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# ACG Practice Guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts

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**The diagnosis and management of pancreatic cystic lesions is a common problem. At least 1% of hospitalized patients at major medical centers will have a pancreatic cystic lesion on cross sectional imaging. Up to a quarter of all pancreata examined in an autopsy series contained a pancreatic cyst, 16% of which were lined by an "atypical" epithelium and 3% of which had progressed to carcinoma-in-situ (high grade dysplasia). in the past, it was thought these cystic lesions were benign, but increasing evidence points to the cystic lesions as being the origin of some pancreatic malignancies.**

**The most important clinical tools in the diagnosis and management of pancreatic cystic lesions are cross sectional imaging, endoscopic ultrasound, and cyst fluid analysis. The most important differential diagnosis is distinguishing mucinous (pre-malignant) and non-mucinous cystic lesions. The findings of a macrocystic lesion containing viscous fluid rich in CEA are supportive of a diagnosis of a mucinous lesion. Serous lesion are the most common non-mucinous cyst and are characterized by a microcystic morphology, non-viscous fluid and a low concentration of CEA in the cyst fluid.**

**The following document includes a description of neoplastic pancreatic cysts, a critical review of relevant diagnostic tests, and a discussion of treatment options. We have proposed a set of guidelines for the diagnonis and management of patients with neoplastic pancreatic cysts. The guidelines are based on published data backed by an analysis of the quality of the data and are designed to address the most frequent and important clinical scenarios. In addition to providing a summary of the diagnostic data, we offer diagnostic and management suggestions based on 13 common clinical problems. Although the field is rapidly evolving, a set of core principles is provided based on a balance between the risk of malignancy and the benefit of pancreatic resection.**

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## INTRODUCTION

Pancreatic cysts are receiving increased attention due to widespread use of high-resolution noninvasive abdominal imaging. While there has been increased awareness of these lesions, their natural history and optimal management is unclear. To address some of these issues, guidelines for the diagnosis and management of pancreatic cysts have been developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. These guidelines have been developed to assist clinicians in managing patients with pancreatic cysts. Alternative strategies to those described may be best for select patients, based on their unique circumstances.

The following guidelines are based on a critical review of the world's available scientific literature identified in a PubMed search on February 1, 2006. These guidelines are intended to apply to adult and not pediatric patients. They are focused on differentiating (a) premalignant and malignant pancreatic cysts, and (b) pancreatic cysts with malignant potential from those without.

Most pancreatic cysts are detected incidentally when noninvasive abdominal imaging is performed for unrelated indications. At least 1% of inpatients in a major medical center at any one time are likely to have a pancreatic cyst detectable by CT or MRI, of which more than half are neoplastic (1). Up to a quarter of all pancreata examined in an autopsy series contained a pancreatic cyst, 16% of which were lined by an "atypical" epithelium and 3% of which had progressed to carcinoma *in situ* (high-grade dysplasia) (2).

Among pancreatic cysts, pseudocysts are most likely to be symptomatic, while intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) are the most prevalent (and usually asymptomatic) pancreatic cysts (3).

A patient with a pancreatic cyst strongly suspected to be benign without malignant potential may be managed expectantly. A patient with a pancreatic cyst strongly suspected to be malignant may be managed surgically. A patient with a pancreatic cyst strongly suspected to be benign with malignant potential (precancerous) may be managed expectantly or surgically. Emerging data support observation as the preferred approach to managing patients with small incidental cysts (4), but comprehensive data are lacking on the natural history of such lesions, which prevents confident calculations of the risk and benefit of competing management strategies.

**Table 1.** WHO Histological Classification of Neoplastic Pancreatic Cysts

| |
|---|
| Serous cystic tumors |
| Serous cystadenoma |
| Serous cystadenocarcinoma |
| Mucinous cystic tumors |
| Mucinous cystadenoma |
| Mucinous cystadenoma with moderate dysplasia |
| Mucinous cystadenocarcinoma |
| Noninfiltrating |
| Infiltrating |
| Intraductal papillary mucinous adenoma |
| Intraductal papillary mucinous neoplasm with moderate dysplasia |
| Intraductal papillary mucinous carcinoma |
| Noninfiltrating |
| Infiltrating |
| Solid pseudopapillary tumors |

*Adapted from* Kloppel G SE, Longnecker DS, Capella C, Sobin LH. Histological typing of tumors of the exocrine pancreas. World Health Organization International Histological Classification of Tumors. Berlin: Springer-Verlag, 1996.

The following document includes a description of neoplastic pancreatic cysts, a critical review of relevant diagnostic tests, and a discussion of treatment options, followed by guidelines for the diagnosis and management of patients with neoplastic pancreatic cysts. A discussion of the management of pancreatic pseudocysts is beyond the scope of this guideline, but is included in the ACG's guideline on the management of acute pancreatitis.

Data regarding the natural history and clinical impact of diagnostic and therapeutic interventions in patients with pancreatic cysts remain limited. Therefore, preferred strategies for evaluating and managing patients with pancreatic cysts remain in evolution. These guidelines are based on published data and an analysis of its quality, plus expert opinion and the authors' experience when data were lacking. They are designed to address in a practical fashion the most frequent and most important clinical scenarios encountered when caring for patients with pancreatic cysts.

