Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management

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INTRODUCTION

Pancreatic cysts are diagnosed with increasing frequency because of the widespread use of cross-sectional imaging. Pancreatic cysts may be detected in 40 to 50 percent of patients who undergo abdominal magnetic resonance imaging for unrelated reasons. The frequency increases with age [1,2].

This topic will review issues related to the evaluation and management of pancreatic cystic neoplasms, including serous cystic tumors, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, and solid pseudopapillary neoplasms. The classification of pancreatic cysts, the diagnosis and management of pancreatic fluid collections, and more detailed discussions of intraductal papillary mucinous neoplasms of the pancreas are discussed separately:

- (See "Classification of pancreatic cysts".)
- (See "Approach to walled-off pancreatic fluid collections in adults".)
- (See "Endoscopic interventions for walled-off pancreatic fluid collections".)
- (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations".)
- (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management".)

TYPES OF PANCREATIC CYSTIC NEOPLASMS

Most pancreatic cystic neoplasms (PCNs) are detected incidentally when abdominal imaging is performed for other indications [3]. PCNs account for more than 50 percent of pancreatic cysts, even in patients with a history of pancreatitis [3,4]. (See "Classification of pancreatic cysts", section on 'Pancreatic cystic neoplasms'.)

PCNs are categorized using the World Health Organization histologic classification (table 1) [5]. There are four subtypes of PCNs, which have varying malignant potential:

- Serous cystic tumors
- Mucinous cystic neoplasms
- Intraductal papillary mucinous neoplasms (IPMNs)
- Solid pseudopapillary neoplasms

The key demographic and clinical features of PCNs are summarized in the table (table 2).

The relative frequencies of the different PCNs were examined in a retrospective series of 851 patients undergoing surgical resection for a cystic neoplasm of the pancreas between 1978 and 2011 [6]. IPMNs accounted for 38 percent of lesions, mucinous cystic neoplasms for 23 percent, serous cystic tumors for 16 percent, and solid pseudopapillary neoplasms for 3 percent. When only the 376 patients who had surgery between 2005 and 2011 were considered, 49 percent had IPMNs, 16 percent had mucinous cystic neoplasms, 12 percent had serous cystic tumors, and 5 percent had solid pseudopapillary neoplasms. However, this series is subject to sampling bias, as it only evaluated resected PCNs. Most branch-duct IPMNs and serous cystic tumors do not require resection; thus, the relative frequency of these lesions may have been underestimated.

Because pancreatic neuroendocrine tumors occasionally appear cystic, they should be considered in the differential diagnosis of PCNs. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Computed tomography'.)

RISK OF MALIGNANCY

Overall, the risk of malignancy in incidentally detected pancreatic cysts is low. A technical review from the American Gastroenterological Association estimated that the risk of malignancy in a pancreatic cyst at the time of diagnosis is at most 0.01 percent (0.21 percent

for cysts >2 cm) [7]. In the subset of cysts that were surgically resected, it was found that the risk of malignancy was 15 percent. However, there is significant selection bias in the surgical series in which cysts were resected. Factors associated with an increased risk of malignancy included cyst size >3 cm (43 versus 22 percent if the cyst was <3 cm, odds ratio [OR] 3.0) and finding a solid component within the cyst (73 versus 23 percent if there was no solid component, OR 7.7). There was a trend towards an increased risk of malignancy if the main pancreatic duct was dilated (47 versus 33 percent if the duct was not dilated, OR 2.4, 95% CI 0.7-8.0). There was no association between risk of malignancy and cyst enlargement over time.

In addition to the above factors, the malignant potential of a cyst also depends on the cyst type (table 2). Serous cystic tumors are at very low risk for developing malignancy, whereas the risk is moderate to high in mucinous cystic neoplasms, solid pseudopapillary tumors, and some intraductal papillary mucinous tumors of the pancreas (intraductal papillary mucinous neoplasms (IPMNs); up to 70 percent for main-duct IPMNs). (See 'Management' below and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Pancreatic malignancy'.)

CLINICAL MANIFESTATIONS

Many patients with pancreatic cysts are asymptomatic, and the cysts are discovered incidentally when abdominal imaging is obtained for unrelated indications [3]. When symptoms are present, they are often nonspecific (table 2).

- **Serous cystic tumors** – Serous cystic tumors can cause symptoms due to cyst enlargement and resultant space occupation [8-10]. Cysts that are greater than 4 cm in size are more likely to cause symptoms or findings on physical examination [11], including abdominal discomfort, a palpable mass, and bile duct and/or gastric outlet obstruction [12].

- **Mucinous cystic neoplasms** – Mucinous cystic neoplasms can present with abdominal pain, recurrent pancreatitis, gastric outlet obstruction, and/or a palpable mass [12]. Jaundice and/or weight loss are more common with malignant lesions.

- **Intraductal papillary mucinous neoplasms (IPMNs)** – As with the other pancreatic cystic lesions, many patients with IPMNs are asymptomatic. However, some patients have a longstanding history of recurrent acute pancreatitis or symptoms suggestive of chronic pancreatitis, which result from intermittent obstruction of the pancreatic duct

with mucus plugs. Manifestations such as back pain, jaundice, weight loss, anorexia, steatorrhea, and diabetes are harbingers of malignancy. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Clinical presentation'.)

- **Solid pseudopapillary neoplasms (SPNs)** – In the past, approximately 80 percent of patients with SPNs were symptomatic. However, incidental detection of SPNs is becoming more common with widespread use of cross-sectional imaging, and it now accounts for up to 50 percent of cases [13]. The most common symptom is abdominal pain, followed by nausea, vomiting, and weight loss [13]. Other symptoms that occur less frequently include gastrointestinal obstruction, anemia, jaundice, and pancreatitis. Patients may also have a palpable mass, which is the most common presentation in children.

DIAGNOSTIC APPROACH

The major challenge in the evaluation of pancreatic cystic neoplasms is identifying lesions with malignant potential or signs of malignancy while not subjecting patients to unnecessary testing (algorithm 1). Cysts with malignant potential include mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and solid pseudopapillary neoplasms (SPNs). There is little malignant potential with serous cystic tumors (SCTs). (See 'Management' below.)

Cross-sectional imaging — The first step in evaluating a cyst is to obtain contrast-enhanced magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) to further evaluate the cyst if not already done. A dedicated pancreatic protocol computed tomography (CT) scan is an alternative for patients who are unable to undergo MRI/MRCP. Cross-sectional imaging is obtained to determine if there are features present that can identify the specific cyst type and to determine if there are any findings that increase the risk of malignancy (large cyst >3 cm, a solid component within the cyst, main pancreatic duct dilation) (algorithm 1).

Findings on cross-sectional imaging associated with specific cysts include (table 2):

- **Serous cystic tumors** – These appear as a well-demarcated multicystic lesion (image 1). A central scar or "sunburst" calcification is visible in up to 20 percent of SCTs and is considered pathognomonic. The microcystic variant of SCTs can mimic a solid mass on CT. Less often, the lesions are oligocystic.

- **Mucinous cystic neoplasms** – MCNs classically appear as a septated cystic lesion, although they can be unilocular (image 2) [14]. The cyst is lined by a mucinous epithelium with variable atypia and may contain eccentric calcifications (seen in up to 15 percent of patients) [15].

  Findings associated with malignant transformation in MCNs include [14,16,17]:

  - Larger size (5 cm or larger in one series [17]).
  - A thickened or irregular cyst wall.
  - An internal solid component or mass.
  - Calcification of the cyst wall.

