CME

ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts

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Pancreatic cysts are very common with the majority incidentally identified. There are several types of pancreatic cysts; some types can contain cancer or have malignant potential, whereas others are benign. However, even the types of cysts with malignant potential rarely progress to cancer. At the present time, the only viable treatment for pancreatic cysts is surgical excision, which is associated with a high morbidity and occasional mortality. The small risk of malignant transformation, the high risks of surgical treatment, and the lack of high-quality prospective studies have led to contradictory recommendations for their immediate management and for their surveillance. This guideline will provide a practical approach to pancreatic cyst management and recommendations for cyst surveillance for the general gastroenterologist.

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INTRODUCTION

Pancreatic cysts are often detected on abdominal imaging performed for non-pancreatic indications. Their prevalence in an asymptomatic population is reported from 2.4 to 13.5% with increasing incidence with age (1). A review of abdominal magnetic resonance imaging (MRIs) performed for non-pancreatic indications in patients over the age of 70 showed a 40% incidence of incidental pancreatic cysts (2). Somewhat reassuring is the low prevalence of cysts >2 cm; in 25,195 subjects in five studies the prevalence of cysts >2 cm was only 0.8% (3). Pancreatic cysts are increasingly being diagnosed because of the use of more abdominal imaging and to the increased quality of that imaging. The overall incidence of pancreatic cancer-related mortality is fairly stable; thus, the increasing incidence of cysts is likely due to the increase in diagnostic scrutiny (4).

Some pancreatic cysts have the potential for malignant transformation to invasive ducal adenocarcinoma of the pancreas, hence the cause for concern. The exact risk of malignant transformation is unclear; however, when considering all individuals with pancreatic cysts, the potential risk for malignant transformation is small (5). Using the assumption that all pancreatic cancer arises in patients within pancreatic cysts, an analysis of the SEER database found the probability that a cyst harbors malignancy at the time of imaging is 0.25%, with the overall conversion rate to invasive cancer being 0.24% per year (3). However, retrospective series of surgically resected cysts have reported higher rates, with the pooled proportion of cysts with pancreatic cancer of 15% in 27 studies of 2,796 patients (3). The approach of including all pancreatic cysts has been criticized, as many pancreatic cysts have no malignant potential (6,7). When only intraductal papillary mucinous neoplasms (IPMNs) are included, a review of 99 studies of 9,249 patients with IPMNs who underwent surgical resection found that the incidence of either high-grade dysplasia or pancreatic cancer was 42% (ref. 3). The data evaluating the long-term risk of an IPMN developing pancreatic cancer are also contradictory. One review of 3,980 patients with suspected IPMNs reported an overall risk of developing pancreatic cancer of 2.8% (95% confidence interval (CI), 1.8–4.0%), which was consistent with an estimated risk of developing pancreatic cancer of 0.72% per year (95% CI, 0.48–1.08) (3). In contrast, a recent systematic review and meta-analysis of 3,236 patients divided IPMNs into low and high risk, the latter being defined as the presence of a mural nodule or dilated main pancreatic duct. They reported a pooled cumulative incidence of high-grade dysplasia or pancreatic cancer of 0.02% (95% CI, 0.0–0.23%) at 1 year, 3.12% (95% CI, 1.12–5.90%) at 5 years, and 7.77% (95% CI, 4.09–12.39%) at 10 years for low-risk IPMNs. The pooled cumulative incidence was 1.95% (95% CI, 0.0–5.99%) at 1 year, 9.77% (95% CI, 3.04–19.29%) at 5 years, and 24.68 (95% CI, 14.87–35.90%) at 10 years for high-risk IPMNs (8). Large, prospective, multicenter studies following cysts that are presumed to be mucinous are required to answer the critical question of the cumulative risk of high-grade dysplasia or cancer.

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Management decisions for pancreatic cysts must take into account their low risk of malignancy vs. their frequent detection. The cost of cyst analysis and cyst surveillance is high, and the benefit in terms of cancer prevention is unproven. There have been no dedicated cost effectiveness analyses about surveillance of incidental pancreatic cysts. The risks of pancreatic surgery are relatively high. A recent review of the literature suggests that the mortality rate from pancreatic resection for pancreatic cysts is 2.1% with a morbidity rate of 30% (3). Large worrisome cysts are more commonly found in elderly individuals with comorbidities. Individual life expectancy and risk of death from other factors must be carefully considered in analyzing the risks that pancreatic cysts pose.

This guideline will review the various types of pancreatic cysts (**Table 1**), address common clinical questions regarding their management, and provide guidance on when to refer for further evaluation by using a combination of a systematic review of the literature and expert recommendations (**Figure 1**). The guideline does not apply to patients with strong family history of pancreatic cancer or genetic mutations known to predispose to pancreatic cancer.

TYPES OF PANCREATIC CYSTS

Cystic lesions of the pancreas have a large differential diagnosis (**Table 2**). They can be broadly categorized as neoplastic or non-neoplastic (i.e., pseudocysts) and as mucin-producing (IPMNs or mucinous cystic neoplasms (MCNs)) vs. non-mucin producing. Cystic lesions with malignant potential include IPMNs, MCNs, solid-pseudopapillary tumors, and pancreatic neuroendocrine tumors. The diagnosis of cyst type relies on imaging characteristics and, for some cysts, on the analysis of cyst fluid. Despite high-quality imaging with computed tomography (CT), MRI, and cyst fluid analysis, the correct classification of cyst type can be challenging.

Pseudocysts

Most pseudocysts occur in patients with a known history of acute or chronic pancreatitis. Neoplastic cysts are much more common than pseudocysts, but it is important to rule out pseudocysts since they have no malignant potential and do not require surveillance or treatment when asymptomatic. One must be careful to consider that a neoplasm can cause unexplained pancreatitis in up to 20% of individuals over the age of 40. Therefore, one must be vigilant to consider that an incidental cyst could be a cystic neoplasm that caused the episode of pancreatitis. When the diagnosis is uncertain, endoscopic ultrasound (EUS) is often helpful in assessing for chronic pancreatitis with fine needle aspiration (FNA) assessing cyst fluid characteristics; pseudocyst aspirates are usually brown in color, have very high cyst fluid lipase or amylase, and have low carcinoembryonic antigen level (CEA). This assessment is not always accurate, given that side-branch IPMNs with connection to the main pancreatic duct also have very high lipase and amylase levels and the CEA may be in the "indeterminate" range. The differentiation of a pseudocyst from a neoplastic cyst in symptomatic patients is critical for an additional reason: most pseudocysts can be treated with endoscopic drainage instead of surgery.

Intraductal papillary mucinous neoplasms

IPMNs may involve side branches only, the main duct, or a combination of both termed mixed IPMN. By far, the most common IPMN, and indeed the most common pancreatic cyst, is a side-branch IPMN. In up to 40% of cases, multiple IPMNs occur; however, there is no evidence that the risk of malignant transformation is higher in multifocal IPMNs (9). Although these are mucin-producing cysts with malignant potential, as discussed previously, the vast majority of side-branch IPMNs will not progress to pancreatic cancer. Main duct IPMN is much less common and appears to have a high risk of malignancy, with 38–68% of main duct IPMNs harboring high-grade dysplasia or pancreatic cancer in resected specimens (10). A patulous, mucin-extruding papillary orifice can be seen in the main duct variety. Both side-branch and main-duct IPMNs may rarely give rise to pancreatitis, presumably due to thick mucin occluding the pancreatic duct orifice. The vast majority of IPMNs are given this diagnosis based on clinical and radiographic parameters rather than tissue diagnosis; when fluid is obtained, the cyst fluid CEA is usually elevated.

Mucinous cystic neoplasms

MCNs occur almost exclusively in women and are most often present in middle age. The most common location is the body or tail of the pancreas. Unlike side-branch IPMNs, there is usually no communication with the pancreatic duct. Their columnar epithelium is surrounded by ovarian-type stroma. MCNs have the potential to develop into pancreatic cancer; however, the risk is lower than previously thought. A recent review of 90 resected MCNs found that only 10% of them contained either high-grade dysplasia or pancreatic cancer (11). In this study, and a large review of 344 MCNs, there were no cases of high-grade dysplasia or pancreatic cancer in MCNs less than 3 cm in size with a normal serum CA 19-9 and no concerning features (11,12).