## NEOPLASTIC PANCREATIC CYSTS

The WHO histological classification of neoplastic pancreatic cysts is provided in Table 1. Table 2 summarizes the salient features of these lesions followed by a discussion of individual categories.

## INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Intraductal papillary mucinous neoplasm (IPMN) is an intraductal papillary neoplasm affecting men and women equally, which exhibits variable cellular atypia, secretes mucin, and causes dilation of the pancreatic ducts (5). IPMN is usually located in the head of the pancreas, may involve the main pancreatic duct or side branches of the pancreatic duct, is often multifocal or diffuse, and can extend microscopically from the recognized lesion. IPMN is classified histologically as adenoma, borderline, or carcinoma. The natural history of IPMN is not clear, but an interval of 5 yr has been observed between adenoma and transformation to invasive carcinoma

**Table 2.** Key Features of Neoplastic Pancreatic Cysts

| | Intraductal Papillary Mucinous Neoplasms | Mucinous Cystic Neoplasms | Serous Cystadenomas | Solid and Pseudopapillary Tumors |
|---|---|---|---|---|
| Sex distribution | M = F | F > M | F > M | F > M |
| Historical age of presentation | 7th decade | 5th to 7th decade | 7th decade | 2nd and 3rd decade |
| Clinical presentation | Incidental, abdominal pain, pancreatitis, symptoms or signs of malabsorption | Incidental, abdominal pain, or palpable mass | Usually incidental, rarely abdominal pain or palpable mass | Usually incidental, rarely abdominal pain or palpable mass |
| Morphology/imaging characteristics | Dilated main pancreatic duct or pancreatic duct branches; solid component, if present may suggest malignancy | Unilocular cyst. Septations and wall calcifications may be present. Solid component, if present may suggest malignancy | Microcystic/honeycomb appearance typical. Oligocystic appearance less common | Solid and cystic mass |
| Fluid characteristics | Usually thick | Usually viscous | Thin, if sufficient fluid aspirated from a dominant cyst | Often bloody |
| Cytology | Stains positive for mucin. Columnar cells with variable atypia; yield <50% | Stains positive for mucin. Columnar cells with variable atypia; yield <50% | Cuboidal cells stain positive for glycogen; yield <50% | Characteristic branching papillae with myxoid stroma; yield very high from solid component. |
| Accuracy of cyst CEA (ng/mL) | >192, 0.79 area under curve on receiver operator characteristic* | | <5, 67% | |
| Malignant potential | Yes | Yes | No | Yes |
| Treatment | Resection for main duct IPMN and resection or surveillance for branch duct IPMN depending upon the clinical situation | Resection is generally recommended in appropriate candidates | No surveillance or treatment unless symptomatic | Resection |

*The performance characteristics of fluid CEA level in IPMN and mucinous cystadenoma have not been studied separately.
M = male; F = female; CEA = carcinoembryonic antigen.

**Table 3.** Ratings of Evidence Used for This Guideline

| Ratings of the Quality of Evidence | |
|---|---|
| Level 1 | Strong evidence from at least one published systematic review of multiple well-designed randomized controlled trials |
| Level 2 | Strong evidence from at least one published well-designed randomized controlled trial |
| Level 3 | Evidence from published well-designed single group, cohort, time series or matched case-controlled studies |
| Level 4 | Evidence from well-designed nonexperimental studies from more than one center or research group or opinion of respected authorities, based on clinical evidence, descriptive studies, or reports of expert consensus committees |

(6). Historically, IPMN was usually not diagnosed until the seventh decade of life (6), but is now being discovered at younger ages. The risk of malignancy being present at the time of diagnosis increases with older age, presence of symptoms, involvement of the main pancreatic duct, dilation of the main pancreatic duct over 10 mm, the presence of mural nodules, and size over 3 cm for side-branch IPMN. However, a measurable risk of malignant IPMN exists even in the absence of symptoms (3). Risk of recurrence following resection with curative intent is high in IPMN with invasive cancer (60–70%) but low in noninvasive disease (<10%) (7).

Historically, IPMN was diagnosed by endoscopic retrograde pancreatography (ERP). However, contrast-enhanced multidetector thin-cut computed tomography (CT) is the diagnostic test of choice (Fig. 1). When uncertainty persists, EUS may discriminate between diagnostic possibilities. EUS can identify focal or diffuse dilation of the pancreatic duct in the absence of chronic pancreatitis or obstructing mass, or multiple dilated pancreatic duct side branches (referred to as a "cluster of grapes"). Endoscopic visualization of mucus extruding from a patulous ampulla (referred to as a "fish mouth") supports the diagnosis. Compared with abdominal ultrasonography, CT, and ERP, EUS provides higher resolution imaging of the pancreatic duct and is more sensitive in detecting mural nodules (8). In addition, cytological analysis, determination of tumor marker concentrations, and molecular diagnostic evaluations from samples obtained by EUS-guided fine-needle aspiration (EUS-FNA) may further guide management (9, 10). In IPMN of the main pancreatic duct, intraductal ultrasound can help to determine its extent and identify parenchymal invasion. Pancreatoscopy, like ERCP, can distinguish main duct from side-branch IPMN, but in addition may identify papillary projections associated with malignant transformation, and determine the longitudinal extent of tumor (11). Secretin-stimulated magnetic resonance cholangiopancreatogram (MRCP) also provides excellent imaging of the pancreatic duct, including identification of communication between a cystic lesion and the main pancreatic duct, *e.g.*, in the case of branch-duct IPMN (12).