- **Intraductal papillary mucinous neoplasms** – IPMNs may involve the main pancreatic duct (image 3), the branch ducts, or both (image 4). Main duct involvement is characterized by a diffusely or partially dilated main pancreatic duct filled with mucin [18]. It is predominantly found in the pancreatic head, but can involve any part of the pancreas. Branch-duct (BD) IPMN is characterized by dilation of side branches of the pancreatic duct. It is often seen in the pancreatic head or the uncinate process.

  While both CT scan and MRCP can assess the neoplasm, its relationship to surrounding structures, whether there is lymph node involvement, and if there is metastatic disease [19-22], MRCP appears to be superior to CT scan for determining whether side-branch lesions communicate with the main pancreatic duct [23]. Compared with endoscopic retrograde cholangiopancreatography (ERCP), MRCP is more sensitive for differentiating mural nodules from mucin globs since mucin has the same signal intensity as pancreatic fluid [19,24-27]. MRCP is also superior for demonstrating the internal architecture of the main duct and the extent of IPMN.

- **Solid pseudopapillary neoplasms** – SPNs may appear as a mixed solid and cystic pancreatic lesion on cross-sectional imaging. On MRI, the lesions may appear as well-demarcated solid tumors. In a study of MRI characteristics of small solid tumors of the pancreas, SPNs had significantly lower signal intensity on T1-weighted images, higher signal intensity on T2-weighted images, and had early heterogeneous and progressive enhancement on MRI compared with adenocarcinomas and endocrine tumors [28].

Endoscopic ultrasound-guided pancreatic cyst fluid sampling — The optimal approach to evaluating pancreatic cysts is unclear. In 2015, the American Gastroenterological Association (AGA) published new guidelines on the evaluation and management of pancreatic cysts [29]. The guidelines took into account the general low risk of malignancy in pancreatic cysts and

attempted to limit invasive evaluations to patients with features associated with an increased risk of malignancy. However, these guidelines have not been validated in prospective studies and are based on low-quality evidence. In addition, data are becoming available that suggest if the AGA guidelines are applied, many cysts with advanced neoplasia will be missed. Our group examined 225 patients who underwent endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) for pancreatic cysts [30]. Pathology results were available for 41 patients, 13 of whom (6 percent of the overall population) harbored advanced neoplasia. The AGA guideline, when applied to this cohort, was 62 percent sensitive and 79 percent specific for detecting advanced neoplasia and missed 45 percent of IPMNs with adenocarcinoma or high-grade dysplasia. In addition, 27 of 184 patients (15 percent) with serous cystadenomas based on EUS-FNA findings would have required ongoing, but unnecessary, surveillance. As a result of this study, we devised a new algorithmic approach to the evaluation of pancreatic cysts that includes integrative molecular testing (algorithm 1). Application of this algorithm to the study cohort detected advanced neoplasias with 100 percent sensitivity, 90 percent specificity, 79 percent positive predictive value (PPV), and 100 percent negative predictive value (NPV).

The algorithm represents what we believe to be the appropriate approach to the evaluation of pancreatic cysts based on current knowledge. However, the approach to the evaluation of pancreatic cysts still needs to be prospectively validated and may change as more data become available. We use EUS-FNA for diagnosis and risk stratification in cystic lesions >1.5 cm in size and/or for lesions with worrisome features (solid component within the cyst, main pancreatic duct >0.5 cm in size, symptoms related to the cyst, family history of pancreatic cancer) (algorithm 1). We believe that identifying benign lesions like SCTs that do not require surveillance has cost benefits in the long run and provides reassurance for patients, while identifying IPMN and MCN more accurately provides justification for surveillance. To increase the diagnostic yield of EUS and FNA, we use molecular markers along with cytology, carcinoembryonic antigen (CEA), and glucose. The optimal approach to evaluation will likely be refined as more data become available.

Our threshold for evaluating cysts is lower than that in the AGA, ASGE, and ACG guidelines. The AGA guidelines recommend patients undergo further evaluation only if the cyst has two or more high-risk features (defined as size ≥3 cm, a solid component, or a dilated main pancreatic duct). However, the AGA guidelines note that the evidence behind this recommendation is low quality and that it is reasonable to pursue additional evaluation if only one worrisome feature is present [29].

A 2016 guideline from the American Society of Gastrointestinal Endoscopy has a lower

threshold than the AGA guideline for recommending EUS-FNA [31]. It recommends EUS-FNA of cysts with any one of the following features: >3cm in size, presence of an epithelial nodule, association with a dilated main pancreatic duct, or presence of a suspicious mass lesion. The guideline also suggests that EUS-FNA is optional for cysts <3 cm without other indications for performing EUS-FNA.

The 2018 ACG guidelines recommend EUS-FNA for high risk features (main duct diameter >5 mm, cyst ≥3 cm, and change in main duct caliber with upstream atrophy) [32]. If an associated solid mass is present, referral to a multidisciplinary group with consideration for EUS-FNA is advised. For cysts 2 to 3 cm in size, if not clearly an IPMN or MCN based on cross-sectional imaging, EUS-FNA is recommended. If the cyst is determined to be a mucinous lesion by EUS-FNA, MRI or EUS is recommended every 6 to 12 months for three years for surveillance. If stable, then the ACG guidelines recommend annual MRI for an additional four years, to be followed by a lengthened interval if the cyst demonstrates stability. Interval MRI surveillance of smaller cysts is based upon cyst size.

In some cases, resection will be indicated based on the findings from cross-sectional imaging (eg, if a main-duct [MD] IPMN or a SPN is diagnosed) or because the lesion is causing complications (eg, pancreatitis), so additional evaluation will not be necessary. (See 'Management' below.)

Cyst fluid analysis — The cyst fluid obtained via EUS-FNA can be analyzed for cytology, tumor markers, and molecular markers (table 2). Our approach is to test fluid for cytology, CEA, and glucose levels, diagnostic molecular markers (*KRAS*, *GNAS*, *VHL*, *CTNNB1*), and prognostic molecular markers (*TP53*, *PIK3CA*, *PTEN, SMAD4*).

- **Cytology** – EUS-FNA of PCNs often yields a paucicellular specimen, which limits the yield of cytology. Cytological examination of the cystic fluid may permit diagnosis if either glycogen-rich cells (SCTs) or mucin-containing cells (MCNs and IPMNs) are present, but the sensitivity is low.

  In a prospective study of 341 patients undergoing EUS-FNA of pancreatic cysts, 112 had their cysts surgically resected. When the cytology results were compared with the histologic findings, the sensitivity of cytology for detecting mucinous lesions (MCNs and IPMNs) was 35 percent and the specificity was 83 percent [33]. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract".)

  The addition of cytology brushings may improve the yield of EUS-FNA for diagnosing mucinous lesions. In a study of 37 patients with 39 cystic lesions measuring at least 20

mm in diameter, the yield of cytology brushings for mucinous epithelium was compared with FNA in patients with suspected mucinous lesions [34]. Cytobrushings were significantly more likely to detect intracellular mucin than was FNA (62 versus 23 percent).

- **Histology**

  - **EUS-guided through-the-needle biopsy (TTNB)** – We currently reserve EUS-TTNB for select larger cysts (that have failed previous diagnostic FNA) where a definitive histologic diagnosis would significantly alter management. Histologic samples of the cyst wall may be obtained via EUS-guided TTNB utilizing microforceps. This requires use of a 19-gauge needle, therefore, larger indeterminate cysts are more frequently targeted. TTNB has a higher diagnostic yield as compared with FNA cytology and CEA analysis, particularly for mucinous cysts [35,36]. Additionally, there is a very high concordance rate when comparing TTNB histology with the corresponding surgical specimen. A meta-analysis incorporating eight studies and 426 patients showed a significantly higher diagnostic yield and concordance rate with surgical pathology for TTNB as compared with FNA. The pooled sensitivity and specificity of TTNB for mucinous cysts was 90 and 94 percent, respectively. When performing EUS-TTNB, two macroscopically visible tissue samples have been shown to maximize histologic adequacy, and interobserver agreement among expert pathologists is high for interpreting these specimens [37-39].