Serous cystadenomas

Serous cystadenomas (SCAs) occur more commonly in women (75%), who usually present in their 50s. A recent multicenter study in over 2,500 SCAs found that the risk of serous cystadenocarcinoma was extremely low at 0.1% (13). Although rare, benign SCAs can cause symptoms because of their size; however, the vast majority of SCAs are asymptomatic. The classic imaging characteristics are microcystic or honeycomb appearance, although macrocystic lesions are not rare. A central scar is a characteristic imaging feature, but is present in less than 30% of SCAs. Cyst fluid analysis reveals very low CEA levels and low viscosity. Most asymptomatic SCAs do not require surveillance.

Solid-pseudopapillary neoplasms

Solid-pseudopapillary neoplasms (SPNs) are rare lesions, which are more common in women (10:1). They most frequently present in women in their 20s but have a wide age range, and are

Table 1. Summary and strength of recommendations

Pancreatic cyst diagnosis
1. We recommend caution when attributing symptoms to a pancreatic cyst. The majority of pancreatic cysts are asymptomatic and the nonspecific nature of symptoms requires clinical discernment (Conditional recommendation, very low quality of evidence)
2. Magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) are the tests of choice because of their non-invasiveness, lack of radiation, and greater accuracy in assessing communication between the main pancreatic duct and the cyst (which is a characteristic of side-branch IPMNs). Pancreatic protocol computed tomography (CT) or endoscopic ultrasound (EUS) are excellent alternatives in patients who are unable to undergo MRI. Indeterminate cysts may benefit from a second imaging modality or cyst fluid analysis via EUS (Conditional recommendation, very low quality of evidence)
3. Use caution when using imaging to diagnose cyst type or concomitant malignancy; the accuracy of MRI or MRCP in diagnosing cyst type is 40–50% and in determining benign vs. malignant is 55–76%. The accuracy for CT and EUS without FNA is similar (Conditional recommendation, very low quality of evidence)
Pancreatic cyst management
4. Patients who are not medically fit for surgery should not undergo further evaluation of incidentally found pancreatic cysts, irrespective of cyst size (Strong recommendation, low quality of evidence).
5. Patients with asymptomatic cysts that are diagnosed as pseudocysts on initial imaging and clinical history, or that have a very low risk of malignant transformation (such as serous cystadenomas) do not require treatment or further evaluation (Conditional recommendation, low quality of evidence)
6. EUS-FNA and cyst fluid analysis should be considered in cysts in which the diagnosis is unclear, and where the results are likely to alter management. Analysis of cyst fluid CEA may be considered to differentiate IPMNs and MCNs from other cyst types, but cannot be used to identify IPMNs and MCNs with high-grade dysplasia or pancreatic cancer (Conditional recommendation, very low quality of evidence)
7. Cyst fluid cytology should be sent to assess for the presence of high-grade dysplasia or pancreatic cancer when the imaging features alone are insufficient to warrant surgery (Conditional recommendation, very low quality of evidence)
8. Molecular markers may help identify IPMNs and MCNs. Their use may be considered in cases in which the diagnosis is unclear and the results are likely to change management (Conditional recommendation, very low quality of evidence)
Pancreatic cyst surveillance
9. Cyst surveillance should be offered to surgically fit candidates with asymptomatic cysts that are presumed to be IPMNs or MCNs (Conditional recommendation, very low quality of evidence)
10. Patients with IPMNs or MCNs with new-onset or worsening diabetes mellitus, or a rapid increase in cyst size (of >3 mm/year) during surveillance, may have an increased risk of malignancy, so should undergo a short-interval MRI or EUS±FNA (Conditional recommendation, very low level of evidence)
11. Patients with IPMNs or MCNs with any of the following features should undergo EUS±FNA and/or be referred to a multidisciplinary group for further evaluation (Strong recommendation, very low quality of evidence)
(a) Any of the following symptoms or signs: jaundice secondary to the cyst, acute pancreatitis secondary to the cyst, significantly elevated serum CA 19-9
(b) Any of the following imaging findings: the presence of a mural nodule or solid component either within the cyst or in the pancreatic parenchyma, dilation of the main pancreatic of >5 mm, a focal dilation of the pancreatic duct concerning for main duct IPMN or an obstructing lesion, mucin-producing cysts measuring ≥3 cm in diameter
(c) The presence of high-grade dysplasia or pancreatic cancer on cytology
12. Patients with a solid-pseudopapillary neoplasm should be referred to a multidisciplinary group for consideration of surgical resection (Strong recommendation, low quality of evidence)
13. MRCP is the preferred modality for pancreatic cyst surveillance, given the lack of radiation and improved delineation of the main pancreatic duct. EUS may also be the primary surveillance tool in patients who cannot or choose not to have MRI scans (Conditional recommendation, very low quality of evidence)
14. In the absence of concerning features (**Table 3**), which warrant increased surveillance or referral for further evaluation, cyst size guides surveillance intervals for presumed IPMNs and MCNs (**Figure 2**; Conditional recommendation, very low quality of evidence)
15. Surveillance should be discontinued if a patient is no longer a surgical candidate (Strong recommendation, very low quality of evidence)
16. It is reasonable to assess the utility of ongoing surveillance in those >75 years old. An individualized approach for those 76–85 years should be considered including an informed discussion about surgery (Conditional recommendation, very low quality of evidence)
17. Patients with a surgically resected serous cystadenoma, pseudocyst, or other benign cysts do not require any follow-up after resection (Strong recommendation, very low quality of evidence)
18. Resected MCNs without pancreatic cancer do not require postoperative surveillance (Strong recommendation, low quality of evidence)
19. All surgically resected IPMN require postoperative surveillance (Strong recommendation, very low quality of evidence)
20. Patients should be followed on a yearly basis for at least 5 years following resection of a solid-pseudopapillary neoplasm (Conditional recommendation, very low quality of evidence)

CEA, carcinoembryonic antigen; EUS, Endoscopic ultrasound; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm.

Table 2. Characteristics of pancreatic cysts

Cyst type	Clinical associations	Imaging and fluid analysis
Non-neoplastic		
Pseudocyst	Acute and/or chronic pancreatitis	May contain fluid alone or debris Aspirate: Brown fluid, high amylase/lipase, low CEA
Neoplastic		
Serous cystadenoma	75% in women 6th decade	Microcystic / honeycomb, oligocystic less common Aspirate: low CEA, low amylase/lipase
IPMN	Men=Women 7th decade	Mucin producing, Aspirate: high CEA, high amylase
Side branch	Most common incidental cyst Low risk of cancer progression May be multifocal	Communication with main pancreatic duct Aspirate: high CEA, high amylase
Main duct	Much less common than side branch Higher risk of cancer	Dilated main pancreatic duct, may be segmental, patulous orifice in 50%
Mixed	Rare; appears to have same cancer risk as main duct	Side Branch IPMN combined with main duct IPMN
Mucinous cystic neoplasm	Almost exclusively in women 5th to 7th decade	Vast majority found in the body or tail Unilocular, may have septations or wall calcification, no main duct communication Mucin-producing Aspirate: high CEA, variable amylase
Solid-pseudopapillary neoplasm	10:1 women:men ratio Most commonly present in 20s, although wide age range	Single cysts occur anywhere in pancreas, smaller ones more solid without cystic degeneration
Cystic pancreatic neuroendocrine tumor	Usually non-functioning Men=Women incidence, 5th-6th decade May be associated with MEN I	Cytology: neuroendocrine tumor Aspirate: low CEA, low amylase/lipase

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

also described in children and in adults over the age of 50. They can occur in any part of the pancreas. A systematic review of 484 studies showed that the most common presentations were abdominal pain (63%) or were incidental/asymptomatic (38%). (14) Smaller tumors are mostly solid with larger ones having a mixed solid and cystic appearance. Aggressive tumor behavior is found pathologically in ~10%. Unlike pancreatic adenocarcinoma, outcomes are excellent with a 5-year disease-specific survival of over 98% (14).

Cystic pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors are rare and usually nonfunctioning. They may be solid, cystic, or mixed in morphology. They may occur sporadically or in individuals with multiple endocrine neoplasia type 1. They are equally common in women and men with peak presentation in the 60 s. EUS-guided fine needle aspiration (FNA) is often required for an accurate diagnosis.