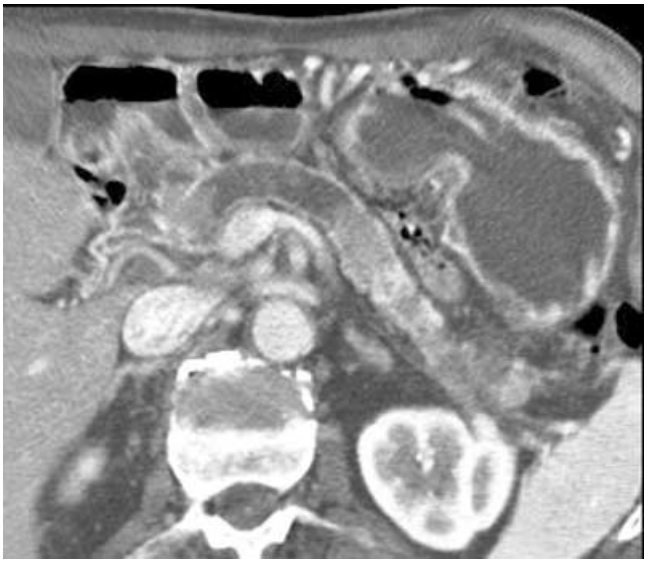

**Figure 1.** Contrast-enhanced CT scan shows a markedly dilated main pancreatic duct with pancreatic parenchymal atrophy. Multiple areas of soft tissue growth are seen within the pancreatic duct consistent with multifocal cancer arising in main duct IPMN.

Given the challenges of excluding malignancy with confidence, combined with uncertainty regarding the natural history of IPMN, resection is recommended for patients considered to be at acceptable risk for perioperative complications, especially in the main-duct variety. Firm recommendations as to the management of branch-duct IPMN cannot be made at this time and the evidence is still evolving. The approach will probably encompass a combination of surveillance and resection depending upon factors like the presence of symptoms, cyst distribution and size, and patient-related factors. IPMN can extend microscopically from the recognized lesion, so submission of frozen sections from the resection margin is appropriate when anticipating partial pancreatectomy.

## MUCINOUS CYSTIC NEOPLASMS

Like IPMN, mucinous cystic neoplasm (MCN) is a neoplasm which exhibits variable cellular atypia and secretes mucin (13, 14). In contrast to IPMN, MCN does not extend along the pancreatic ducts, demonstrates ovarian-like stroma (15), typically involves the tail or body of the pancreas, and affects women more often than men. MCN is classified as either mucinous cystadenoma or mucinous cystadenocarcinoma. Historically, MCN was discovered in the fifth to seventh decades of life, often in the evaluation of symptoms which heralded malignancy. As with IPMN, the natural history of MCN is not clear. However, the risk of malignancy appears to be less than that associated with IPMN of the main pancreatic duct (15).

Contrast-enhanced multidetector thin-cut CT is the test of choice to diagnose MCN, followed by EUS for further characterization or fluid analysis if the diagnosis remains in doubt. In contrast to IPMN, MCN do not communicate with the pancreatic duct. This feature may be useful in differentiating these lesions, *e.g.*, on ERCP or less invasively by

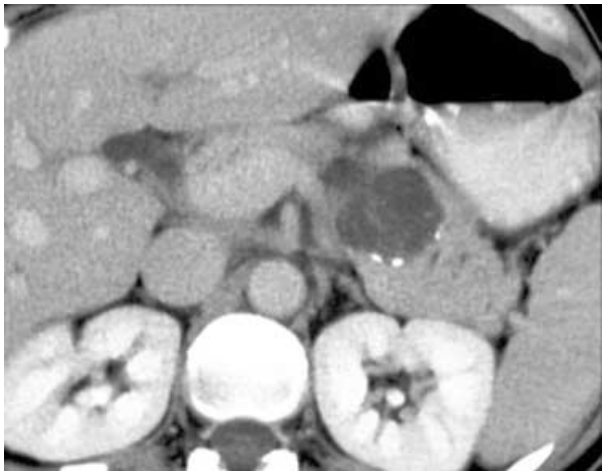

**Figure 2.** Contrast-enhanced CT scan of the abdomen reveals a hypodense well-circumscribed lesion in the body of the pancreas. Internal septations are seen as are calcifications in the wall-suggestive of a mucinous cystic neoplasm.