Given the need to puncture the cyst with a 19-gauge needle, it is not surprising that the complication rate is higher, up to 23 percent, as compared with standard cyst aspiration using a 22- or 25-gauge needle [35,38]. Intracystic hemorrhage and pancreatitis are the two most common complications and have generally been self-limited and mild. The pooled adverse event rate in the above mentioned meta-analysis was 7 percent. EUS-TTNB has, for the most part, been limited to larger (>2 cm) indeterminate cysts with high-risk stigmata or for cases of failed diagnostic EUS-FNA.

  - **Cyst wall fine needle biopsy (FNB)** – With the advent of specifically designed FNB needles, core histologic samples can be reliably obtained under EUS guidance. A study reported use of 19- or 22-gauge FNB needles to biopsy collapsed or partially collapsed cyst walls. After aspiration of fluid, the fanning technique was used to traverse septations (if present) and/or the cyst wall. Of 47 patients undergoing FNB, the diagnostic yield was 87 percent. The mean cyst size was 38.3 mm in this study. Minor complications, which included minor bleeding and postprocedural pain, were

seen in 8.5 percent of patients [40].

- **Tumor markers** – CEA is the best studied and most accurate tumor marker for diagnosing a mucinous PCN, although the accuracy and the cutoff level vary among laboratories. Approximately 0.2 to 1 mL of cyst fluid is required to run the test depending on the laboratory.

  Studies have attempted to determine the optimal cutoff for CEA in predicting a mucinous cyst [33,41,42]. In one study that included 112 patients who had a PCN surgically resected, a cutoff of 192 ng/mL had a sensitivity of 73 percent for diagnosing a mucinous PCN and a specificity of 83 percent [33]. A second study from the same institution with 198 patients who had PCNs surgically resected reported that a cutoff of 110 ng/mL had a sensitivity of 81 percent and a specificity of 98 percent for diagnosing a mucinous cyst [41]. However, a third study with 226 patients found that a cutoff of 105 ng/mL only had a sensitivity of 70 percent, with a specificity of 63 percent for differentiating a mucinous PCN from a nonmucinous pancreatic cyst [42]. In general, a higher CEA level yields a higher likelihood that a cyst is mucinous [33]. However, there is no direct correlation of CEA concentration with malignancy [33,41].

- **Glucose** – Intracystic glucose measurement to differentiate mucinous versus nonmucinous cysts has gained considerable interest as it is widely available and low cost. In a 93-patient multicenter study, intracystic glucose outperformed CEA for diagnosing mucinous cysts. A glucose level <25 mg/dL had a sensitivity and specificity of 88.1 percent and 91.2 percent (area under the curve [AUC] 0.96), respectively, compared with a 62.7 percent sensitivity and 88.2 percent specificity for CEA >192 ng/mL (AUC 0.81) [43]. Low intracystic glucose levels (<50 mg/dL) may be more accurate than CEA (>192 ng/mL) for diagnosing mucinous pancreatic cysts [44,45]. Combination testing did not improve the diagnostic accuracy over glucose alone. Additional advantages of glucose include real-time in-room measurement with use of a glucometer and minimal amount of fluid needed. Intracystic glucose measurement may have potential diagnostic value in indeterminate cysts with CEA levels between 5 and 192 ng/mL, but this warrants further study.

- **Mutational analysis** – Molecular markers and cyst fluid DNA have been used to differentiate mucinous PCNs from nonmucinous lesions [30,46-52]. *KRAS* mutations are often seen in patients with mucinous PCNs [47,53-55]. Studies have suggested *KRAS* mutations have a sensitivity of 45 to 65 percent and a specificity of 96 to 100 percent for detecting mucinous PCNs [47,54,55]. In one study, the presence of a *KRAS* mutation in

cyst fluid had a sensitivity of 45 percent for diagnosing a mucinous PCN, with a specificity of 96 percent [47]. In addition, a high amount of DNA with high-amplitude allelic loss of tumor suppressor genes (over 80 percent of the cyst fluid DNA affected) was associated with malignancy, with a sensitivity of 70 percent and a specificity of 85 percent [51,52].

Somatic mutations in *GNAS* (R201C or R201H) are highly specific for IPMN (identified in 41 to 66 percent of cases) but are not associated with dysplasia grade or carcinoma. The detection of mutant *GNAS* in cyst fluid therefore confirms the diagnosis of IPMN [56,57].

Mutations in the tumor suppressor gene *TP53* have been associated with IPMNs with high-grade dysplasia or invasive carcinoma. In one study of 180 patients at high risk for pancreatic cancer, mutations in *TP53* were found in 38 percent of IPMNs with high-grade dysplasia and 75 percent of invasive carcinomas [58]. Other mutations that have been associated with invasive carcinoma in patients with IPMN include *PIK3CA* [59] and *PTEN* [60].

In a large prospective series of EUS-guided cyst aspirates from 626 pancreatic cysts, next-generation sequencing detected *KRAS/GNAS* mutations in 49 percent of cysts. *TP53/PIK3CA/PTEN* alterations were detected in 6 percent of cases. Of 102 surgical correlates, *KRAS/GNAS* were 89 percent sensitive and 100 percent specific for a mucinous cyst. *GNAS* mutations were 100 percent specific for IPMN. However, *KRAS* mutations were only seen in 30 percent of MCNs. The combination of *KRAS/GNAS* and *TP53/PIK3CA/PTEN* alterations in cyst fluid had 89 percent sensitivity and 100 percent specificity for advanced neoplasia. These operating characteristics outperformed those of ductal dilatation, presence of a mural nodule, and malignant cytology for advanced neoplasia [61].

Mutations in *VHL* are highly specific for SCTs, whereas mutations in *CTNNB1* have been associated with SPNs [53].

- **Mucin profiling** – In a study of proteomic mucin profiling on pancreatic fluid from 79 cysts, proteomic analysis was more accurate than cytology or cyst fluid CEA level for identifying lesions with malignant potential (98 versus 71 and 78 percent, respectively) [51]. In addition, the mucin profiling results were associated with the risk of malignant transformation.

  Further studies are required to validate these results and to determine the clinical utility of many of these markers.

EUS-FNA findings associated with specific cysts — Features suggestive of specific cyst types include (table 2):

- **Serous cystic tumors** – EUS often demonstrates a honeycomb appearance with the microcystic variety (image 5). The oligocystic version is made up of fewer, larger cysts and can be difficult to distinguish from MCN or branch duct (BD)-IPMN.

  EUS-FNA of targeted cystic compartments reveals a thin fluid, which is often bloody. Cytologic analysis reveals the cuboidal glycogen-staining cells characteristic of a serous cystic neoplasm in less than 50 percent of cases [62-64]. The cyst fluid CEA level is typically low (<5 ng/mL) and glucose is typically high (>50 mg/dL).

- **Mucinous cystic neoplasms** – As is seen on cross-sectional imaging, MCNs appear as septated cystic lesions or, less often, as unilocular lesions [65]. Fluid aspirated from the cyst is typically viscous. Cytology may reveal columnar cells with varying levels of atypia. Aspirates taken from solid components within the cyst have a high yield for malignancy. Staining for mucin is positive in <50 percent. The CEA level is typically high (>200 ng/mL) and glucose is typically low (<50 mg/dL).