Other pancreatic cysts

Other, very rare pancreatic cysts include simple cysts with true epithelia lining, lymphoepithelial cysts, and mucinous non-neoplastic cysts. All of these have no known malignancy risk. Pancreatic ductal adenocarcinoma, and the extremely rare acinar cell adenocarcinoma, may have cystic degeneration on imaging and mimic other pancreatic cysts.

METHODOLOGY

A literature search was performed by a health sciences librarian of Pubmed and Embase through July 2016 using the subject headings pancreatic cyst and pancreatic neoplasm. A second search combined the first one with the imaging modalities of EUS, CT, MRI, and endoscopic retrograde cholangiopancreatography (ERCP). A search was also performed of the MeSH term cyst fluid with a subheading of analysis. The searches were limited to English language, and excluded case reports, comments, editorials, or letters. Additional articles were obtained from review of references from retrieved articles as well as articles that were known to the authors.

The strength of recommendation and the quality of evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology based on study design, study quality, consistency, and directness (15). The strength of recommendation was assigned as "strong" when the evidence shows the benefit of the treatment clearly outweighs any risk, and as "conditional" when uncertainty exists about

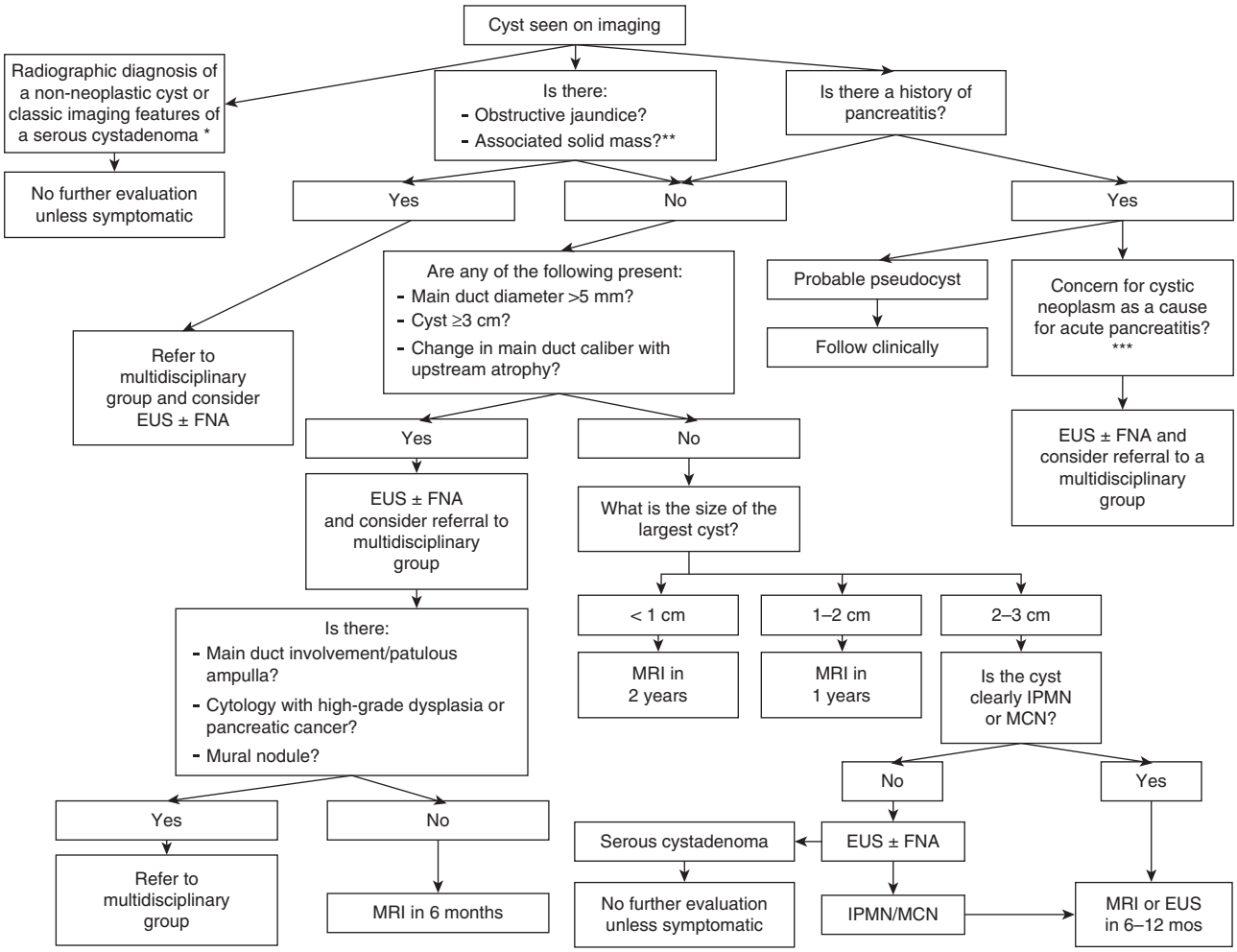

Figure 1. Approach to a patient with a pancreatic cyst. *Pathognomonic radiographic features of a serous cystadenoma are a microcystic appearance with a central stellate scar. **Occasionally benign lesions can have a solid appearance. In cases where the diagnosis is unclear EUS±FNA should be performed. ***Unusual cystic features or present at initial onset of acute pancreatitis. EUS, endoscopic ultrasound; FNA, fine needle aspiration.

Table 3. High-risk characteristics for mucinous pancreatic cysts

Symptoms
Jaundice secondary to the cyst
Acute pancreatitis secondary to the cyst
Elevated serum CA 19-9 when no benign cause for elevation is present
Imaging findings
Mural nodule or solid component within the cyst or pancreatic parenchyma
Main pancreatic duct diameter of >5 mm
Change in main duct caliber with upstream atrophy
Size ≥3 cm
Increase in cyst size ≥3 mm/year
Cytology
High-grade dysplasia or pancreatic cancer

the risk-benefit ratio. Four levels of evidence were used, high, moderate, low, and very low. The quality of the evidence is graded as follows: "high" if further research is unlikely to change our confidence in the estimate of the effect; "moderate", if further research is likely to have an impact and may change the estimate; "low", if further research is very likely to change the estimate; "very low", if an effect is very uncertain.

PANCREATIC CYST DIAGNOSIS

Question: Is the pancreatic cyst causing symptoms?

Recommendations

1. We recommend caution when attributing symptoms to a pancreatic cyst. The majority of pancreatic cysts are asymptomatic and the nonspecific nature of symptoms requires clinical discernment (Conditional recommendation, very low quality of evidence).