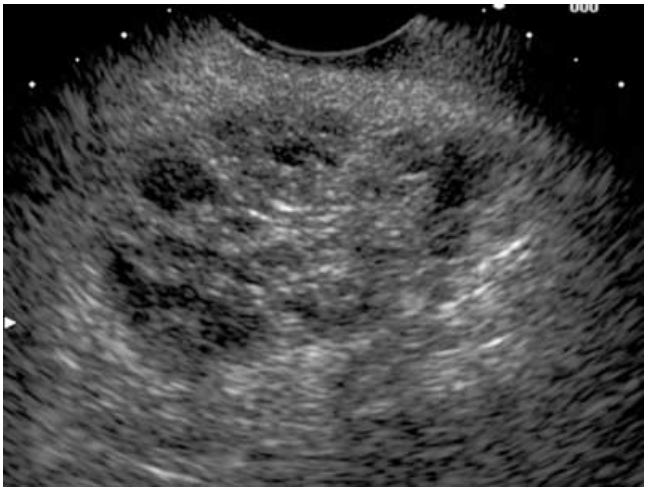

**Figure 3.** Convex linear array endoscopic ultrasound exam reveals a lobular multimacro and microcystic lesion in the pancreas with posterior acoustic enhancement reminiscent of a honeycomb. This imaging is classic for a serous cystadenoma/microcystic adenoma.

secretin-stimulated MRCP. MCN appear as septated cysts with a wall (16). The wall lining may contain eccentric calcifications in about 15% of patients (13) (Fig. 2). Malignant transformation is suggested by greater size (>2 cm), cyst wall irregularity and thickening, intracystic solid regions, an adjacent solid mass, and perhaps calcification of the cyst wall (14, 16).

EUS-FNA can be used to aspirate cyst fluid, to support the diagnosis of MCN (or IPMN, which possesses indistinguishable cyst fluid characteristics). CEA concentration in cyst fluid is elevated above 200 in approximately 80% of MCN (9), and cytological analysis reveals cuboidal or columnar epithelial cells in approximately 50% (17). Detection of malignant cells is diagnostic of a mucinous cystadenocarcinoma or malignant IPMN. Unfortunately, the sensitivity of cytology is suboptimal (<50%) (17).

Resection is recommended for patients with MCN considered to be at acceptable risk for perioperative complications, for the same reasons used to support this recommendation in IPMN. The prognosis is good in those that have not undergone malignant degeneration (18, 19).

## SEROUS CYSTADENOMA

Serous cystadenomas (SCA) are considered to be benign neoplasms originating from centro-acinar cells. SCA are usually comprised of multiple small fluid-filled cysts, and can arise in any region of the pancreas. Historically, SCA was diagnosed in women during their seventh decade of life, in evaluation of symptoms caused by continued enlargement of the neoplasm (20–22). Small, incidental SCA are now being identified more frequently. Occasionally, SCA manifests as an oligocystic lesion, which can be difficult to distinguish from MCN if it appears in the pancreas tail or body (23–25). On imaging, SCA appears as a focal, well-demarcated lesion. A central scar or "sunburst" calcification will be visible in 20% of SCA. EUS often demonstrates a honeycomb appearance (23) (Fig. 3). FNA of fluid within SCA microcysts can be challenging. When obtained, the fluid is usually thin, and cytological analysis reveals cuboidal glycogen-staining cells in 50% of cases (26–28). Given their benign nature, SCA should be resected only if symptomatic, or if the diagnosis remains in doubt.

## SOLID PSEUDOPAPILLARY TUMORS

Solid pseudopapillary tumors (SPT) of the pancreas are rare neoplasms with malignant potential diagnosed in young women. Historically, SPT were diagnosed in the evaluation of signs or symptoms of an abdominal mass, as the growth rate of SPT can be dramatic (29, 30). SPT often contain both solid and cystic components and occasionally calcifications (31, 32). Though not yet reported, SPT are now being discovered with increasing frequency at an asymptomatic stage. EUS-guided FNA cytological analysis reveals characteristic branching papillae with myxoid stroma, best seen in cell-block material (33). When identified, regardless of the stage, resection should be considered. Malignant SPT can be cured when completely excised, and prolonged survival can be seen even in the presence of metastatic disease (29, 30).

## LYMPHOEPITHELIAL CYST

Lymphoepithelial cysts (LEC) are rare cystic neoplasms lined by mature keratinizing squamous epithelium surrounded by a distinct layer of lymphoid tissue (34). LEC can be present in all age groups and are usually asymptomatic. Unlike the previously described cystic neoplasms, LEC occur most often in men (35). LEC display characteristic intracystic heterogeneous hyperechogenicity on ultrasound, hyperdensity on

precontrast CT, and granular hypointensity on T2-weighted MRI due to abundant intracystic keratinaceous material, which can usually be differentiating from other pancreatic cysts (36). If the diagnosis remains in doubt, FNA will usually reveal characteristic epithelial cells and small, mature lymphocytes in a background of keratinaceous debris, anucleate squamous cells, and multinucleated histiocytes (35).

## NON-NEOPLASTIC PANCREATIC CYSTS

Non-neoplastic pancreatic cystic lesions are reactive lesions without malignant potential, including pseudocysts and inclusion cysts. Diagnostic efforts focus on distinguishing these pancreatic lesions without malignant potential from those that with malignant potential.

