ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts

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Abstract

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.

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 metaanalysis 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.

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

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)

Table 1. Summary and strength of recommendations continued	
Pancreatic cyst management	
4.	Patients who are not medically fi t 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 fi t 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, mucinproducing 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)

Table 1. Summary and strength of recommendations continued	
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, fi ne needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm.	

Types of Pancreatic Cysts

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.		

Methodology

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

Pancreatic Cyst Management

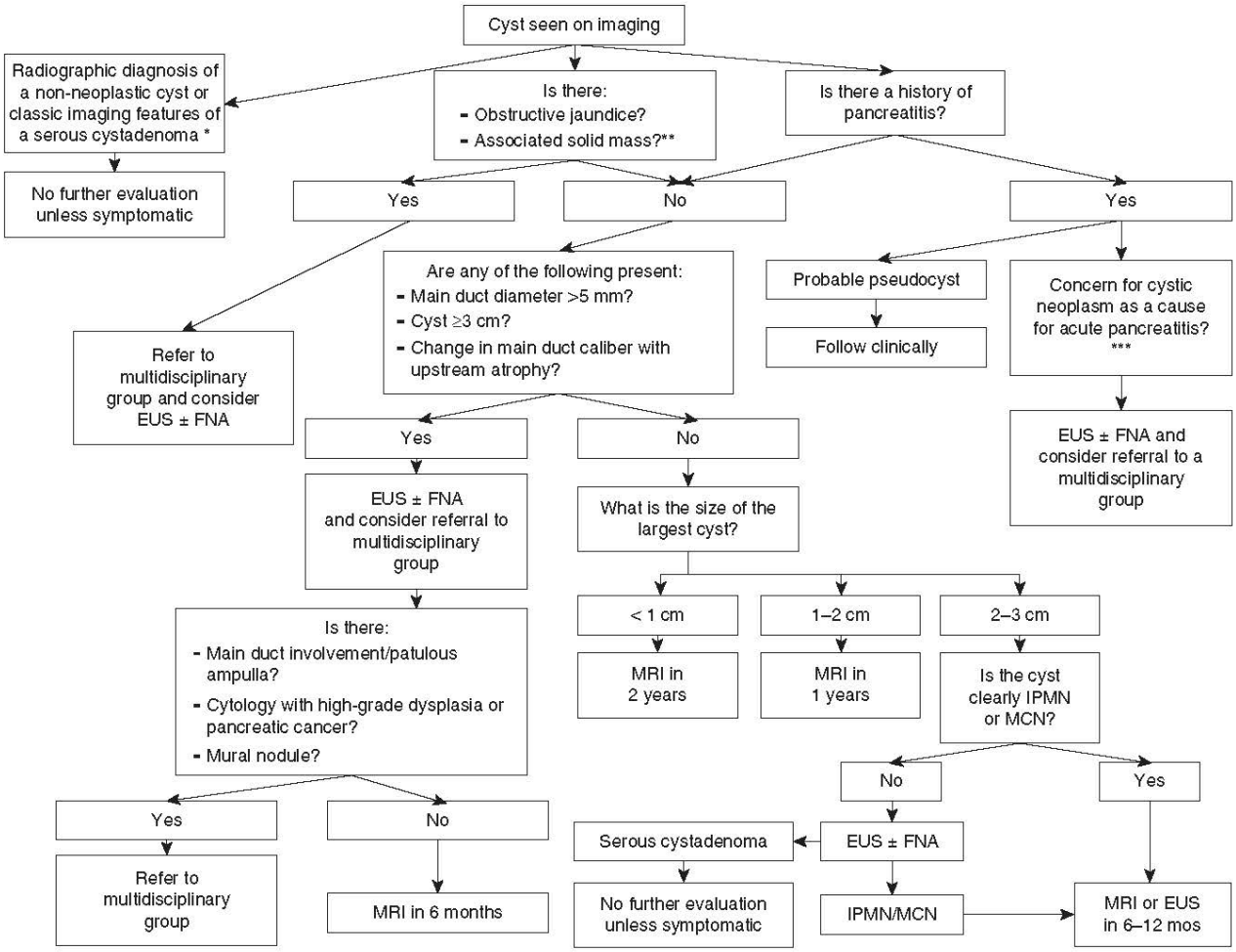

Figure 1. Approach to a patient with a pancreatic cyst. *Pathognomonic radiographic features of a serous cystadenoma are a microcystic appearance with a central stellate scar. **Occasionally benign lesions can have a solid appearance. In cases where the diagnosis is unclear EUS±FNA should be performed.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