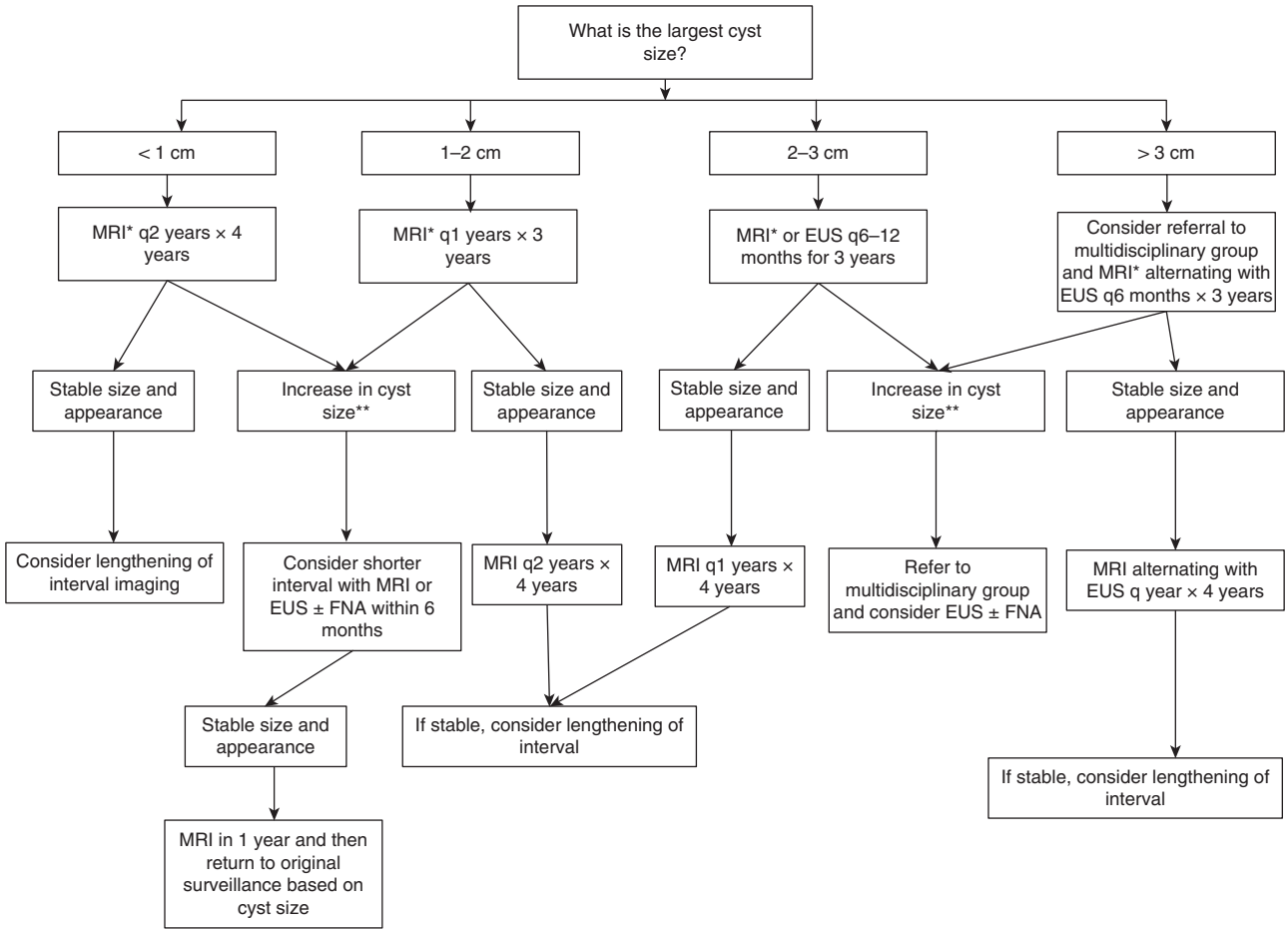

Figure 2. Surveillance of presumed IPMN or MCN. *Surveillance should preferably be performed with same imaging modality in attempt to capture consistency in size measurements. **≥3 mm/year. IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm.

Summary of evidence

Deciding whether a cyst is the cause of symptoms may be straight forward as in the case of biliary obstruction or may be very difficult as in the case of nonspecific abdominal symptoms. Although most pancreatic cysts are incidentally found in asymptomatic patients, symptomatic cysts are reported in 50–84% in surgical case series (16–18). Symptomatic pancreatic cysts are more likely to be malignant in surgical series (19) and mucin-producing cysts are the most common type of resected symptomatic pancreatic cyst. A recent meta-analysis of IPMNs evaluated 13 studies in the analysis of symptoms as a risk for malignancy (20). There was a weak association between symptoms and malignancy with an odds ratio (OR) 1.6 (CI 1.0–2.6). The most common symptom in a surgical case series of 134 patients with symptomatic pancreatic cysts was abdominal pain (69%), followed by weight loss (38%), pancreatitis (36%), jaundice (18%), back pain (18%), palpable mass (5%), and postprandial fullness (4%) (16). Abdominal pain or other nonspecific symptoms are usually not attributable to the cyst even if pain was the indication for the abdominal imaging. In this surgical series, 44% of those who had pancreatitis and a neoplastic cyst were initially misdiagnosed as having a pseudocyst. This emphasizes the important point that neoplastic cysts can cause acute pancreatitis, a consideration that must always be considered in patients over the age of 40 with acute pancreatitis and a cyst.

Question: What imaging techniques should be used to characterize a pancreatic cyst? How accurate are the imaging tests?

Recommendations

2. MRI or magnetic resonance cholangiopancreatography (MRCP) are the tests of choice because of their non-invasiveness, lack of radiation, and greater accuracy in assessing communication between the main pancreatic duct and the cyst (which is a characteristic of side-branch IPMNs). Pancreatic protocol CT or EUS are excellent alternatives in patients who are unable to undergo MRI. Indeterminate cysts may benefit from a second imaging modality or cyst fluid analysis via EUS (Conditional recommendation, very low quality of evidence).
3. Use caution when using imaging to diagnose cyst type or concomitant malignancy; the accuracy of MRI or MRCP in

diagnosing cyst type is 40–50% and in determining benign vs. malignant is 55–76%. The accuracy for CT and EUS without FNA is similar (Conditional recommendation, very low quality of evidence).

Summary of evidence

The goal of imaging is to characterize the type of cyst and to assess for high-grade dysplasia or pancreatic cancer. A systematic review of imaging modalities for pancreatic cysts concluded that "CT is a good initial investigation" with MRCP being used only when added information is needed (21). Nineteen studies (three prospective) of 1,060 patients with definitive histology results were included. The accuracy of CT for identifying benign from malignant cysts was 71–80%. CT was able to assess communication between the main pancreatic duct and the cyst with 80% sensitivity in distinguishing IPMN vs. other cyst type. The accuracy of MRI or MRCP for differentiating a benign from a malignant cyst ranged from 55 to 76%, with 96% sensitivity for diagnosing an IPMN from other cyst types, presumably due to its high accuracy in identifying main pancreatic duct communication with the cyst. In this systematic review, there were eight studies directly comparing imaging modalities. Three of four studies that compared MRI with CT found them equivalent; one study found MRI superior for the diagnosis of an IPMN. Although this systematic review concluded that CT should be the initial study, they did not take into account the lack of radiation with MRI and the greater accuracy in characterizing IPMNs. A recent review on imaging for pancreatic cysts concluded that MRI has superior sensitivity for detecting cysts, although both modalities are limited by a substantial rate of misdiagnosis for cyst type (22). MRI is better than CT for depicting internal morphology of the cyst, although it has lower spatial resolution, is insensitive for identifying calcification, and can be affected by motion artifact.

EUS imaging alone (without cyst fluid evaluation) was accurate for diagnosing a benign from a malignant cyst 65–96% of the time. (22) This was similar to the accuracy of MRI and CT scan and, given its more invasive nature, we do not recommend it as first-line examination for small cysts with a clear diagnosis and no concerning features. However, EUS is more accurate for identifying a mural nodule than MRI. Contrast-enhanced EUS is helpful for differentiating a mural nodule from mucin; however, it is currently not FDA-approved (23). There are a small number of studies assessing the effect of combining imaging modalities. A multicenter, prospective, observational study found increased sensitivity for identifying IPMNs and MCNs, as well as cysts with high-grade dysplasia or pancreatic cancer, when MRI was combined with EUS compared with either modality alone.(24) Larger, retrospective studies have shown similar findings when combining CT or MRI with EUS (25).

A systematic review evaluated four positron emission tomography (PET) studies to identify benign from malignant pancreatic cysts (21). PET alone was inferior to CT, but when combined with CT it was superior to CT alone. A recent prospective study of 18 F-FDG PET/CT, MDCT, and MRI combined with MRCP in 31 patients with definitive histology found that PET/CT had a diagnostic accuracy of 94% compared with 77% for MDCT and 87% for MR (26). There is insufficient evidence to support the use of PET-CT currently.

Historically, ERCP has been utilized to evaluate pancreatic cysts but, given its procedural risks and the superiority of EUS and MRCP, ERCP is no longer recommended for either cyst diagnosis or surveillance except for a limited role in the evaluation of main duct IPMN.

Other novel imaging techniques include secretin-stimulated MRCP. The addition of secretin to MRCP improves visualization of communication between the main pancreatic duct and a pancreatic cyst, although the communication was visualized *solely* on the secretin-stimulated study in only 5% of patients (27). This small incremental value may not justify the cost of secretin.

PANCREATIC CYST MANAGEMENT

Question: Which patients should have no further evaluation?

Recommendations

4. Patients who are not medically fit for surgery should not undergo further evaluation of incidentally found pancreatic cysts, irrespective of cyst size (Strong recommendation, low quality of evidence).
5. Patients with asymptomatic cysts that are diagnosed as pseudocysts on initial imaging and clinical history, or that have a very low risk of malignant transformation (such as SCAs) do not require treatment or further evaluation (Conditional recommendation, low quality of evidence).