## CYSTIC DEGENERATION IN SOLID PANCREATIC TUMORS

Varying degrees of cystic degeneration may be seen in solid pancreatic tumors including islet cell tumors, ductal carcinoma, and acinar cell cancer. Cystic islet cell tumors may be indistinguishable from a MCN or side-branch IPMN. In the authors' experience EUS-FNA cytology evaluation is almost always diagnostic in cystic islet cell tumors; however, this has not been rigorously studied.

## DIAGNOSTIC TESTS FOR PANCREATIC CYSTS (TABLE 3)

***Imaging (Level 2–3)***

The data available on the accuracy of preoperative imaging of pancreatic cysts is not encouraging especially when it comes to differentiating the various types of pancreatic cystic lesions at an incidental stage. This is primarily due to the morphologic overlap between the early MCN and IPMN, and benign neoplastic cysts and reactive cystic lesions (37). However, certain imaging characteristics have very good predictive value, *e.g.*, an asymptomatic microcystic lesion with honeycomb appearance and a central scar on cross-sectional imaging is very predictive of an SCA. Likewise, the infrequently seen peripheral eggshell calcification on CT is specific to a mucinous cystic neoplasm and may predict malignancy (38). On the other hand a unilocular cyst that communicates with the pancreatic duct and is found in the setting of acute pancreatitis may represent a pseudocyst or an IPMN.

A CT scan typically identifies the pancreatic cyst or is the first test ordered to evaluate it. The primary advantage of cross-sectional imaging such as CT scan and magnetic resonance (MR) of pancreatic cystic lesions over endoscopic techniques lies in determining the extent of malignant spread (39, 40). Features predictive of invasive carcinoma in IPMN by CT and other imaging studies include involvement of the main pancreatic duct, marked dilatation of the main pancreatic duct, diffuse or multifocal involvement, the presence of a large mural nodule or solid mass, large size of the mass, and obstruction of the common bile duct. The presence of intracystic mural nodules >3 mm in size on CT also suggests malignancy (39–41). MRP is more sensitive than ERCP in differentiating mural nodules from mucin globules (40–44). It also consistently demonstrates the internal architecture of the main duct and the extent of IPMN better than ERP.

ERP affords inspection of the duodenal papillae, pancreatography, and pancreatoscopy in the evaluation of pancreatic cysts. In IPMN, mucus is seen extruding from a patulous ampulla in 20–50% of patients and may be seen more frequently in malignant disease (45–48). A variety of findings are seen during pancreatography, unfortunately, most of which are nonspecific. Conflicting values are reported for the accuracy of tissue sampling (mucus aspiration, brush cytology, and biopsies) during ERP in IPMN (45, 48, 49). Pancreatoscopy in IPMN may be facilitated by an enlarged papilla and provides an assessment of disease extent and direct biopsies. The combination of pancreatoscopy and intraductal US in IPMN may detect malignancy with high accuracy (11).

The role of EUS lies in improved visualization of the cyst or pancreatic duct wall (looking for a small mass or mural nodules), or FNA.

A variety of studies have assessed the role of EUS imaging in discriminating benign pancreatic cysts from the mucinous varieties. For example, pseudocysts are more likely to be unilocular and exhibit internal echogenic debris and surrounding pancreatic parenchymal abnormalities suggestive of pancreatitis, whereas cyst septations, solid component, and mural nodules occur more frequently in cystic tumors (50). SCA on the other hand are more likely to have a honeycomb appearance or multiple small (<3 mm) cysts (50), although an oligocystic variety with fewer and larger cysts is less frequently encountered. Predicting malignancy in MCN and IPMN based on EUS imaging, however, remains impossible in the absence of advanced disease (9). EUS is also confounded by the apparent subjectivity of its interpretation. For example, a study evaluating the degree of agreement among experienced endosonographers for EUS diagnosis of neoplastic *versus* non-neoplastic pancreatic cystic lesions and the specific type of cystic lesion found fair interobserver agreement between endosonographers for diagnosis of SCA (kappa = 0.46) and presence or absence of a solid component (kappa = 0.43). Agreement among experienced endosonographers for diagnosis of neoplastic *versus* non-neoplastic, specific cyst type, and other EUS characteristics (presence of septations, parenchymal and ductal abnormalities, etc.) was poor (51). In summary, while EUS findings may add some diagnostic information, its greatest utility in the evaluation of pancreatic cystic lesions may be from data obtained via FNA.

One study (52) compared the accuracy of preoperative CT (25 patients), ERP (29 patients), and EUS (21 patients) to detect malignancy in 47 patients who were ultimately found to have IPMN and MCN (43% of whom had invasive carcinoma and 21% with carcinoma *in situ*). The overall accuracy of CT, ERP, and EUS in distinguishing between invasive and

