extent of involvement of IPMN and is not reliable in distinguishing malignant from benign forms of this neoplasm.<sup>9,13,14,16</sup> Intraductal US (IDUS) may suggest malignant IPMN by the presence of protruding lesions  $\geq 4$  mm.<sup>17</sup>

Areas of uncertainty likely reflect the only fair to moderate agreement among experienced endosonographers about the presence or the absence of the particular EUS findings or specific diagnoses.<sup>18</sup> Knowledge of a patient's clinical history may help improve the accuracy of EUS for diagnosing pseudocysts and IPMNs but not other types of cystic lesions.<sup>10</sup>

EUS findings may help identify those patients with mucinous lesions that have malignant potential who might benefit from surgical resection. One study found that the presence of any one of the following had a sensitivity of 91% but a specificity of 60% for detecting a lesion with malignant potential: (1) cyst-wall thickness greater than 3 mm, (2) intracystic compartments larger than 10 mm ("macroseptations"), (3) intramural masses, or (4) cystic dilatation of the main pancreatic duct.<sup>5</sup> Another study found the accuracy for detecting those lesions with malignant potential varied from 40% to 93%.<sup>18</sup> This suggests that, whereas EUS findings may add some diagnostic information, results may not be reliable enough for making management decisions.

## FNA

EUS-guided FNA (EUS-FNA) of pancreatic cystic lesions yields fluid for cytologic and chemical analyses. In addition, any solid components associated with a lesion

or regional lymph nodes can be aspirated for cytology or histology. Dilated pancreatic ducts can be safely targeted for FNA when IPMN is suspected.<sup>8,19</sup> There is no standardized method for EUS-FNA of a cystic lesion. Both 19- and 22-gauge needles have been used. Aspirated cyst contents may be submitted for cytologic, chemical, and/or tumor marker analysis. An effort should be made to completely drain the cystic lesion, potentially to avoid infection. FNA of the cyst wall may provide additional cytologic material. Aspirated material can be stained for glycogen with a periodic acid-Schiff (PAS) stain and stained for mucin by using PAS, alcian blue, or mucicarmine stains (Table 1). FNA biopsy specimens also can be placed in formalin for histologic analysis.<sup>20</sup> In one study, this provided positive results in 10 of 10 IPMNs.<sup>20</sup>

## Cytology

FNA can provide material for a cytologic diagnosis in up to 80% of cases of pancreatic cystic lesions.<sup>7,8,10,19,21</sup> Findings suggestive of a pseudocyst include macrophages, histiocytes, and neutrophils. The presence of mucin indicates a mucinous neoplasm and is seen in 35% or more of cases.<sup>10,22</sup> The presence of glycogen-rich cuboidal cells indicates a serous cystadenoma and is present in 10% or more of cases.<sup>3,10</sup> Overall, the accuracy for diagnosing various cystic lesions by EUS-FNA is 54% to 97%.<sup>7,8,10,19,21,22</sup> FNA of small cysts may have a lower yield than that of larger cysts.<sup>10</sup> Malignancy within a cystic neoplasm can be identified by cytology with 83% to almost 100% specificity, although reported sensitivities vary from 25% to 88%.<sup>3,8,10,19,20,23</sup>

Serous cystadenoma	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 sero sanguinous	Thin, clear	Bloody + necrotic debris	Bloody ± debris
Cuboidal epithelium that stains positive for glycogen	Monomorphic endocrine tumor cells; stains positive for chromogranin and synaptophysin	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin and $\alpha$ -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

### 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 carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 (Table 2). Unfortunately, reported sensitivities and specificities of chemical analyses have broad ranges making interpretation difficult.<sup>10,22,24</sup>

One prospective, multicenter study of 112 cysts diagnosed by surgical resection or biopsy found an optimal CEA cutoff of 192 ng/mL for differentiating mucinous tumors from other cystic lesions, providing a sensitivity of 75% and a specificity of 84%.<sup>22</sup> Malignant tumors tend to have the highest levels of CEA, but there are no published cutoff values that provide sufficient accuracy for clinical use.<sup>3,10,22</sup> CEA < 5 ng/mL in one study was seen in 7% of mucinous cystadenomas and all serous cystadenomas.<sup>15</sup> Other tumor markers studied have included CA 19-9, CA 125, CA 72-4, and CA 15-3 (Table 2), but none of these appear accurate enough to provide a definitive diagnosis.