Summary of evidence

Two studies have evaluated the risk of death from factors other than pancreatic cancer in patients with IPMNs (28,29). Sahora used the Charlson comorbidity index (CACI) in 725 patients with IPMNs, of which 55% underwent resection and 45% underwent surveillance. The CACI scores a total of 22 conditions and each condition is assigned a score of 1, 2, 3, or 6 with the sum of the scores being used to predict mortality (30). After a median follow-up of 5 years, 24% of the patients had died and 78% of the deaths were not related to IPMNs. Multivariate regression analysis showed that the chance of a non-IPMN-related death within 3 years of diagnosis is 11-fold higher for patients with a CACI of 7 or more. The median survival time for patients with a CACI score of $\geq$7 was 43 months. The authors concluded that the CACI can be used to identify patients who are not likely to benefit from pancreatic resection. Kawakubo *et al.* used an alternative comorbidity scoring system, the Adult Comorbidity Evaluation 27 (ACE-27) to evaluate 793 patients with IPMN, 6.8% of whom were resected. The ACE-27 grades patients into the following four comorbidity categories: none, mild, moderate, and severe. During a median follow-up of 50 months, 15% died with the cause of death being pancreatic cancer in 26%, extrapancreatic cancer in 38%, other diseases in 32%, and unknown in 3.4%. Both age at diagnosis and an ACE-27 category of moderate or severe significantly increased the risk of a non-pancreatic cancer death. These data suggest that patients with multiple comorbidities have a high risk of dying

from causes unrelated to their IPMNs, and are unlikely to benefit from surveillance. The exception to the rule of avoiding further evaluation in inoperable patients is in symptomatic cysts, for example, palliative stenting in patients with jaundice.

If an asymptomatic cyst is diagnosed as a non-neoplastic cyst on initial imaging, no further treatment or evaluation is warranted (**Figure 1**). The most common non-neoplastic cysts are pseudocysts, which usually present in the setting of acute or chronic pancreatitis. They require no further evaluation when asymptomatic (31). Similarly, if the initial imaging shows classic findings of a SCA—microcystic changes with a central scar—no further evaluation is warranted, given their very low risk of malignancy. (13) Some SCAs are macrocystic, resembling IPMNs or MCNs on imaging, and require cyst fluid analysis to confirm the diagnosis.

Question: What is the role of EUS-FNA and cyst fluid analysis in management decisions?

Recommendations

6. EUS-FNA and cyst fluid analysis should be considered in cysts in which the diagnosis is unclear, and where the results are likely to alter management. Analysis of cyst fluid CEA may be considered to differentiate IPMNs and MCNs from other cyst types, but cannot be used to identify IPMNs and MCNs with high-grade dysplasia or pancreatic cancer (Conditional recommendation, very low quality of evidence).
7. Cyst fluid cytology should be sent to assess for the presence of high-grade dysplasia or pancreatic cancer when the imaging features alone are insufficient to warrant surgery (Conditional recommendation, very low quality of evidence).
8. Molecular markers can help identify IPMNs or MCNs. Their use may be considered in cases in which the diagnosis is unclear and the results are likely to change management (Conditional recommendation, very low quality of evidence).

Summary of the evidence

Identifying cyst type. EUS-FNA has two potential roles. The first is characterizing the type of pancreatic cyst. The most commonly used marker is cyst fluid CEA, which was found to have a pooled sensitivity of 63% (95% CI 59–67) and specificity of 93% (95% CI 90–95) for identifying IPMNs and MCNs in a systematic review and meta-analysis of 18 papers (32). The most commonly used cutoff level is 192 ng/ml (33). Varying the cutoff level to either a very high (>800 ng/ml), or a very low level (<5 ng/ml), increases the specificity to over 95% for IPMNs or MCNs, and non-mucin-producing cysts, respectively, but at a cost of decreasing sensitivity to 50% (34). Other cyst fluid protein biomarkers have been examined, including CA 72-4, CA 125, CA 19-9, or CA 15-3, but were found to have a lower accuracy than CEA and are, therefore, not routinely used (34). Cyst fluid amylase levels can be useful when trying to exclude the presence of a pseudocyst, with very low levels (<250 IU/l) excluding a pseudocyst in 98% of cases (34). The evaluation of cytological specimens in pancreatic cysts is hampered by the low cellularity of the samples. This is highlighted in a prospective study that found that only 34% of cytology samples had adequate cellular material for evaluation (35). Two systematic reviews and meta-analyses evaluated studies from 937 and 1,438 patients, respectively, and found a pooled sensitivity of 54% (95% CI: 49–59) to 63% (95% CI, 56–70) and specificity of 88% (95% CI, 0.83–0.93) to 93% (95% CI, 90–95%) for identifying IPMNs or MCNs (35,36).

A number of DNA, RNA, protein, and metabolomic markers have been evaluated in cyst fluid (37). The majority of these are still early in development and not yet ready for translation into clinical practice. However, analysis of DNA mutations in cyst fluid has shown promise in identifying IPMNs and MCNs (38). Whole-exome sequencing of the major neoplastic pancreatic cysts identified distinct genetic profiles that can be used diagnostically to classify pancreatic cysts (39). Using highly sensitive techniques, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and/or a guanine nucleotide-binding protein (*GNAS*) mutation have between 84 and 96% sensitivity and 80 and 100% specificity for identifying an IPMN or MCN (40–44). Recent studies have shown that integrating molecular testing with cyst clinical features increases the sensitivity and specificity for identifying IPMNs or MCNs (41,43,44). Unfortunately, they are costly and have not helped determine cancer risk. In cases in which the diagnosis is unclear, and a change in diagnosis will alter management, analysis of these mutations using highly sensitive techniques may be considered.

Several devices have been developed to improve tissue acquisition, and thus diagnostic yield. A cytology brush (EchoBrush; Cook Endosocpy, Winston-Salem, NC, USA) showed variable results, and was associated with a high rate of adverse events in some studies (45–47). We do not recommend its use. A new through the needle micro biopsy forcep (Moray micro forceps; US Endoscopy, Mentor, Ohio) has been developed. Preliminary case reports are promising, but larger, prospective, multicenter studies are required. Needle confocal microscopy (nCLE) probes can be placed directly into pancreatic cysts via a 19-gauge FNA needle and generates an *in vivo* microscopic image of the cyst epithelium. It has been evaluated in a number of studies showing a sensitivity of 59–69%, with 100% specificity, for differentiating SCAs from other types of pancreatic cysts (48–50). A prospective, single center study again had an excellent specificity with 80% sensitivity for differentiating IPMNs and MCNs from other cyst types (51). Although promising, only a small number of cases in these studies were compared with the gold-standard histopathology. We await the results of ongoing studies to provide additional data as to its potential role.

Identifying high-grade dysplasia or pancreatic cancer. In contrast to determining the type of cyst, cyst fluid CEA is not helpful for identifying the presence of high-grade dysplasia or pancreatic cancer. This was highlighted in a systematic review and meta-analysis of 504 patients, which found a pooled sensitivity of 65% (95% CI, 57–73) and specificity of 66% (95% CI, 59–72)

for identifying high-grade dysplasia or pancreatic cancer in IPMNs or MCNs (52). In contrast, cytology can be helpful. A recent systematic review and meta-analysis found that cytology has an excellent pooled specificity for pancreatic cancer of 90.6% (95% CI, 0.81–0.96), but suffers from a low sensitivity of 64.8% (95% CI, 0.44–0.82) (53). There are a large number of studies examining different molecular markers for identifying high-grade dysplasia or pancreatic cancer in IPMNs or MCNs; however, these are still early in development and there is insufficient evidence to recommend their routine use in clinical practice (37,54). Similarly, new devices such as the needle micro biopsy forceps may be helpful, but there are no data currently published to support its use for this indication.