**Table 4.** Pancreatic Cyst Fluid Tumor Markers

| | Cyst Types | Cytology | CEA | CA 19-9 | CA 72-4 | CA 15-3 | Mucin Antigens |
|---|---|---|---|---|---|---|---|
| Hammel 1995 (57), prospective, non-EUS aspirate | 50; 12 mucinous cysts, 7 SCA, 31 pseudocysts | | <5 ng/mL, 100% sensitive and 86% specific for SCA | >50,000 U/mL, 75% sensitive and 90% specific for mucinous cysts | | | |
| Sperti 1996 (59), retrospective, non-EUS aspirate | 48; 14 mucinous cysts, 7 SCA, 21 pseudocysts, 6 ductal cancers | 48% sensitive and 100% specific | | | 80% sensitive and 95% specific for mucinous cysts | | |
| Hammel 1997 (60), retrospective, non-EUS aspirate | 65; 9 MCA, 8 MCAC, 6 IPMN, 12 SCA, 30 pseudocysts | | >20 ng/mL, 82% sensitive and 100% specific for differentiating mucinous cysts from SCA<br>>300 ng/mL, 56% sensitive and 100% specific for differentiating mucinous cysts from pseudocysts | | | | Gastric mucins >50 U M1/mL, 78% sensitive and 100% specific for differentiating mucinous cysts from SCA<br>> 1,200 U M1/mL, 30% sensitive and 100% specific for differentiating mucinous cysts from pseudocysts |
| Sperti 1997 (61), retrospective, non-EUS aspirate | 24; 8 mucinous cysts, 6 SCA, 10 pseudocysts | 50% sensitive and 100% specific for mucinous cysts | 87% sensitive and 44% specific for mucinous cysts | | 87% sensitive and 94% specific for mucinous cysts | 50% sensitive and 94% specific for mucinous cysts | Carcinoma associated; 87% sensitive and 100% specific for mucinous cysts |
| Hammel 1998 (62), prospective, non-EUS aspirate | 91; 16 MCA, 14 MCAC, 16 SCA, 45 pseudocysts | | >400 ng/mL, 57% sensitive and 100% specific for mucinous cysts<br><4 ng/mL, 100% sensitive and 93% specific for SCA | | >40 U/mL, 63% sensitive and 98% specific for mucinous cysts | | |
| Frossard 2003 (26), prospective, EUS aspirate | 67; 17 mucinous cysts, 9 MCAC, 14 SCA, 6 pseudocysts | | | >50,000 U/mL, 15% sensitive and 81% specific for mucinous cysts and 86% sensitive and 85% specific for MCAC | | | |
| Brugge 2004 (9), prospective, multicenter, EUS aspirate | 112; 68 mucinous cysts, 7 SCA, 27 pseudocysts, 5 endocrine, 5 others | 34% sensitive and 83% specific for mucinous cyst, 22% sensitivity for malignancy in mucinous cysts | >192 ng/mL, 73% sensitive and 84% specific for mucinous cysts | >2,900 ng/mL; 68% sensitive and 62% specific for mucinous cysts | >7 ng/mL 80% sensitive and 61% specific for mucinous cysts | >121 ng/mL, 19% sensitive and 94% specific for mucinous cysts | |

IPMN = intraductal papillary mucinous neoplasia; SCA = serous cystadenoma; MCA = mucinous cystadenoma; MCAC = Mucinous cystadenocarcinoma.

**Table 5.** Cyst Fluid Amylase, CEA, and CA 19-9 Levels in Pancreatic Cysts

| Cyst Fluid Marker | Total Patients | Cystic Lesion | # of Cases | Median Value | Performance Characteristics |
|---|---|---|---|---|---|
| Amylase U/L | 155 | Pseudocyst | 60 | 11,000 | <250, 44% sensitive & 98% specific for SCA/ MCA/MCAC |
| | | SCA | 32 | 250 | |
| | | MCA | 32 | 8,000 | |
| | | MCAC | 31 | 150 | |
| CEA ng/mL | 332 | Pseudocyst | 125 | 10 | <5, 50% sensitive & 95% specific for SCA/pseudocyst |
| | | SCA | 79 | 3 | |
| | | MCA | 64 | 400 | >800, 48% sensitive & 98% specific for MCA/MCAC |
| | | MCAC | 64 | 2,000 | |
| CA 19-9 U/L | 136 | Pseudocyst | 66 | 4,000 | <37, 19% sensitive & 98% specific for SCA/pseudocyst |
| | | SCA | 24 | 500 | |
| | | MCA | 24 | 15,000 | |
| | | MCAC | 22 | 20,000 | |

CEA = carcinoembryonic antigen; SCA = serous cystadenoma; MCA = mucinous cystadenoma; MCAC = mucinous cystadenocarcinoma.
A variety of other markers have also been evaluated in pancreatic cyst fluid with reported yield that varies significantly. Some of the salient studies have been summarized in Table 4. In situations in which duplication of the patient populations may have occurred across reports, only the most recent reports have been included.

noninvasive tumors was less than 80% for each of the imaging studies evaluated. Differentiating cysts with malignant potential from benign cystic lesions by imaging techniques is suboptimal.

### *EUS-FNA (Level 2)*

EUS-FNA of pancreatic cysts is performed using a method similar to that used for solid masses. One distinction, however, is that usually a single pass is performed with a needle to aspirate fluid and attempt to sample the cyst wall. A variety of needles are available and their use should be tailored to the lesion and clinical situation. Principles of FNA for suspected malignant cytology evaluation are similar to other cancers; targeting the highest stage lesion, *e.g.*, liver metastasis, nonregional and regional lymph nodes near the gastroduodenal lumen, solid component/mural nodule, and fluid aspiration, in that order. In addition, fluid aspiration for tumor markers, chemical analysis, and molecular analysis, may be performed. Typically a single pass is made into the cyst cavity with intent to aspirate all the fluid for analysis; this is often not feasible if the fluid is thick. It is accepted practice to administer IV antibiotics (*e.g.*, ciprofloxacin 400 mg) prior to cyst aspiration followed by oral antibiotics for 3 days to prevent infection. Controlled studies to support this practice are lacking. Subjecting pseudocysts with internal debris, organized necrosis, etc., to FNA in particular should be avoided to prevent introducing an infection.