- **Intraductal papillary mucinous neoplasms** – EUS findings of main duct (MD)-IPMN include segmental or diffuse dilation of the main pancreatic duct and intraductal (mural) nodules. In BD-IPMN, there are often multiple small cysts (5 to 20 mm). EUS can help distinguish between BD-IPMN and other cysts if communication with the main pancreatic duct (present in BD-IPMN) can be demonstrated. Certain EUS features suggest malignancy, although their sensitivity and specificity have not been well established. These findings include [66-70]:

  - A main pancreatic duct ≥7 mm in MD-IPMN
  - Cystic lesion >30 mm with an irregular, thick septum or wall in BD-IPMN
  - Mural nodules >10 mm for both MD- and BD-IPMN

  FNA of cyst fluid and mural nodules can also be performed for cytologic evaluation and assessment of tumor markers [68]. The cyst fluid is similar to that seen with MCNs. The fluid is typically viscous, and cytology may reveal columnar cells with varying levels of atypia. Aspirates taken from solid components within the cyst have a high yield for malignancy. Staining for mucin is positive in <50 percent, and the CEA level is typically high (>200 ng/mL), whereas glucose levels are low (<50 mg/dL).

  Because 50 to 60 percent of fluid samples are nondiagnostic or acellular, the absence of

atypical or malignant cells does **not** exclude the presence of malignant IPMN [71]. (See 'Cyst fluid analysis' above and "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract".)

EUS may also be useful for distinguishing IPMN from chronic pancreatitis [72]. (See "Endoscopic ultrasound in chronic pancreatitis".)

- **Solid pseudopapillary neoplasms** – The characteristic appearance on EUS is a well-demarcated, echo-poor, solid-appearing mass, although it can also appear as a mixed solid and cystic lesion or a purely cystic lesion. Irregular calcifications are present in up to 20 percent of cases [73]. Fluid aspirated from the cyst is typically bloody.

  EUS-FNA cytologic analysis reveals characteristic branching papillae with myxoid stroma, best seen in cellblock material [74]. Cytology is diagnostic in 75 percent of cases [73]. Special stains, including vimentin, CD10, and beta-catenin, may be required to differentiate an SPN from a pancreatic neuroendocrine tumor (eg, insulinoma) [75].

Other tests

ERCP — Endoscopic retrograde cholangiopancreatography (ERCP) was traditionally used in the evaluation of IPMNs. However, it has largely been replaced with other imaging modalities, such as MRCP, EUS, and multidetector CT.

Typical ERCP findings of IPMN include a diffusely or segmentally dilated pancreatic duct without stricturing. The side branches may also be dilated. Filling defects may be seen due to mucus or mural nodules. The papilla is patulous and resembles a "fish mouth," frequently with mucus extruding from the orifice (image 6 and picture 1) [66,76,77]. An advantage of ERCP is the ability to obtain pancreatic fluid for cytology and molecular markers by aspiration of the duct contents or brushings.

Other tests sometimes done in the evaluation of IPMN include pancreatoscopy and intraductal ultrasound. These tests are typically done to determine the extent of IPMN and to diagnose malignancy. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Other tests'.)

Confocal laser endomicroscopy (nCLE) — nCLE via a 19-gauge needle enables real-time imaging of the cyst wall. Imaging patterns have been associated with specific cyst types. The ability to differentiate mucinous from nonmucinous cysts is still the major primary objective. A prospective single-center 144-patient study compared nCLE with cytology and CEA obtained in the same setting [78]. The mean cyst size in this study was 36 mm; not surprising

given the need for cyst puncture with a 19-gauge needle. nCLE imaging duration was 7.3 minutes (mean). Sixty-five patients underwent surgical resection, serving as the reference standard. Compared with CEA and cytology, nCLE diagnosed mucinous cysts with higher sensitivity (98 versus 74 percent), specificity (94 versus 61 percent), and accuracy (97 versus 71 percent). The complication rate was 3.5 percent (mild pancreatitis). Papillary width and darkness may be predictive of advanced neoplasia in IPMN [79].

The impact of combined TTNB and nCLE for diagnosis and management of pancreatic cysts has also been evaluated. When combined with the composite standard (clinical, morphologic, cytologic, and chemical analysis), the addition of both TTNB and nCLE resulted in a diagnostic yield of 93 percent. This combination also led to a change in clinical management in 52 percent of cases [80].

MANAGEMENT

The management of pancreatic cystic neoplasms is reviewed in practice guidelines in 2012 by the International Association of Pancreatology [81], in 2015 by the American Gastroenterological Association (AGA) [29], and in 2018 by the American College of Gastroenterology (ACG) [32]. The discussion that follows is generally consistent with the ACG guideline, but is more conservative than the AGA guideline. The optimal approach to management will likely be refined as more data become available.

Many pancreatic cysts can be followed with surveillance imaging (algorithm 1). In general, surgery is indicated for cysts with cytology revealing advanced neoplasia or malignancy; cysts causing complications (eg, pancreatitis); cysts with features concerning for malignancy; and cysts with significant malignant potential, including mucinous cystic neoplasms (MCNs), main-duct intraductal papillary mucinous neoplasms (IPMNs), and solid pseudopapillary neoplasms (SPNs). The management of branch-duct IPMNs continues to evolve. However, the decision to recommend surgery should take into account factors such as the patient's age and general health, the malignant risk of the specific lesion, and the suspicion for malignancy (eg, malignancy is more likely if there are several worrisome features present). (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Management'.)

If surgery is performed, lesions in the body or tail of the pancreas require a distal pancreatectomy, whereas those in the head of the gland are resected by pancreaticoduodenectomy. (See "Surgical resection of lesions of the head of the pancreas"

and "Surgical resection of lesions of the body and tail of the pancreas".)

Alternative treatments are also being studied, including endoscopic cyst ablation methods in which the cyst is injected with ethanol or chemotherapeutic agents during endoscopic ultrasound (EUS) [82-84]. For early studies utilizing ethanol-only injection, the calculated complete cyst resolution rate was 33 percent, with a 21 percent adverse event rate. The addition of paclitaxel to the ablation regiment has resulted in much higher cyst resolution rates (50 to 79 percent) [85].

The relatively high complication rate (pancreatitis, intracystic hemorrhage, abdominal pain) associated with cyst ablation is likely from the ethanol lavage component of the ablation and can potentially be avoided with the adoption of chemotherapeutic-only ablation protocols [86]. EUS-guided paclitaxel ablation has better cyst resolution rates than other ablation techniques to include ethanol injection and radiofrequency ablation [87]. Cyst ablation holds promise for the treatment of symptomatic cysts or cysts with malignant potential in select patients. The safety and efficacy of these approaches continues to be examined, and the effect on reducing cancer risk remains unknown.

Mucinous cyst, specific type unknown — Incidental detection of pancreatic cysts is common, and not all cysts require a diagnostic evaluation to determine the exact cyst type. In addition, in some cases a diagnosis may not be clear despite a diagnostic evaluation that includes EUS-guided fine-needle aspiration (FNA).

The management of these cysts depends on whether there are features seen on imaging that increase the risk of malignancy or if cytology/histology is positive for malignancy or high-grade dysplasia (algorithm 1) [29].

We suggest surgery for patients who are good candidates if any of the following features are present:

- Cytology/histology that is suspicious or positive for a malignant neoplasm
- A mucinous cyst ≥3 cm associated with main duct dilation and/or a definitive mural nodule
- *KRAS* and/or *GNAS* mutations with *TP53* and *PIK3CA* or *PTEN* mutations by molecular testing

We perform surveillance in patients who do not meet these criteria (algorithm 1). The approach to surveillance will depend on various patient-related factors (age, comorbidities, personal choice) and cyst-related features (size, location, fluid analysis).

If the patient develops symptoms referable to the pancreas or there are worrisome changes in the cyst during surveillance (increase in size, dilation of the main pancreatic duct, development of a mural nodule), we obtain an EUS-FNA unless a clear indication for surgery has developed.