Cyst ablation. A number of studies have examined whether ethanol alone, or in combination with paclitaxel, can be used to ablate pancreatic cyst epithelium and thus obviate the need for surgery. The results have been varied, with cyst resolution reported in 33–79% of the cases (55–63). The reported rate of adverse events (~12%) is higher than that reported for routine EUS-FNA, and include fever, abdominal pain, pancreatitis, peritonitis, and splenic and portal vein thrombosis. Radiofrequency ablation is an alternative to alcohol or Paclitaxel. A preliminary study of radiofrequency ablation in six cysts reported resolution of the cyst in two cases, and a 49% decrease in size in three cysts (64). To date, it has not been shown that decreasing cyst size in IPMNs or MCNs eradicates the risk of progression to high-grade dysplasia or pancreatic cancer, with one report of pancreatic cancer developing following alcohol ablation (55). Furthermore, patients with IPMNs are at increased risk of pancreatic cancer at a site separate to the cyst, and thus ablation does not remove the need for surveillance. There is insufficient evidence to support the routine use of cyst ablation. It may be considered in patients who refuse, or are not a candidate for surgery. Ideally, these patients should be enrolled in a clinical trial to further evaluate the efficacy of this therapy.

CYST SURVEILLANCE

Question: Which patients should enter into a cyst surveillance program?

Recommendations

9. Cyst surveillance should be offered to surgically fit candidates with asymptomatic cysts that are presumed to be IPMN or MCNs (Conditional recommendation, very low quality of evidence).

Summary of evidence

There are several significant clinical questions that surround surveillance of pancreatic cysts. It is unclear whether there is any survival benefit of surveillance over no surveillance, given the relatively low rates of malignancy (15–42%) in surgically resected specimens in the literature. There are currently no prospective studies determining whether cyst surveillance alters mortality; therefore, the utility of surveillance is unproven (3). However, there is strong direct evidence that IPMNs and MCNs are present for years before they progress to pancreatic cancer. Furthermore, patients who do undergo surgery for high-grade dysplasia or very early pancreatic cancer have improved survival rates, suggesting that early detection and intervention may be beneficial (65–67). Surveillance of pancreatic cysts, therefore, affords us the opportunity of reducing cancer deaths related to pancreatic cancer (68).

Before embarking on cyst surveillance, the physician should review the patient's risk of developing pancreatic malignancy, their approximate life expectancy, their comorbid conditions, and whether they are a surgical candidate. It is important to convey to the patient that uncertainty remains in the value of surveillance. The risks of pancreatic surgical resection need to be weighed against the risk of malignant transformation of the cyst and the inherent limitations of surveillance. The site of the cystic lesion must also be taken into account; the threshold for a distal pancreatectomy for a lesion in the body or tail may be lower than a pancreaticoduodenectomy for a lesion in the head of the pancreas. Pancreatic cyst surveillance should be offered to surgically fit patients with asymptomatic IPMNs or MCNs.

Patients with non-neoplastic cysts such as pseudocysts do not need surveillance. As discussed previously, patients with SCAs have a tiny risk of malignant transformation (13). If imaging has classic features of a SCA, such as a microcystic appearance with a central stellate scar, then we do not recommend surveillance. If the diagnosis is unclear, EUS-FNA with cyst fluid analysis should be considered to confirm the diagnosis.

Question: Which cysts need increased surveillance or referral to a multidisciplinary group for further evaluation?

Recommendations

10. Patients with IPMNs or MCNs with new onset or worsening diabetes mellitus, or a rapid increase in cyst size (of >3 mm/year) during surveillance, may have an increased risk of malignancy so should undergo a short-interval MRI or EUS±FNA. (Conditional recommendation, very low quality of evidence).
11. Patients with IPMNs or MCNs with any of the following features should undergo EUS±FNA and/or be referred to a multidisciplinary pancreatic group for further evaluation (Strong recommendation, very low quality of evidence):

(a) Any of the following symptoms or signs: jaundice secondary to the cyst, acute pancreatitis secondary to the cyst, significantly elevated serum CA 19-9.

(b) Any of the following imaging findings: the presence of a mural nodule or solid component either within the cyst or in the pancreatic parenchyma, dilation of the main pancreatic duct of >5 mm, a focal dilation of the pancreatic duct concerning for main duct IPMN or an obstructing lesion, IPMNs or MCNs measuring ≥3 cm in diameter.

(c) The presence of high-grade dysplasia or pancreatic cancer on cytology.

12. Patients with a solid-pseudopapillary neoplasm should be referred to a multidisciplinary group for consideration of surgical resection (Strong recommendation, low quality of evidence).

Summary of evidence

IPMNs and MCNs. Certain features in IPMNs and MCNs are associated with an increased risk of the cyst harboring high-grade dysplasia or pancreatic cancer. This risk varies greatly depending on the clinical and imaging findings. Some features such as a solid component or jaundice are associated with a high risk of malignancy, whereas others, such as a slight increase in cyst size, carry a far lower risk. The decision whether or not to resect a cystic lesion is best determined by a pancreatic team that integrates multiple different factors, such as patient comorbidities and life expectancy, the type of surgery required to remove the lesion, and the estimated morbidity and mortality associated with surgery. In the sections below, we recommend referral to a multidisciplinary group not only for patients with cysts, which clearly require surgical resection, but also for cysts with concerning features. In the latter group many patients may not require surgical resection at that point in time; however, a careful evaluation, and review of the benefits of surveillance vs. surgery, is appropriate. In addition, it is essential to include the patient in the decision-making process. Patients should understand the potential risks and benefits of surgery and surveillance. We therefore recommend referral to a multidisciplinary team with expertise in pancreatic cysts and pancreatic surgery. Input from a pancreatic multidisciplinary group has been shown to alter patient management, including changing the management plan from surgery to careful surveillance in 30% of patients seen (69). If surgery is considered, it should be performed at a tertiary referral center, and by an experienced surgeon, where both the center and the surgeon perform a large number of pancreatic operations. The mortality rate is almost threefold higher when a pancreaticoduodenectomy is performed by an inexperienced surgeon at a low-volume center, as compared with when it is performed by experienced surgeons at high volume centers (~11–15% vs. ~1–5%) (70,71).

Concerning symptoms. The presence of obstructive jaundice due to the cyst is concerning for the presence of pancreatic cancer, and these patients should be urgently referred for further evaluation by a multidisciplinary group and consideration of surgical resection (72,73). An elevated CA19-9 (>37 U/ml) has been found in a meta-analysis to have a pooled sensitivity of 40%, a specificity of 89%, and an OR of 4.34 (95% CI, 2.65–7.10) for the presence of high-grade dysplasia or cancer in IPMNs (74). It is important to remember that a number of benign diseases can cause an elevation of CA19-9. Patients with an IPMN and an elevated CA19-9, in whom no benign cause for an elevated CA19-9 is found, should be referred for evaluation at a multidisciplinary clinic. There are a number of other features, which have been shown in some, but not all studies to be associated with an increased risk of high-grade dysplasia or pancreatic cancer. The presence of acute pancreatitis secondary to the cyst is associated with an increased risk of cancer in several (72,75), but not all studies (76). There is also an association between new-onset diabetes mellitus and the risk of pancreatic cancer. Approximately 1% of adults over than 50 years with new-onset diabetes will develop pancreatic cancer within 3 years of diagnosis, whereas almost two-thirds of patients with pancreatic cancer have diabetes mellitus (77). Several studies have shown that patients with IPMNs who have new onset, or worsening control of diabetes mellitus, have an increased risk of high-grade dysplasia or pancreatic cancer (73,78,79). We recommend careful evaluation of patients with pancreatic cysts and new onset, or worsening diabetes mellitus, with consideration of EUS or MRI.

Concerning imaging. There are a number of features associated with an increased risk of an IPMN or MCN harboring high-grade dysplasia or pancreatic cancer. One of the most concerning features is the presence of a mural nodule, which was associated with an OR 9.3 (CI 5.3–16.1) in a systematic review and meta-analysis of over 1,400 patients (20). A second systematic review found similar results with an OR 7.73 (95% CI, 3.38–17.67) (3). Patients with IPMNs, but not patients with MCNs, are at risk of developing malignancy in the pancreatic parenchyma anatomically separate from the cyst, which is called a "concomitant" pancreatic cancer. In a large, multicenter retrospective study in almost 350 patients 2% of patients developed concomitant pancreatic cancer (80), whereas a smaller prospective study found that 4% of patients with IPMNs developed a concomitant pancreatic cancer over a 17-year period (81). This highlights the importance of evaluating not only the cyst, but also the entire parenchyma on imaging. The presence of a mural nodule or solid component within a cyst or the pancreatic parenchyma warrants referral further evaluation by a multidisciplinary group with consideration of EUS±FNA and surgical resection.