### *Cytology (Level 2)*

A number of studies have reported varying accuracy of pancreatic cyst EUS-FNA cytology, but the overall accuracy is around 50% (9, 26, 45, 53–55). The yield in smaller pancreatic cysts may be lower still (26). Findings suggestive of a pseudocyst include macrophages, histiocytes, and neutrophils. The presence of mucin indicates a mucinous pancreatic cyst and is seen in around a third of cases (26, 55). FNA from a minority of SCA may reveal the presence of glycogen-rich cuboidal cells (26). The cytologic diagnosis of a malignant cyst has a high specificity (approaching 100%), although the sensitivity is low (26, 45, 54, 55). The role of tru-cut biopsy to obtain a larger sample of the cyst wall has been evaluated in a small sample of patients and appears to be safe (56). Its impact on the diagnostic yield cannot be assessed at this time and requires further studies.

### *Chemistries and Tumor Marker Analysis (Level 2)*

Cyst fluid may be analyzed for levels of pancreatic enzymes and tumor marker analysis. Cyst fluid amylase, CEA, and CA 19-9 have been reported in a number of studies and the results of a recent meta-analysis have been summarized in Table 4. A broad range of sensitivities and specificities has been reported for these markers, making interpretation difficult. However, using certain cutoffs provides a high specificity, *e.g.*, an amylase <250 and CEA >800 essentially excludes a pseudocyst. Likewise, a CEA <5 and CA19-9 <37 virtually excludes a mucinous cyst (Table 5) (17, 26, 57).

A recent prospective, multicenter study of 112 cysts diagnosed by surgical resection or positive FNA found a CEA level of 192 ng/mL to be accurate in differentiating mucinous from nonmucinous pancreatic cysts (sensitivity 75% and specificity 84%) (9). This finding is also supported by a recent meta-analysis (17) and a cost-benefit analysis (58). The CEA level is not predictive of malignancy, however. The accuracy of fluid CEA level in predicting mucinous cystadenomas and IPMN separately instead of as a group (bunched together) has not been rigorously studied, and may be divergent.