By contrast, the AGA guideline suggests that patients with pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct undergo magnetic resonance imaging for surveillance in one year and then every two years for a total of five years if there is no change in size or characteristics [29]. The guideline also suggests obtaining a magnetic resonance imaging (MRI) at one year and then every two years for patients who undergo EUS-FNA (eg, patients with at least two high-risk features [size ≥3 cm, dilated main pancreatic duct, or the presence of a solid component within the cyst]) and do not have concerning features. In general, the guideline recommends discontinuing surveillance if there has been no significant change in the characteristics of the cyst after five years of surveillance. The ACG guidelines recommend continued surveillance for IPMN and MCN, the interval of which is based upon the cyst size [32]. For cysts 2 to 3 cm in size, MRI or EUS is recommended every 6 to 12 months for three years for surveillance. If stable, then an annual MRI is recommended for an additional four years, to be followed by a lengthened interval if the cyst demonstrates stability. Interval MRI surveillance of smaller cysts is more conservative.

Serous cystic tumors — Malignant transformation into serous cystadenocarcinoma is exceedingly rare, with only a few case reports in existence [88,89]. If the diagnosis of a serous cystic tumor is made with certainty and the patient is asymptomatic, no additional treatment or evaluation is needed. Surgery is only indicated if the cyst is thought to be causing symptoms. We repeat cross-sectional imaging if symptoms develop in a previously asymptomatic patient.

Mucinous cystic neoplasms — MCNs have significant malignant potential. In two series, each with 56 patients with MCNs, carcinoma (noninvasive plus invasive) was present in 11 and 38 percent, respectively [16,17]. The prognosis is excellent if the MCN is removed prior to invasion. As a result, resection is recommended for MCNs in patients with acceptable surgical risk.

In a patient who is not a surgical candidate and has a small, incidentally discovered lesion, we do not recommend follow-up. If the lesion has significant malignant potential or is symptomatic, EUS-guided cyst ablation is an option [85]. (See 'Management' above.)

Intraductal papillary mucinous neoplasms — Main-duct IPMNs are typically resected,

whereas branch-duct IPMNs are managed either with surveillance or resection. The management of IPMNs is discussed in detail elsewhere. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Pancreatic malignancy' and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Management'.)

Solid pseudopapillary neoplasms — SPNs have malignant potential, though the actual risk has not been well studied. In a series of 62 patients, nine patients (15 percent) had malignant SPNs [90]. No factors were identified that predicted malignancy. In a second series with 106 patients who underwent surgery for SPN, 17 patients (16 percent) had high-grade malignant SPNs [91]. Tumor size ≥5 cm was associated with an increased risk of high-grade malignancy.

Given the lesion's malignant potential, the finding of a pancreatic mixed solid and cystic lesion in a young woman on CT or MRI, or a diagnosis of SPN following EUS-FNA, should lead to resection in most cases. Even if malignancy is already present, malignant SPNs can often be cured when completely excised [92] and prolonged survival can be seen even in the presence of metastatic disease with surgical debulking [93,94].

FOLLOW-UP AFTER SURGERY

For patients who undergo cyst resection, follow-up depends on the pathologic findings. If there is evidence of invasive cancer or high-grade dysplasia, magnetic resonance imaging surveillance of the remaining pancreas should be performed every two years [29]. If there is no high-grade dysplasia or malignancy, surveillance is not needed for patients who do not have papillary mucinous neoplasms (IPMN) or a strong family history of pancreatic cancer. The management of patients with IPMN or a strong family history of pancreatic cancer is discussed separately. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients" and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Surveillance following surgery'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pancreatic cysts".)

SUMMARY AND RECOMMENDATIONS

- Many pancreatic cysts are discovered incidentally when abdominal imaging is obtained for unrelated indications. (See 'Clinical manifestations' above.)

- There are four subtypes of PCNs, with varying malignant potential (table 1 and table 2):

  - Serous cystic tumors
  - Mucinous cystic neoplasms (MCNs)
  - Intraductal papillary mucinous neoplasms (IPMNs)
  - Solid pseudopapillary neoplasms (SPNs)

- The major challenge in the evaluation of PCNs is identifying lesions with malignant potential or signs of malignancy while not subjecting patients to unnecessary worry and testing. Cysts with malignant potential include MCNs, IPMNs, and SPNs. There is little to no malignant potential with serous cystic tumors. (See 'Risk of malignancy' above.)

- The first step in evaluating a cyst is to obtain magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) to further evaluate the cyst if not already done (algorithm 1). A dedicated pancreatic protocol computed tomography scan is an alternative for patients who are unable to undergo MRI/MRCP. Cross-sectional imaging is obtained to determine if there are features present that can identify the specific cyst type and to determine if there are any findings that increase the risk of malignancy (large cyst, a solid component within the cyst, main pancreatic duct dilation). (See 'Diagnostic approach' above.)

  In some cases, resection will be indicated based on the findings from cross-sectional imaging alone (eg, if a main-duct IPMN or a SPN is diagnosed) or because the cyst is causing complications (eg, pancreatitis), so additional evaluation will not be necessary.

  For patients who do not have an indication for resection based on cross-sectional imaging alone, we pursue additional evaluation with endoscopic ultrasound with fine-needle aspiration in cysts >1.5 cm in size and for lesions with worrisome features (solid component within the cyst, main pancreatic duct >0.5 cm in size, symptoms related to the cyst, family history of pancreatic cancer).

- Many pancreatic cysts can be followed with surveillance imaging (algorithm 1). In general, surgery is indicated for cysts with malignant cytology; cysts that are causing complications; cysts with features concerning for malignancy; and cysts with significant

malignant potential, including MCNs, main-duct IPMNs, and SPNs. The management of branch-duct IPMNs continues to evolve. However, the decision to recommend surgery should take into account factors such as the patient's age and general health, the malignant risk of the specific lesion, and the suspicion for malignancy (eg, malignancy is more likely if there are several worrisome features present). (See 'Management' above and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Management'.)

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Topic 5642 Version 31.0

GRAPHICS

World Health Organization classification of pancreatic cystic neoplasms

Serous neoplasms
Serous cystadenoma
Microcystic serous cystadenoma
Macrocystic (oligocystic) serous cystadenoma
Solid serous adenoma
Von Hippel-Lindau syndrome-associated serous cystic neoplasm
Mixed serous-neuroendocrine neoplasm
Serous cystadenocarcinoma
Mucinous cystic neoplasm
Mucinous cystic neoplasm with low-grade dysplasia
Mucinous cystic neoplasm with high-grade dysplasia
Mucinous cystic neoplasm with associated invasive carcinoma
Intraductal papillary mucinous neoplasm
Intraductal papillary mucinous neoplasm with low-grade dysplasia
Intraductal papillary mucinous neoplasm with high-grade dysplasia
Intraductal papillary mucinous neoplasm with associated invasive carcinoma
Solid pseudopapillary neoplasm
Solid pseudopapillary neoplasm
Solid pseudopapillary neoplasm with high-grade carcinoma

Data from: Zamboni G, Kloeppel G, Hruban RH, et al. Mucinous cystic neoplasms. Tumours of the pancreas. In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System, 5th ed, Aaltonen LA, Hamilton SR (Eds), IARC Press, Lyon 2019.