Cyst Surveillance

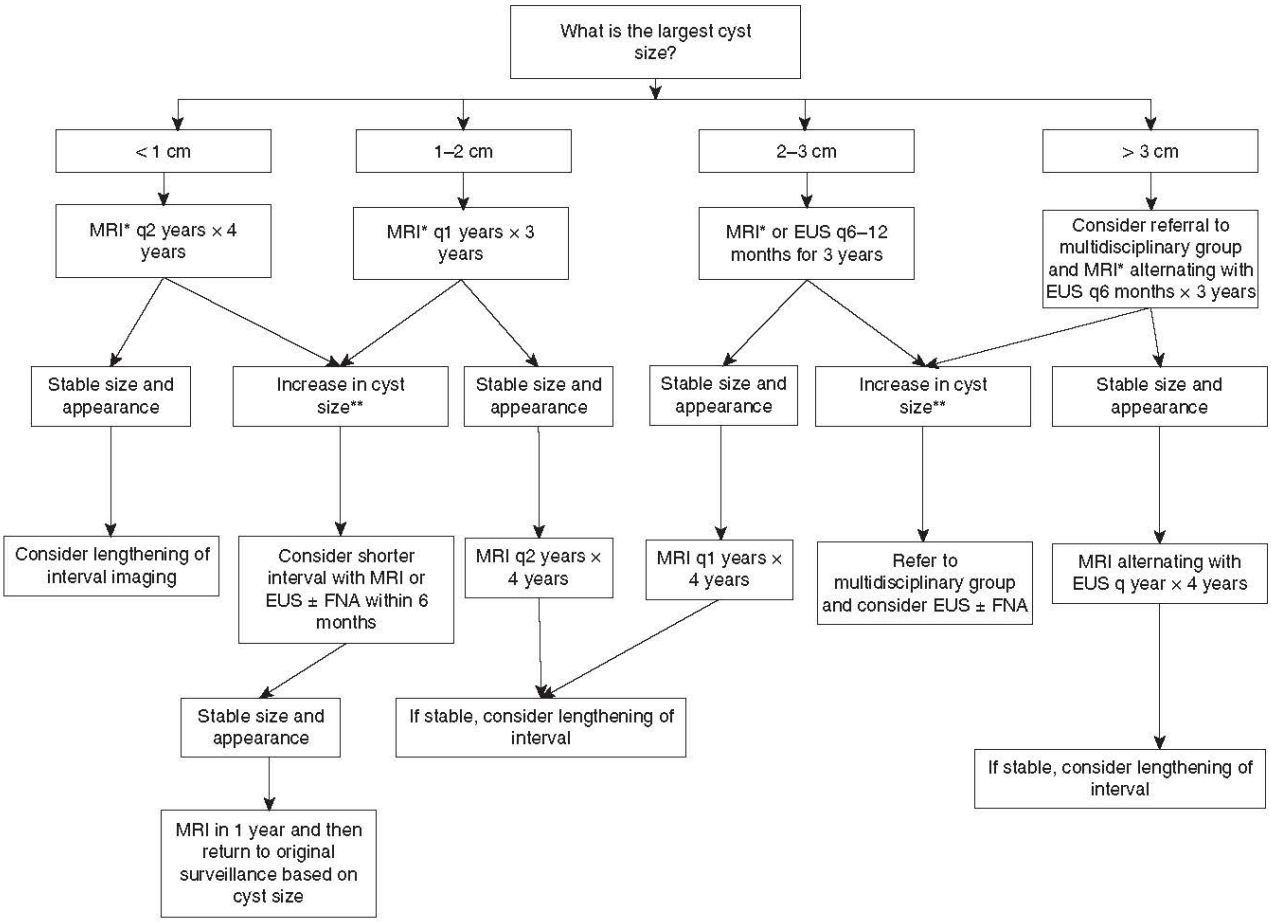

Figure 2. Surveillance of presumed IPMN or MCN. *Surveillance should preferably be performed with same imaging modality in attempt to capture consistency in size measurements. **≥3 mm/year. IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm.

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.