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. Cytology and CEA without morphologic criteria had an improved specificity (71%), but sensitivity fell to 82%.<sup>22</sup>

### Complications

Complications specific to EUS-FNA of pancreatic cystic lesions include pancreatitis (2%-3%),<sup>25</sup> hemorrhage within the cyst (<1%)<sup>8,10,22</sup> and infection (<1%).<sup>10,21,25</sup> The prevailing opinion is to administer an antibiotic, e.g., a

fluoroquinolone, during and for 3 to 5 days after EUS-FNA of a pancreatic cystic lesion.

### DIAGNOSIS BY ERCP

Inspection of the duodenal papillas, pancreatography, and pancreatoscopy are valuable tools in the evaluation of IPMN and cystic neoplasms of the pancreas. In IPMN, duodenoscopy may reveal the highly specific finding of mucus extruding from a patulous pancreatic orifice.<sup>26</sup> This pathognomonic finding is seen in 20% to 55% of patients with IPMN and was seen more frequently in malignant disease in some, but not all, studies.<sup>17,20,26,27</sup> A pancreaticoduodenal fistula extruding mucous is seen in 2% of IPMN cases and suggests malignant invasion.<sup>28</sup>

Pancreatographic findings in the setting of cystic neoplasms may include displacement of the main pancreatic duct, strictures, and obstruction. In the absence of other risk factors for ductal stenosis, such as chronic pancreatitis or pancreatic trauma, a narrowed pancreatic duct suggests malignancy.<sup>28</sup> Communication with the main pancreatic duct suggests either a pseudocyst or an IPMN and is rare in mucinous or serous cystadenomas. Rarely, a mucinous cystadenocarcinoma that has formed a fistula may also communicate with the main pancreatic duct. 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 main pancreatic duct (seen in over 70% of cases) or focal side-branch dilatation (seen in over 50% of cases). Filling defects in the main pancreatic duct caused by mucus may

**TABLE 2. Performance of measurements of fluid chemistries and tumor markers for specific diagnoses of pancreatic cystic lesions**

	<b>Chemistry/ tumor marker</b>	<b>Cutoff value</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>
Pseudocysts	Amylase	> 5000 U/mL	61-94	58-74
	Lipase	> 2000 U/mL	41-100	56-59
Serous cystadenomas	Amylase	< 5000 U/mL	87-100	59-77
	Lipase	< 2000 U/mL	78-86	52-86
	CEA	< 5 ng/mL	54-100	77-86
Mucinous neoplasms	Amylase	> 5000 U/mL	42	26
	Lipase	> 2000 U/mL	50	16
	CEA	> 400 ng/mL	13-50	75-100
	CEA	> 192 ng/mL	75	84
	CA19-9	> 50,000 U/mL	15-75	81-90
	CA19-9	> 2900 U/mL	68	62
	CA125	> 9 ng/mL	83	37
	CA72-4	> 7 ng/mL	80	61
CA15-3	> 121 ng/mL	19	94	

be distinguished from stones by their transient nature and movement when passed with a catheter or a guidewire. Persistent filling defects that represent polypoid lesions also may be seen.

Pancreatoscopy in IPMN may be facilitated by an enlarged papillary opening and provides direct visualization of mucus, stones, or tumor. The extent of disease may be determined, and directed biopsy specimens may be obtained. One study found the combination of pancreatoscopy and intraductal US in IPMN capable of distinguishing benign from malignant disease with an accuracy of 88%.<sup>17</sup>

Tissue sampling in the setting of IPMN includes the evaluation of aspirated mucus, brush cytology, and/or biopsy specimens of fixed filling defects and strictures, and random biopsy specimens of dilated duct walls. In one study, transpapillary biopsy with standard or pediatric-sized forceps yielded positive specimens in 11 of 13 patients.<sup>20</sup>

Pancreatic-duct fluid can be collected for cytologic examination during ERP after secretin stimulation.<sup>29</sup> In one study, this technique could distinguish malignant from benign IPMN, with a 91% sensitivity and a 100% specificity.<sup>29</sup> Another study, however, found an accuracy of 53% for ERCP alone and 60% with the inclusion of cytologic analysis of aspirated fluid.<sup>30</sup>

## ENDOSCOPIC TREATMENT OF CYSTIC LESIONS

There currently are no accepted endoscopic therapies for cystic neoplasms of the pancreas. However, there is

a role for the endoscopic drainage of inflammatory pancreatic-fluid collections (PFC).

## INFLAMMATORY PFCs

PFC arise as a complication of acute and chronic pancreatitis, pancreatic trauma, and pancreatic surgery, and include acute fluid collections, acute and chronic pancreatic pseudocysts, pancreatic abscesses, and pancreatic necrosis (Table 3). The majority of acute fluid collections will resolve spontaneously. ERCP before percutaneous or surgical drainage allows pancreatic anatomy to be defined and guides therapy.<sup>31,32</sup> When done as part of preoperative planning, ERCP should be done shortly before surgery because of the risk of infecting the PFC.