Graphic 69594 Version 4.0

Key demographic and clinical features of patients with pancreatic cystic neoplasms[1-4]

	Serous cystic tumor	Mucinous neoplasm	Main-duct intraductal papillary mucinous neoplasm	Branch-duct intraductal papillary mucinous neoplasm	pse
Age of presentation	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Usu dec
Gender distribution	Females >males	Almost exclusively females	Females = males	Females = males	Fem
Typical clinical presentation	Incidental or abdominal pain or mass effect	Incidental or abdominal pain or malignancy related	Incidental or pancreatitis or pancreatic insufficiency or malignancy related	Incidental or pancreatitis or malignancy related	Inci abd mas
Typical imaging characteristics	Microcystic/honeycomb appearance Oligocystic appearance less common	Unilocular or septated cyst ± wall calcifications Solid component, if present, may suggest malignancy	Dilated main pancreatic duct ± parenchymal atrophy Solid component, if present, may suggest malignancy	Dilated pancreatic duct branch or branches Solid component, if present, may suggest malignancy	Soli mas calc
Typical aspirate characteristic	Thin, often bloody	Viscous	Viscous	Viscous or thin	Blo

Typical cytology findings	Cuboidal cells that stain positive for glycogen; yield <50%	Columnar cells with variable atypia Stains positive for mucin; yield <50% High yield from solid component for malignancy	Columnar cells with variable atypia Stains positive for mucin; yield <50% High yield from solid component for malignancy	Columnar cells with variable atypia Stains positive for mucin; yield <50% High yield from solid component for malignancy	Cha bra with Hig soli
Typical carcinoembryonic antigen (CEA) level	<5 to 20 ng/mL in majority of lesions	>200 ng/mL in approximately 75% of lesions	>200 ng/mL in approximately 75% of lesions	>200 ng/mL in approximately 75% of lesions	Insu
Typical glucose level	>50 mg/dL in majority	<50 mg/dL in majority	<50 mg/dL (limited data)	<50 mg/dL in majority	Insu
Typical DNA analysis	Allelic loss affecting chromosome 3p and VHL mutation specific	K-ras mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	K-ras and GNAS mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	K-ras and GNAS mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	CTN spe
Relative malignant potential	Negligible	Moderate	High	Low to moderate	Mo
Treatment	Resect if symptomatic	Resection	Resection and post-resection surveillance	Closely monitor or resect Post-resection surveillance	Res

				required	

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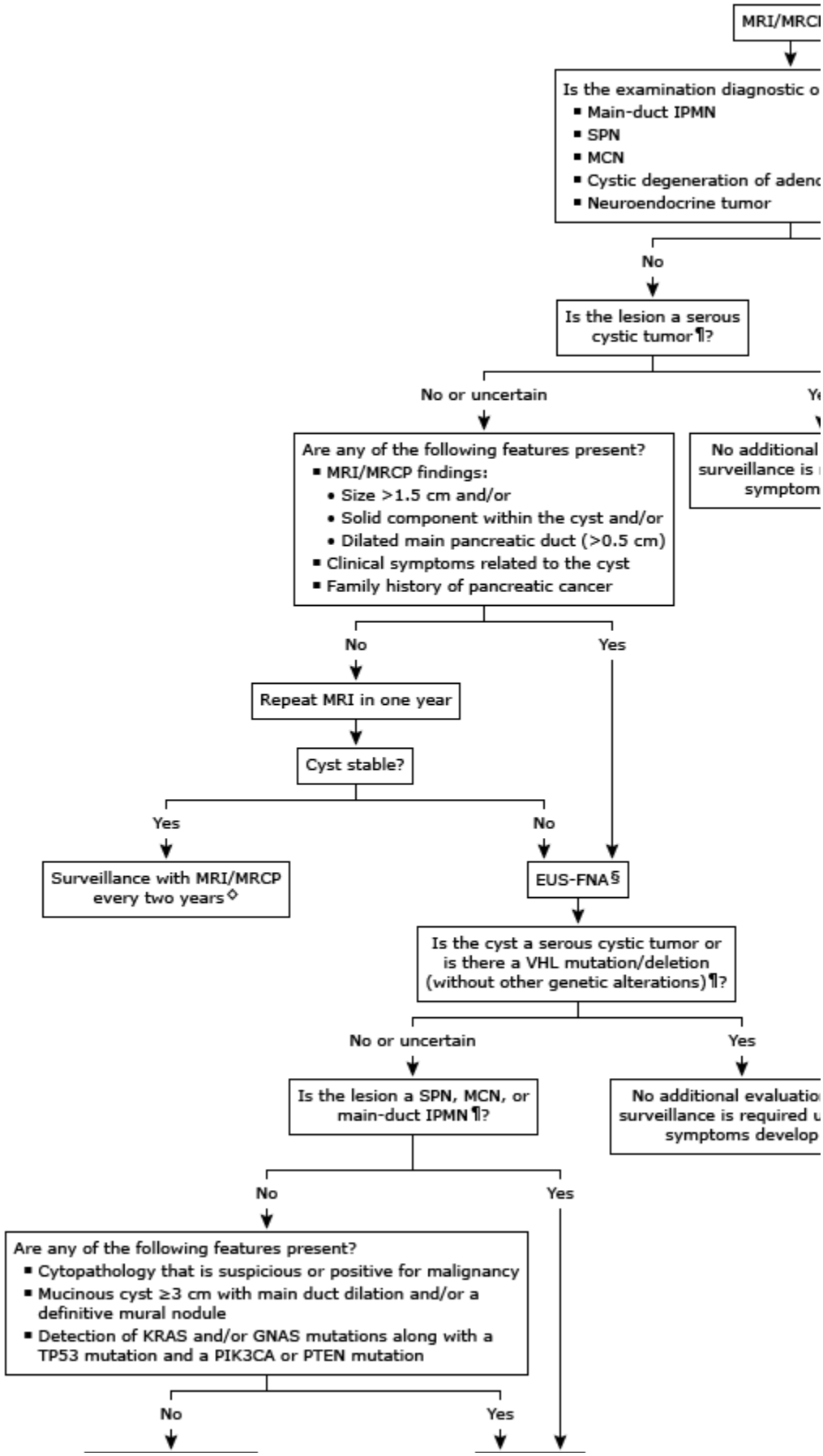
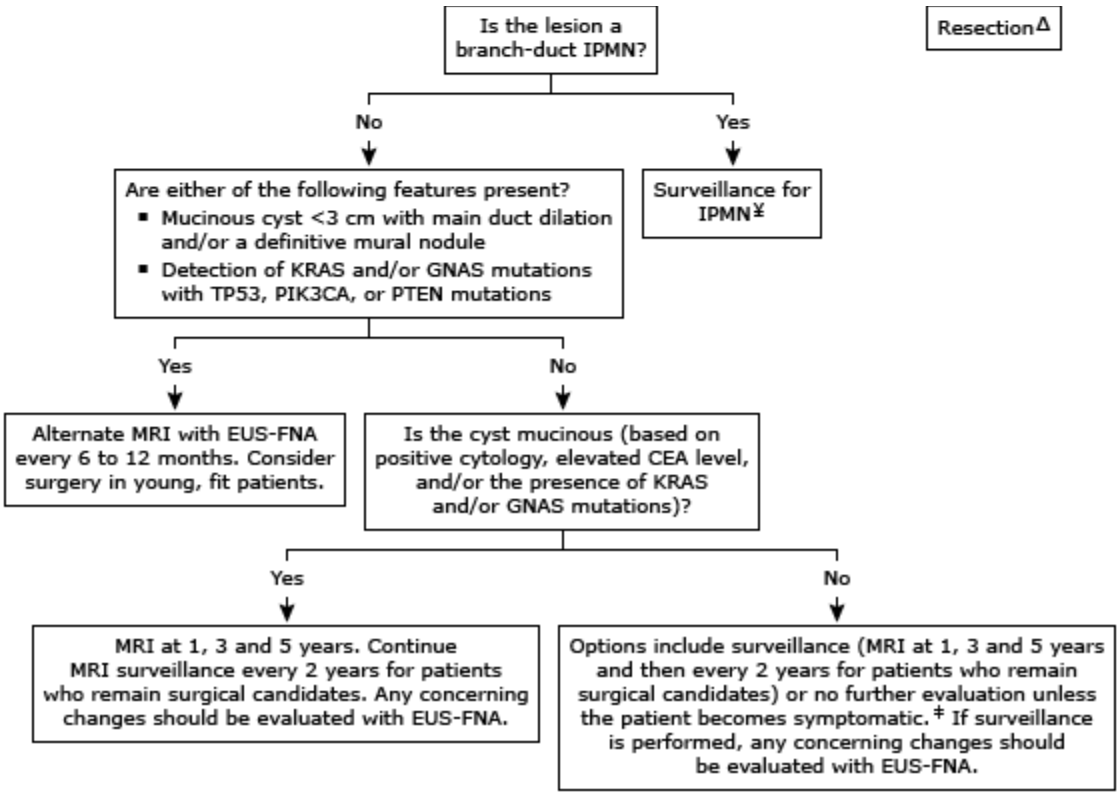
Graphic 57759 Version 9.0