In a systematic review and meta-analysis of 358 IPMNs from eight studies, main pancreatic ductal dilation of >6 mm was associated with an increased risk of high-grade dysplasia or pancreatic cancer with a pooled OR 7.27 (95% CI, 3.0–17.4) (20). Interestingly, a different systematic review of four studies found an increased OR (2.38) but with wide, and not significant CIs (95% CI 0.71–8.00) (3). Large surgical series have consistently reported an increased risk of high-grade dysplasia of ~60% (range 36–100%), with a rate of pancreatic cancer of ~44% (range 11–81%) (82,83). There is significant debate as to the optimal diameter of the main pancreatic duct to use as a cutoff. It is clear that the larger the duct diameter, the greater the risk of high-grade dysplasia or pancreatic cancer. We recommend use of a conservative duct diameter, >5 mm, for referring a patient for further evaluation. Similarly, an abrupt change in the caliber of the pancreatic duct with upstream dilation concerning for obstruction also warrants referral for further evaluation. Most patients with only minimal ductal dilation will not require surgical resection; however, early referral is appropriate.

A large cyst diameter is also associated with increased risk of high-grade dysplasia or pancreatic cancer in IPMNs and MCNs.

There is ongoing debate as to the optimal size cutoff to use, with some groups reporting a small number cases of high-grade dysplasia and pancreatic cancer in IPMNs measuring less than 3 cm (84); other studies found that a cutoff of >3 cm has a low specificity for high-grade dysplasia or pancreatic cancer (85,86); with still other groups recommending a higher cutoff of ≥4 cm (87,88). Most centers start considering surgical resection when an IPMN or MCN measures >3 cm. This size cutoff is supported by a systematic review of 644 cysts from six studies (OR for high-grade dysplasia or pancreatic cancer of 2.97 (95% CI 1.82–4.85)), as well as by a systematic review and meta-analysis of 1,058 IPMNs from 16 studies (OR 62.4 (95% CI, 30.8-126.3)) (3,20). On the basis of these data, we recommend referral for IPMNs or MCNs measuring ≥3 cm. It may be appropriate for many of these patients to undergo surveillance in the absence of any other concerning features. However, referral is appropriate, so that the pros and cons of surgery vs. surveillance can be discussed.

A rapid increase in cyst size was associated with an increased risk of high-grade dysplasia or pancreatic cancer in two retrospective studies, which found that IPMNs with an increase in cyst size of ≥2 mm/year were associated with a higher risk of high-grade dysplasia or pancreatic cancer. The evidence to support this cutoff is limited. In addition, studies have shown that the interobserver variability in measuring pancreatic cysts may be as high as 4 mm. (89) Despite these limitations, based on the available data, we recommend that IPMNs or MCNs, which rapidly increase in size, should undergo careful surveillance with a short-interval MRI or EUS±FNA within 6 months. If there are concerning features, or ongoing rapid increase in cyst size, patients should be referred for further evaluation.

Concerning cytology. Cytology has a low sensitivity of 64.8% (95% CI, 0.44–0.82), but has excellent specificity of 90.6% (95% CI, 0.81–0.96) for pancreatic cancer.(53) The presence of high-grade dysplasia or pancreatic cancer warrants urgent referral to a multidisciplinary pancreatic group.

Solid-pseudopapillary neoplasms. Solid-pseudopapillary neoplasms are rare tumors that occur in young women. They carry a risk of aggressive behavior, with vascular involvement in 4.6%, lymph node in 1.6%, and distant metastases reported in 7.7% of patients.(14) Surgical resection is recommended for these patients and we recommend referral to a high-volume pancreatic center.

Question: Which imaging modality should we use for surveillance?

Recommendations

13. MRCP is the preferred modality for pancreatic cyst surveillance, given the lack of radiation and improved delineation of the main pancreatic duct. EUS may also be the primary surveillance tool in patients who cannot or choose not to have MRI scans (Conditional recommendation, very low quality of evidence).

Summary of evidence

There is no clear best surveillance imaging modality at this time based on the available data. Pancreatic protocol CT or MRI with MRCP are the most commonly utilized methods for evaluating cyst size, morphology, location, internal contents, multiplicity, and communication with the main pancreatic duct (90–94). In general, pancreatic cyst detection is higher with MRI than with CT (19.9% vs. 1.2–2.6%) (95–97). A consensus statement by radiologists recommended a dedicated MRI with MRCP as the imaging modality of choice for pancreatic cysts, given its superior contrast resolution that allows excellent evaluation of main duct communication, septae, and mural nodules (98). In addition, MRI has the advantage of avoiding radiation exposure, especially if patients are expected to undergo long-term or frequent surveillance imaging.

One key requirement of surveillance is to identify malignant transformation within a cyst. A recent meta-analysis of 37 studies incorporating 4,073 patients evaluated this question (99). A subset of four studies (159 patients) specifically evaluated the prediction of malignancy by CT and/or MRI by meta-analysis. The pooled sensitivity and specificity of CT or MRI to detect malignancy (compared with resected specimens) was 0.809 (95% CI, 0.71–0.88) and 0.762 (95% CI, 0.65–0.85). The same study evaluated PET in predicting malignancy and the meta-analysis of three studies (106 patients) revealed a pooled sensitivity of 0.968 (95% CI, 0.90–0.99) and specificity was 0.911 (95% CI, 0.81–0.99) (99). We await further studies evaluating PET-CT and there is insufficient evidence to support its routine use currently.

Radiologic imaging studies are less invasive than EUS; however, EUS may be more helpful for the diagnosis and differentiation of pancreatic cystic lesions because of its higher resolution than cross-sectional imaging modalities. EUS also allows for FNA of cystic lesions for biochemical, cytological, and molecular analysis that might be further helpful for diagnosis and differentiation. Overall, EUS has a higher sensitivity for differentiating benign vs. malignant, varying in most studies from 86 to 96%, but a lower specificity of 30 to 99%, when compared with CT or MRI (100–103). It is favored over other imaging studies when FNA is warranted for cytology, chemical, and/or molecular studies, although EUS is likely more operator-dependent than MRI or CT (80,91,92). EUS allows differentiation between true solid cyst components vs. mucin that appears as a smooth, well-defined hyperechoic rim with a hypoechoic center (104). True mural nodules have ill-defined borders with an isoechoic or hyperechoic center (104). The addition of EUS, with or without FNA, to CT or MRI increased the overall diagnostic accuracy for the diagnosis of pancreatic cystic neoplasms by 36% and 54%, respectively (25).

Question: How often should surveillance occur and what cyst size/characteristics should that depend upon?

Recommendations

14. In the absence of concerning features (**Table 3**) that warrant increased surveillance or referral for further evaluation, cyst size guides surveillance intervals for

presumed IPMNs and MCNs (**Figure 2**; Conditional recommendation, very low quality of evidence).

Summary of evidence

The goal of surveillance is to identify cysts that are likely to have either high-grade dysplasia or early pancreatic cancer that represent opportunities to intervene and ideally prevent the development of pancreatic cancer. Surveillance is therefore only appropriate for cysts that are presumed to be IPMN or MCNs, and is not indicated for other types of benign cysts. The diagnosis of an IPMN or MCN is usually a presumed diagnosis without actual tissue histology. In a small number of cases the diagnosis may be unclear despite EUS-FNA. In these cases, patients should be followed as presumed IPMNs/MCNs.

The data on which to base decisions on the optimal surveillance intervals are of low quality; however, most published guidelines agree that cyst surveillance intervals should generally be stratified based on cyst features and size. Where the literature does not have evidence to support guideline decisions, we provide practical recommendations. **Figure 2** provides an algorithm for surveillance of presumed IPMNs or MCNs. The cyst surveillance strategy is stratified based on cyst size. As previously discussed, cyst size is an imperfect surrogate for high-grade dysplasia or early pancreatic cancer.(3,20,84,105–115) However, at present, cyst size is the most practical surrogate we have. If an experienced radiologist reviews high-quality cross-sectional imaging, and reports no features concerning for malignancy, then radiographic surveillance is appropriate for the majority of IPMNs and MCNs (**Figure 2**).