**Table 6.** Common Clinical Scenarios and Frequently Asked Questions About Neoplastic Pancreatic Cysts

1. What are the initial imaging tests to evaluate a pancreatic cyst?
   A contrast-enhanced triphasic multidetector CT scan is the first test, which may be followed by an EUS depending on the clinical situation, *e.g.*, if FNA is desired for CEA level to differentiate a mucinous from nonmucinous cyst or to target a solid component.
2. Do incidental/asymptomatic pancreatic cysts need to be evaluated?
   Yes, most cysts detected today are asymptomatic and more than half of these are premalignant (MCN and IPMN). Furthermore, 1/6 asymptomatic cysts may be malignant. The absence of symptoms and size less than 2 cm supports indolence, especially in a unilocular cyst; however, the decision regarding surgery *versus* surveillance *versus* "no further follow-up" depends upon whether the cyst is mucinous (premalignant) or not. The most accurate test to make this diagnosis is the cyst aspirate CEA level.
3. But what if the asymptomatic cyst is very small, say 5 mm?
   A reasonable approach may be to repeat cross-sectional imaging in a year to assess for change. There are no firm guidelines for this situation but the chances of a very small incidental cyst (<1 cm) becoming malignant in a year are likely small. This is being supported by more recent studies (12, 66) and will likely be true especially in the case of side-branch IPMN. Hopefully, as we learn more about the natural history of these lesions a surveillance strategy will evolve. Increasing size or the development of symptoms should lead to further investigation.
4. Do all cystic neoplasms have to be evaluated with EUS?
   No, in some cases, the clinical and CT findings are sufficient to diagnose the type of cystic lesion with confidence. For example, a 50-yr-old healthy woman without a history of pancreatitis with a 3-cm thick-walled, septated cyst in the tail of the pancreas should not necessarily undergo an EUS. The clinical picture is sufficiently compelling for an MCN and she should undergo a distal pancreatectomy.
5. Is EUS imaging alone all we need for the evaluation of a pancreatic cystic lesion?
   No, determination of morphology based on EUS imaging is not specific enough. Cyst fluid needs to be evaluated with cytology and tumor markers.
6. Should all cysts be aspirated?
   No, in some situations aspiration is not indicated or may even be contraindicated. For example, the classic imaging of a lobulated microcystic lesion is diagnostic of a serous cystadenoma, and FNA will not add any information. Another example is an immature pseudocyst with internal debris. EUS-FNA will pose a risk of introducing an infection and is therefore contraindicated.
7. How many passes should be made to sample a cyst?
   Typically one pass is made to acquire fluid from a pancreatic cyst. During this pass the cyst wall may be targeted to increase the cytologic yield, but the data to support this practice are lacking. If there is an associated solid component then additional passes may be made for cytology evaluation.
8. Are all cysts occurring in the setting of pancreatitis pseudocysts?
   No, IPMN may present with pancreatitis. Only half of the cysts associated with pancreatitis may be pseudocysts (3). If a pancreatic cyst cannot be confirmed to have developed coincident with acute pancreatitis, then further evaluation is indicated. Following recovery from the attack of pancreatitis, the cyst should be evaluated with EUS, and in the absence of intracystic debris, should be aspirated for CEA, amylase, and cytology.
9. If minimal fluid is acquired during aspiration, for what analysis should it be sent?
   Frequently, pancreatic cyst aspiration may yield very little fluid due to either a small cyst or thick mucinous fluid. For thick fluid a larger bore needle may yield a bigger sample. Since cyst fluid CEA is the most sensitive indicator of a mucinous cyst, priority should be given to this test. The minimum fluid required for cyst fluid CEA analysis may vary between laboratories and should be confirmed. The remaining fluid can be divided for cytology exam and DNA analysis (0.4 mL required). In the setting of minimal fluid, some experts may opt to centrifuge the sample, submitting the supernatant for CEA analysis and the sediment for cytology. However, the affect of centrifugation on pancreatic cyst fluid CEA measurements has not been studied.
10. Can fluid analysis differentiate between MCN and IPMN?
    No, cyst aspirate cytology exam and CEA (or other tumor markers) are not helpful in differentiating between MCN and IPMN. In theory, cyst fluid amylase should be higher in IPMN, but this has not been rigorously examined.
11. Can cyst fluid analysis detect malignancy in a mucinous cyst?
    In the absence of a solid component with directed FNA, the yield of cytology for malignant cysts is low. Although very high CEA levels are sometimes seen in malignant cysts, in general, the CEA level does not differentiate between malignant and premalignant cysts. Cyst fluid DNA analysis has been shown to be an accurate marker of malignancy in mucinous cysts, but there is only one published study.
12. Should antibiotics be administered at the time of cyst FNA?
    It is accepted practice to administer a broad spectrum IV antibiotic (*e.g.*, a quinolone) at the time of cyst aspiration. For large or incompletely aspirated cysts or cysts with internal debris, oral antibiotics may be given for 3 days following the EUS-FNA. Data to support this practice are lacking.
13. If surgery is not undertaken, how should these lesions be followed?
    It depends on the lesion and the reason why resection is not performed. If the patient is not a good operative candidate (presumably with time the candidacy will not improve) then interval cross-sectional imaging may suffice, as long as the patient would be considered for resection if the imaging looked more concerning. On the other hand, in high-risk situations (main duct IPMN) or a healthy patient opting for surveillance there are no firm recommendations. Interval cross-sectional imaging, EUS with FNA, pancreatoscopy with sampling, and DNA analysis may be a part of this "surveillance." At the University of Pittsburgh, we perform interval EUS (every 6–12 months) and perform FNA for cytology evaluation and DNA analysis for MCN and side-branch IPMN. Main duct IPMN surveillance also may include pancreatic protocol CT scan and MRCP.

The threshold values identified as possessing the best discrimination between types of lesions may not be applicable to other institutions based on unappreciated differences between patient populations, methods of sampling, or techniques used to assay the samples.

### *DNA Analysis (Level 3)*

A detailed molecular analysis of pancreatic cyst aspirated fluid may be helpful in predicting malignancy. The presence of higher amounts (based on optical density at a 260–280 wavelength) of good quality (based on amount of amplifiable DNA on quantitative PCR) DNA and key tumor suppressor gene allelic loss along with k-ras point mutation correlates with the presence of malignancy in pancreatic cysts. An initial k-ras mutation followed by allelic loss is most predictive (∼90%) of a malignant pancreatic cyst (10). A 2-yr multicenter study is underway to verify these results and a report is expected in 2007.

### *Complication of Pancreatic Cyst EUS-FNA (Level 3)*

EUS-FNA of pancreatic cysts appears to have an overall complication rate of 2%. The most common complication is pancreatitis and most complications are mild (63). Infection is rare and data supporting the use of antibiotics to prevent FNA-related infection are lacking (level 4). Overall, consensus among experts supports this practice.

Intracystic hemorrhage may occur more frequently than recognized, but the clinical significance may not amount to more than transient abdominal pain (up to 6%) (64).

### *Endoscopic Therapy of Neoplastic Pancreatic Cysts (Level 4)*

Ablation of the epithelial lining of a pancreatic cystic neoplasm may decrease or eliminate malignant or metastatic potential in benign and malignant lesions, respectively. Ethanol lavage of MCN and IPMN cystic lesions appears to be safe, but its efficacy has not yet been determined (65).

## SUMMARY AND CONCLUSIONS (TABLE 6)

Pancreatic cystic lesions can be differentiated into mucinous and non-mucinous types through the use of cross sectional imaging, EUS, and cyst fluid analysis. Management is based upon a balance of malignant potential and risk of surgical resection.

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## CONFLICT OF INTEREST

The authors have no potential conflicts of interest.