Evaluation and management of pancreatic cysts





Published guidelines on the management of pancreatic cystic neoplasms are variable. This algorithm ref
approach. Refer to UpToDate topic reviews on pancreatic cystic neoplasms for additional details.

MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; IPMN: intrad
mucinous neoplasm; SPN: solid pseudopapillary neoplasm; MCN: mucinous cystic neoplasm; EUS-FNA: e
ultrasound-guided fine-needle aspiration; CEA: carcinoembryonic antigen.

* A pancreatic protocol computed tomography scan is an alternative for patients who cannot undergo M

¶ Refer to UpToDate topics on the evaluation of pancreatic cystic neoplasms for details on the specific fe
make a diagnosis.

Δ The decision to recommend surgery should take into account factors such as the patient's age and ger
malignant risk of the specific lesion, and the suspicion for malignancy.

◇ Surveillance should be considered because these cysts, despite being small, may be precancerous. The
pursue surveillance should take into account factors such as the patient's age, comorbidities, and willing
surgery if worrisome features develop.

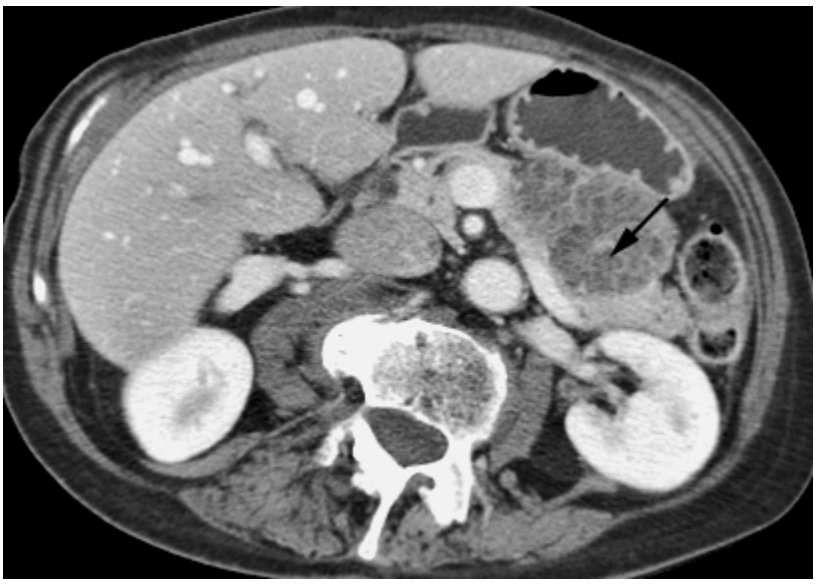
§ Cyst fluid should be tested for cytology; CEA level; and the molecular markers KRAS, GNAS, VHL, CTNNE
and PTEN. KRAS and GNAS have been associated with IPMNs and MCNs, and GNAS appears to be highly
TP53, PIK3CA, and PTEN have been associated with high-grade dysplasia or invasive carcinoma in patien
is seen in serous cystic tumors, whereas CTNNB1 is seen in SPNs.

¥ Refer to UpToDate topic on the management of IPMNs for details.

‡ Refer to UpToDate content on the management of pancreatic cysts for details.

Graphic 105742 Version 2.0

Pancreatic serous cystadenoma



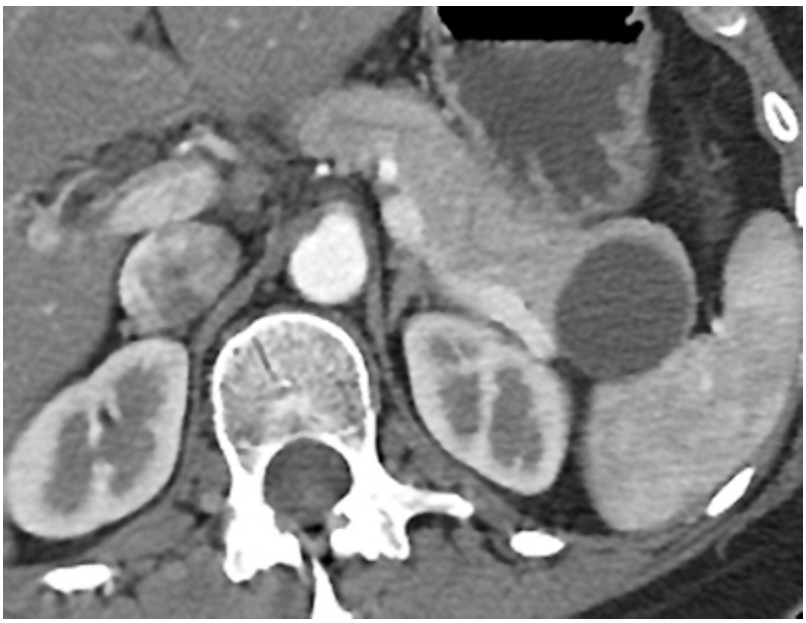
CT showing a serous cystadenoma of the pancreas. Note central calcification of stellate scar (arrow).

CT: computed tomography.

Courtesy of Kevin McGrath, MD.

Graphic 66608 Version 5.0

Pancreatic mucinous cystic neoplasm

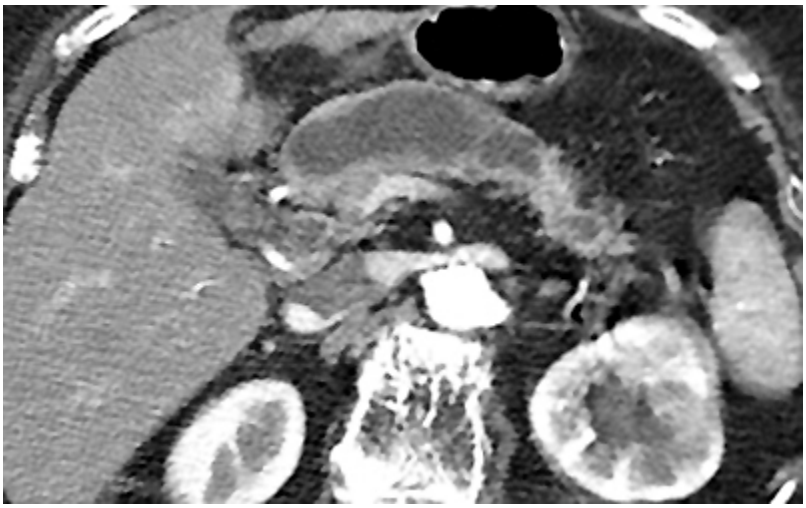


An incidental 3 cm unilocular mucinous cystic neoplasm in the tail of the pancreas.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 65253 Version 3.0

Computed tomography of intraductal papillary mucinous neoplasm with parenchymal atrophy



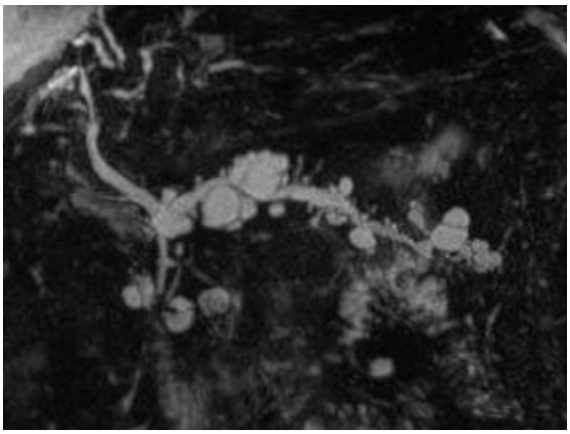
CT scan of main duct intraductal papillary mucinous neoplasm, revealing a markedly dilated pancreatic duct with parenchymal atrophy.