The indications for drainage of a PFC are symptom driven. Endoscopic drainage can be considered as an alternative to surgical or percutaneous drainage for pseudocysts, infected pseudocysts, and in selected cases of organized pancreatic necrosis after pancreatitis. Pseudocyst drainage should be considered for symptomatic lesions (abdominal pain, gastric outlet obstruction, early satiety, weight loss, or jaundice), infected cysts, or enlarging cysts. Prophylactic antibiotics are indicated.<sup>33</sup> Special care must be taken to avoid drainage of cystic neoplasms, pseudoaneurysms, duplication cysts, and other noninflammatory fluid collections. Large pseudocyst size itself is not an indication for drainage, although pseudocysts larger than 6 cm tend to be symptomatic.<sup>34,35</sup> Drainage of organized

**TABLE 3. Definitions of inflammatory pancreatic fluid collections**

<b>Term:</b>	<b>Definition:</b>
Acute fluid collection	Collection of enzyme-rich pancreatic fluid occurring early (within 48 h) in the course of acute pancreatitis located in or near pancreas; always lacks well-defined wall of granulation tissue or fibrous tissue; rarely require drainage
Acute pseudocyst	Collection of pancreatic fluid enclosed by wall of nonepithelialized granulation tissue that arises as a consequence of acute pancreatitis; requires at least 4 wk to form and is devoid of significant solid debris
Chronic pseudocyst	Collection of pancreatic fluid enclosed by wall of fibrous or granulation tissue, which arises as a consequence of chronic pancreatitis
Pancreatic necrosis (early)	Diffuse or focal area of nonviable pancreatic parenchyma >30% of the gland by contrast-enhanced CT, which is typically associated with peripancreatic fat necrosis
Organized (late) pancreatic necrosis	Evolution of acute necrosis to a partially encapsulated, well-defined collection of pancreatic fluid and necrotic debris
Pancreatic abscess	Infected circumscribed intra-abdominal collection of pus, usually in proximity to pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma

sterile pancreatic necrosis can be considered for patients with refractory abdominal pain, gastric outlet obstruction, ongoing systemic illness, anorexia, and weight loss lasting more than 4 weeks after the onset of acute pancreatitis. The management option chosen should be based upon local expertise and the severity of the patient's comorbidities. Infected pancreatic necrosis is considered an indication for drainage. Infected necrosis may not be distinguishable clinically from sterile necrosis and may require percutaneous FNA to determine whether the necrosis is infected.

## ENDOSCOPIC METHODS OF DRAINAGE

The endoscopic approaches for drainage of pseudocysts are transpapillary,<sup>36,37</sup> transmural,<sup>38</sup> or combined transpapillary and transmural.<sup>35,39</sup> The decision to proceed with one approach over another is based upon the anatomic relationship of the collection to the stomach or to the duodenum, the presence of ductal communication with the pseudocyst, and the size of the collection.

If the collection communicates with the main pancreatic duct, placement of a pancreatic endoprosthesis with or without pancreatic sphincterotomy may provide adequate therapy.<sup>40,41</sup> The proximal end of the stent (toward the pancreatic tail) may be placed directly into the collection or may be placed across the area of duct disruption. Recent data suggests that complete bridging of the leak is the best approach.<sup>42</sup> The advantage of the transpapillary approach over the transmural approach is the avoidance of bleeding or perforation that may occur with transmural drainage. The disadvantage of transpapillary drainage is that pancreatic stents may induce scarring of the main pancreatic duct in patients whose pancreatic duct is otherwise normal and may not adequately drain large cysts.<sup>43,44</sup>

Transmural drainage of PFCs is achieved by placing one or more large-bore stents through the gastric or the duodenal wall. Predrainage EUS evaluation has been advocated to limit complications, although this has not been proven in a prospective, randomized trial.<sup>45</sup> EUS can be used to mark the optimal puncture site or to perform EUS-guided cyst puncture and drainage.<sup>46,39,47,48,49</sup> The lack of EUS availability should not preclude transmural drainage except in the following instances: a small "window" of entry based upon CT findings, especially in the absence of an endoscopically defined area of extrinsic compression, or unusual location<sup>50</sup>; documented intervening varices; and prior failed transmural entry when using non-EUS-guided techniques.