As discussed previously, there are a number of clinical, imaging, and cytological features that are associated with an increased risk of high-grade dysplasia or cancer developing in an IPMN or MCN. Imaging features include the development of a mural nodule or solid component either within the cyst or the pancreatic parenchyma, dilation of the main pancreatic >5 mm, a focal dilation of the pancreatic duct concerning for main duct IPMN or an obstructing lesion, or IPMNs or MCNs that measure ≥3 cm in diameter. Many patients with these high-risk features will require close surveillance, rather than surgical resection; however, referral to a multidisciplinary pancreatic center for further evaluation is appropriate. Another high-risk finding, which may be associated with an increased risk of pancreatic cancer, is a rapid increase in cyst size; however, there is less evidence supporting this than the previously mentioned features. Two studies have shown that an increase in size of between 2 and 5 mm/year is associated with an increased risk of pancreatic cancer.(116,117) An important consideration when evaluating either overall cyst size, or increase in cyst size, is that there is considerable variation in the estimation of cyst size by different imaging modalities (CT vs. MRI vs. EUS). (118,119) Even within an imaging modality, such as MRI, the kappa for size agreement among radiologists was only 0.59 with a median s.d. difference of 4 mm.(89) Between multidetector CT and MRI, there was a median size difference of 1.5 mm with an absolute size difference of 2.1±1.8 mm. (120) Consistency in use of imaging modality may help reduce such variability and lead to more meaningful decision-making. On the basis of the current data on cyst growth rates and the interobserver variability in radiographic cyst size evaluation, a cyst growth rate of ≥3 mm/year warrants a shorter follow-up interval, with evaluation with EUS±FNA considered for cysts that undergo a rapid increase in size. There is a higher incidence of pancreatic cancer in patients with newly diagnosed diabetes mellitus. We therefore recommend a shorter surveillance interval of 6 months with either MRI or EUS for these individuals. If there is stabilization of the cyst size, or no concerning features found in the case of a newly diagnosed diabetic, then patients can return to standard surveillance.

Question: When should we stop cyst surveillance?

Recommendations

15. Surveillance should be discontinued if a patient is no longer a surgical candidate (Strong recommendation, very low quality of evidence).
16. It is reasonable to assess the utility of ongoing surveillance in those aged >75 years. An individualized approach for those aged 76–85 years should be considered including an informed discussion about surgery (Conditional recommendation, very low quality of evidence).

Summary of evidence

There are very little data to evaluate whether surveillance intervals can be extended, or whether surveillance should be discontinued if cysts are stable after a specified time period. The current American Gastroenterological Association guidelines are the only guideline that recommends stopping surveillance of pancreatic cysts (3). They recommend that surveillance should stop after 5 years if there are no high-risk features, and size of the cyst is stable. Studies of pancreatic cancer evaluating the progression from a genetic perspective found that it takes between 15 and 20 years for cancer to develop (121). Pancreatic cancer has developed in IPMNs up to 16 years after diagnosis (80,122,123). In contrast, other studies have found that the risk of malignant transformation in a cyst that is stable in size over 3–5 years is low (124). We recommend that surveillance intervals may be increased for cysts with no concerning features that are stable in size (**Figure 2**). Currently, there is insufficient evidence to support discontinuing surveillance after 5 years in patients who are still surgically fit.

It is appropriate to stop surveillance when the patient is no longer a surgical candidate because of comorbid conditions as previously discussed. The decision to pursue ongoing surveillance must take into account the risks of surgery as the patient ages or acquired comorbid conditions and is a decision that must be tailored to each patient's clinical situation.

A separate question is whether it is appropriate to continue surveillance past a certain age in a healthy individual. There are no studies to guide the decision of when to stop surveillance of pancreatic cysts, nor are cost effectiveness analyses available to estimate the cost-benefit ratio of pancreatic cyst surveillance in an elderly population. The United States Preventive Services Taskforce recommends screening for colon cancer until age 75, with

an individualized decision about whether to continue screening in individuals aged between 76 and 85 years (125). It appears reasonable to consider a similar approach to pancreatic cysts. Although there is no evidence to support this, we recommend continuing surveillance in patients until the age of 75 years. For patients between 76 and 85 years, an individualized surveillance plan is appropriate. We recommend having an informed discussion with the patient where their medical comorbidities are reviewed, a discussion of their personal potential morbidity and mortality if surgery was undertaken, and the risk of cyst progression is appraised.

Question: Who should have surveillance after cyst surgery? How often?

Recommendations

17. Patients with a surgically resected SCA, pseudocyst, or other benign cyst do not require any follow-up after resection (Strong recommendation, very low quality if evidence).
18. Resected MCNs without an associated pancreatic cancer do not require postoperative surveillance (Strong recommendation, low quality of evidence).
19. All surgically resected IPMN require postoperative surveillance (Strong recommendation, very low quality of evidence).
20. Patients should be followed on a yearly basis for at least 5 years following resection of a solid-pseudopapillary neoplasm (Conditional recommendation, very low quality of evidence).

Summary of evidence

Benign or very low risk cysts. If the final surgical pathology demonstrates SCAs, pseudocysts, and other benign cysts, they do not require surveillance.

MCNs. A recent large systematic review found that there were no cases of MCNs associated with synchronous lesion or recurrence in the absence of invasive carcinoma (126). Therefore, patients with surgically resected MCNs with low-, intermediate-, or high-grade dysplasia do not require surveillance. Patients with a surgically resected MCN with invasive cancer have no risk of developing a new MCN in the remnant pancreas, but they do carry a 25% risk of recurrence of their original cancer. They should therefore undergo standard surveillance-based pancreatic cancer guidelines for 5 years (127–129). No surveillance is required after 5 years.

IPMNS. IPMNs, unlike the other cystic neoplasms of the pancreas, are often multifocal. The remnant pancreas after the resection of an IPMN is therefore at risk of developing new IPMNs, progression of pre-existing IPMNs, or development of pancreatic cancers unrelated to an IPMN in the remnant pancreas. The development of any of these is called "recurrence" and the risk of recurrence varies depending on the grade of dysplasia in either the resected pancreas or at the margin. Retrospective studies have reported a high risk of recurrence, 17–65% in IPMNs with pancreatic cancer, and these patients should be followed per pancreatic cancer guidelines (130–138).

The second highest risk occurs in patients who have an IPMN with high-grade dysplasia resected, with recurrence rates of 13–31% reported, and these patients warrant careful surveillance (127–135). There are little data to guide the optimum surveillance interval; the median time to recurrence varies from 19 to 47 months, with a wide range of 4–180 months. We recommend surveillance with MRI or EUS on a 6-month basis for these patients.

Patients with a surgically resected IPMN with low- or intermediate-grade dysplasia have a lower rate of recurrence of 0–22% (130–138). Although some studies show a low risk of high-grade dysplasia or cancer after surgical resection, other studies show conflicting results (82,139–141). There is currently insufficient evidence to support no surveillance in these patients, although longer surveillance intervals may be reasonable. In the absence of pancreatic cysts in the remnant, surveillance with MRI every 24 months appears reasonable. If there is an IPMN in the remnant pancreas, then patients should be followed based on the size of the largest IPMN (**Figure 2**). In these cases, the shortest surveillance interval should be followed (i.e., if there is a 1.5 cm cyst then surveillance would be yearly). The development of concerning features in IPMNs in the remnant warrants further investigation as discussed previously.

Other malignant cysts. Patients with surgically resected solid-pseudopapillary neoplasm with negative margins have an excellent prognosis. However, recurrence is reported in 4.4% of patients with the median time to recurrence of 50.5 months (14). Surveillance is, therefore, recommended. There is very little evidence to guide the surveillance interval; however, imaging on a yearly basis for at least 5 years, followed by eventual cessation of surveillance, is reasonable.

CONCLUSION

Pancreatic cysts, and in particular IPMNs, are a common management problem facing gastroenterologists. The majority of incidentally found pancreatic cysts are side-branch IPMNs. The quality of evidence on which guideline recommendations are based is poor. We reviewed the available literature and combined it with expert recommendations to produce a practical management and surveillance approach to pancreatic cysts for the general gastroenterologist. The management algorithms herein do not address every possible clinical scenario and, therefore, it is imperative to tailor management to the individual patient. There is an urgent need for prospective, multicenter studies to provide evidence to guide future guidelines.

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CONFLICT OF INTEREST

Guarantor of the article: Grace H. Elta, MD, FACG.

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