CT: computed tomography.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 51921 Version 4.0

Mixed-type intraductal papillary mucinous neoplasm of the pancreas

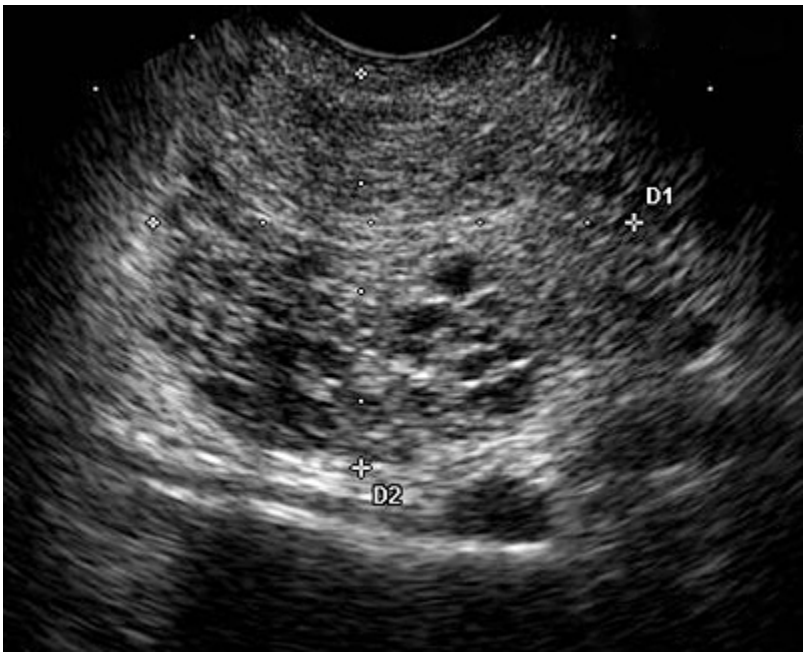


Magnetic resonance cholangiopancreatography revealing mixed-type intraductal papillary mucinous neoplasm. There are multiple dilated branch ducts and a moderately dilated main pancreatic duct in the pancreatic body region.

Courtesy of Kevin McGrath, MD.

Graphic 101892 Version 1.0

EUS image of pancreatic serous cystadenoma (microcystic variety)

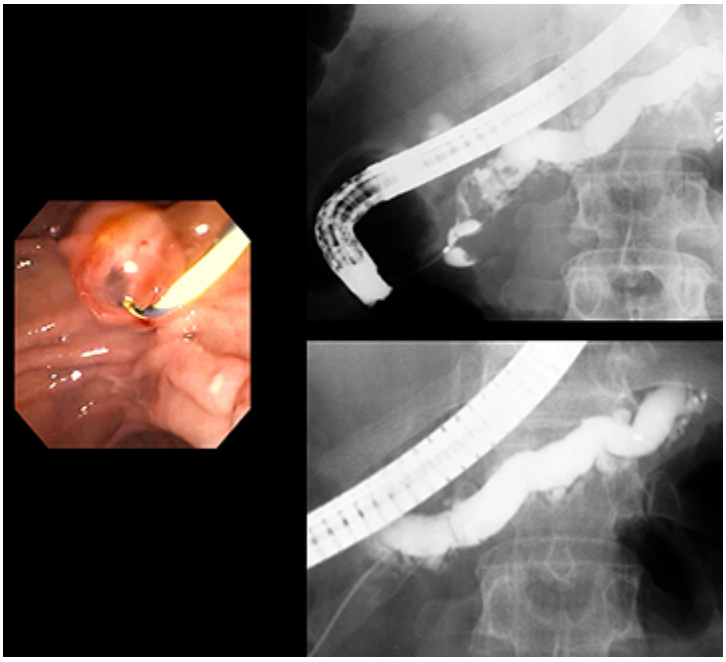


Endoscopic ultrasound image revealing a microcystic lesion with a honeycomb appearance.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 55761 Version 3.0

Intraductal papillary mucinous neoplasm

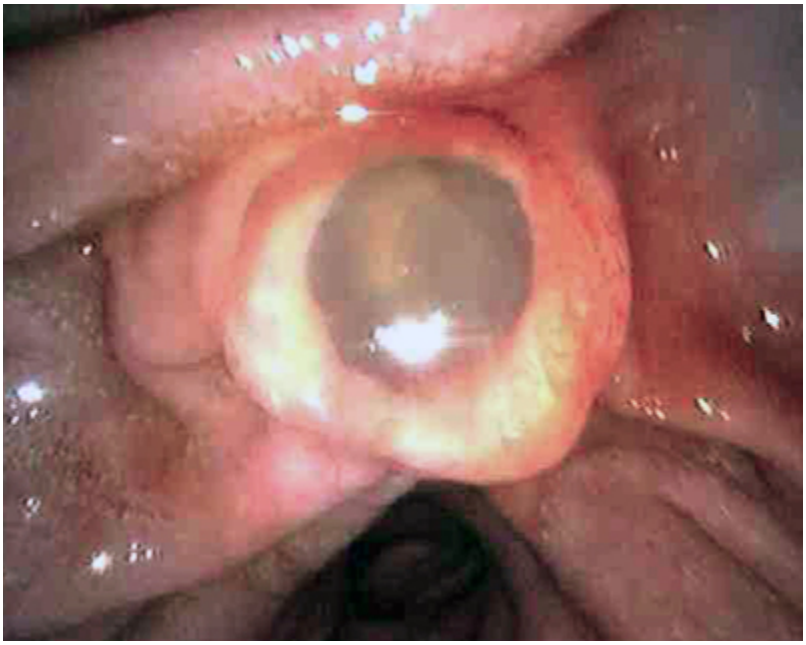


Images obtained during endoscopic retrograde cholangiopancreatography in a 61-year-old patient with steatorrhea, weight loss, and diabetes. The left panel shows an endoscopic image of the papilla, which has a gaping "fisheye" appearance and is exuding mucin. The pancreatogram shows a dilated pancreatic duct and side branches with intraluminal filling defects. The patient underwent a pancreaticoduodenectomy, which confirmed an intraductal papillary mucinous neoplasm.

Courtesy of Maurits Wiersema, MD.

Graphic 66926 Version 3.0

Papilla extruding mucus in a patient with IPMN



A gaping papilla extruding mucus, pathognomonic of main-duct intraductal papillary mucinous neoplasm.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 52643 Version 1.0

Contributor Disclosures

Asif Khalid, MD No relevant financial relationship(s) with ineligible companies to disclose. **Kevin McGrath, MD** No relevant financial relationship(s) with ineligible companies to disclose. **John R Saltzman, MD, FACP, FACG, FASGE, AGAF** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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