When EUS guidance is not used, the PFC is entered at the point of maximum extrinsic compression, as seen endoscopically, with or without prelocalization when using a sclerotherapy needle.<sup>51</sup> Aspiration of fluid and/or injection of water-soluble contrast confirms accurate localization. Puncture of the PFC is achieved by using either a needle knife with electrocautery or a large-caliber needle.<sup>38</sup> A guidewire is placed that allows balloon dilation of the tract and the placement of one or more stents. Enlarging the transmural tract with a sphincterotome appears to increase the risk of bleeding.<sup>52</sup>

After uncomplicated endoscopic drainage of non-infected pancreatic pseudocysts, a short course of oral antibiotics is administered. Most patients do not require hospitalization.<sup>53</sup> A follow-up CT scan is obtained 4 to 6 weeks after the drainage procedure, and the internal stents are removed endoscopically after documented radiographic resolution. In patients with chronic pancreatitis who have undergone transmural drainage, an attempt should be made to correct endoscopically any underlying ductal obstruction that may have led to the pseudocyst, to reduce the recurrence rate.

To drain organized pancreatic necrosis, a transmural endoscopic approach is recommended to allow evacuation of solid material. The techniques used and the postprocedure care of the patient are more extensive than most other endoscopic procedures and require highly skilled endoscopists and support staff.<sup>54,55</sup>

## COMPLICATIONS OF ENDOSCOPIC THERAPY OF PFCs

Serious complications may arise after endoscopic drainage of PFCs and include bleeding, perforation, infection, pancreatitis, aspiration, stent migration/occlusion, pancreatic-duct damage, complications of sedation, and death. It is recommended that endoscopic drainage of PFCs be performed only with the availability of surgical and interventional radiology support.<sup>53</sup> Infectious complications usually occur from inadequate drainage of fluid and/or solid debris. If endoscopic drainage was performed by the transpapillary route, stent exchange, increasing the stent size, or conversion to a transmural approach may resolve the infection.

## OUTCOMES OF ENDOSCOPIC THERAPY OF PFCs

Outcomes after attempted endoscopic therapy depend on the type of collection drained<sup>53</sup> and the experience of the endoscopist.<sup>56</sup> It must be emphasized that there are no prospective studies that compare endoscopic drainage with conservative (medical) therapy, percutaneous drainage, or surgical drainage. Pancreatic pseudocysts can be successfully drained in 82% to 89% of cases, with complication rates occurring in 5% to 16% and recurrence rates ranging from 4% to 18%.<sup>42,54,57</sup>

Experience with endoscopic drainage of organized pancreatic necrosis is more limited but has achieved successful nonsurgical resolution in 31 of 43 patients (72%).<sup>53,54</sup> One report described transmural drainage of pancreatic abscesses, with successful resolution in 10 of 11 abscess cavities, and with only self-limited bleeding occurring in one patient.<sup>58</sup>

## SUMMARY

For the following points: (A), Prospective controlled trials. (B), Observational studies; (C), Expert opinion.

- Cystic lesions of the pancreas, even when found incidentally, may represent malignant or premalignant neoplasms and require diagnostic evaluation regardless of size. (B)

- EUS findings by themselves are not accurate enough to definitively diagnose the type of cystic lesion of the pancreas or to determine its malignant potential. (B)

- Cytologic analysis of cyst fluid obtained by EUS-FNA lacks sensitivity but has high specificity for mucinous cystic neoplasms and malignancies. (B)

- Staining for mucin, and possibly for glycogen, should be performed in the evaluation of pancreatic cyst fluid. (B)

- Measurement of cyst-fluid amylase, lipase, and various tumor markers may provide clinically useful information about the cyst but cannot provide a definitive diagnosis or determine with certainty whether that lesion is malignant. (B)

- FNA of a cystic lesion of the pancreas generally is safe but carries a 2% to 3% risk of pancreatitis. (B)

- Prophylactic antibiotics should be administered to patients undergoing EUS-FNA of cystic lesions of the pancreas, ERCP in patients with cystic lesions, or for patients undergoing endoscopic drainage procedures. (C)

- During ERCP for evaluation of a cystic lesion of the pancreas: (1) a patulous pancreatic orifice exuding mucus is specific but is not sensitive, for IPMN (B); (2) tissue sampling by brushing and/or biopsy and/or pancreatic fluid collection should be performed whenever possible. (B)

- There currently are no established endoscopic therapies for cystic neoplasms of the pancreas. (C)

- ERCP should be considered before surgical or percutaneous drainage of pancreatic pseudocysts to optimize patient selection. (C)

- Endoscopic drainage of PFCs should only be done when there is a high level of certainty that the collection is inflammatory from pancreatitis. (B)

- EUS should be considered before transmural drainage of PFCs. (C)

- Endoscopic drainage of symptomatic pancreatic pseudocysts appears to have outcomes similar to surgical drainage. (B)

- Endoscopic drainage of organized pancreatic necrosis remains controversial but is a viable nonsurgical option in selected patients. (C)

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