Arjun Chatterjee, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Tyler Stevens, MD, FACG, FASGE
Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Prabhleen Chahal, MD, FACG, FASGE
Director, Advanced Endoscopy Training, Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH

Diagnosis and management of pancreatic cystic lesions for the non-gastroenterologist

ABSTRACT

Although most pancreatic cystic lesions do not progress to cancer, they create concern for patients and their primary care physicians. The lack of consensus guidelines on diagnosis and surveillance of these lesions can lead to a management conundrum. We review current guidelines on diagnosis and management.

KEY POINTS

Magnetic resonance cholangiopancreatography with dynamic magnetic resonance imaging is the test of choice for diagnosis and assessment of high-risk or worrisome characteristics in cysts. Pancreatic-protocol computed tomography and endoscopic ultrasonography are suitable options if magnetic resonance imaging is contraindicated.

High-risk clinical and laboratory features include obstructive jaundice, recurrent pancreatitis, elevated serum carbohydrate antigen 19-9, presence of cells demonstrating high-grade dysplasia or neoplasia, and new-onset or worsening diabetes.

Pancreatic cystic lesions with high-risk features and those with a known high risk of malignancy, such as main duct intraductal papillary mucinous neoplasms and solid pseudopapillary tumors, should be referred for surgical excision.

Depending on clinical symptoms, suspected pancreatic cystic lesion type, and the presence of certain high-risk features, the monitoring period might range from 3 months to 2 years.

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With the enhanced quality and increased frequency of abdominal cross-sectional imaging, pancreatic cystic lesions (PCLs) are incidentally detected in apparently asymptomatic individuals,[1] with a pooled prevalence of up to 8%.[2] Although most of these lesions do not progress to cancer, their high prevalence and unclear potential for malignancy raise concern for patients and primary care physicians.[3–5] Thus, before making management decisions, it is necessary to describe PCLs by combining clinical and imaging data to determine the risk of malignancy. Several organizations have released guidelines[6–10] on the diagnosis and surveillance of PCLs, each with subtle distinctions, and none are aimed specifically at primary care physicians. In this review, we present a summary of current guidelines for diagnosis and management.

EPIDEMIOLOGY

The prevalence of PCLs in the general population has not been thoroughly investigated due to the inherent difficulty of examining a typically asymptomatic condition. Due to the increased use of abdominal imaging and developments in high-resolution cross-sectional imaging,[11] the prevalence of PCLs has gradually increased over the past 10 years.[12] Depending on the imaging modality used, the proportion of incidentally discovered PCLs ranges from 0.2% to 45.9%, with a pooled prevalence of 8%.[2,5,13] The estimated prevalence also varies according to geographical region, with an estimated frequency of 12.6% in the United States and

TABLE 1
Characteristics of neoplastic pancreatic cystic lesions

Characteristic	Serous cystic neoplasms	Solid pseudo-papillary tumors	Mucinous cystic neoplasms	Intraductal papillary mucinous neoplasms	Cystic pancreatic endocrine neoplasm	Pancreatic ductal adeno-carcinoma
Malignant potential	Benign	Can progress to malignancy			Malignant	
Age group	50–60	20–30	40–50	60–70	50–60	60–70
Sex predilection	Female more often than male			None		
Characteristic findings on cross-sectional imaging (computed tomography or magnetic resonance imaging)	Multicystic with central stellate scar	Solid growth with cystic degeneration	Solitary, unilocular, found in body or tail	Multifocal, communicates with main pancreatic duct, dilated main pancreatic duct	Complex cystic mass, enhancement of the cyst wall, hypervascular rim, found in body or tail	Irregular hypoechoic mass associated with an abrupt cutoff of the main pancreatic duct with upstream dilation
Endoscopic ultrasonography-guided fine needle aspiration cyst fluid analysis	Lower carcino-embryonic antigen (< 5 ng/mL), higher glucose, lower amylase	Not applicable	Higher carcinoembryonic antigen (> 192 ng/mL), lower glucose (< 50 mg/dL), positive mucin stain		Not applicable	
Treatment	No intervention is recommended if asymptomatic	Surveillance with or without resection			Resection	

Data from references 6–10, 19.

South America, 8.6% in Europe, and 3.1% in Asia.[2] In general, the incidence of PCLs normally increases with age. However, certain PCLs demonstrate a higher propensity to develop in either females or males, as well as at specific ages or in particular locations within the pancreas.[2,14]

PCL CLASSIFICATION

PCLs are categorized as benign or neoplastic. Benign PCLs include simple cysts, lymphoepithelial cysts, and retention cysts. Neoplastic PCLs include serous cystic neoplasms, solid pseudopapillary tumors, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, cystic pancreatic endocrine neoplasms, and pancreatic adenocarcinomas with a cystic component.[2,14–18]

Benign PCLs

Simple cysts (also known as true epithelial cysts) are unilocular, lined by a single epithelial layer, have no communication with the pancreatic ductal system, and have no malignant potential.[16]

Lymphoepithelial cysts are more common in males in their 50s and are observed throughout the pancreas. They are sometimes mistaken for pseudocysts and have a mean size of 5 cm, and around half of them are multilocular.[17,18]

Retention cysts are dilated side branches of the pancreatic duct produced by blockage (eg, calculi, mucin), and they may have mucinous mucosal lining and can be difficult to differentiate from intraductal papillary mucinous neoplasms, PCLs with malignant potential.[19]

In some classification schemes, acute pancreatic fluid collection, pseudocyst, acute necrotic collection, and walled-off necrosis are considered benign inflammatory fluid collections, but these are not true PCLs because the contents are not lined by epithelial cells and the lesions are not always found in the pancreas.

Neoplastic PCLs

Table 1[6–10,19] lists the key epidemiologic, clinical, and imaging characteristics of neoplastic PCLs.

TABLE 2
High-risk and worrisome features in intraductal papillary mucinous neoplasms

High-risk features	Worrisome features
Main pancreatic duct size ≥ 10 mm	Main pancreatic duct size 5–9 mm
Obstructive jaundice and cyst in head of pancreas	Cyst ≥ 3 cm
Solid mass	Lymphadenopathy
Cancer or high-grade dysplasia on cytology	Elevated carbohydrate antigen 19-9 level
Mural nodule ≥ 5 mm	Mural nodule < 5 mm
	Cyst growth ≥ 5 mm/2 years
	Change in caliber of main pancreatic duct with distal pancreatic atrophy
	Thickened or enhancing cyst walls
	New-onset diabetes mellitus

Data from references 6 and 7.

Mucinous cysts are lined with a mucin-producing epithelium and include intraductal papillary mucinous neoplasms and mucinous cystic neoplasms.[6] The difference between mucinous cystic neoplasms and intraductal papillary mucinous neoplasms is the presence of a connection to the pancreatic ductal system. Mucinous cystic neoplasms do not communicate with the ductal system, whereas intraductal papillary mucinous neoplasms originate from the ductal system.[9,20]

Mucinous cystic neoplasms are found in the body and tail of the pancreas and are almost exclusively found in women ages 40 to 60 (with a peak incidence at age 40 to 50). These neoplasms have a characteristic ovarian-type stroma and have been found to be malignant in 0% to 34% of cases.[20,21]

Intraductal papillary mucinous neoplasms are divided into 3 types: main duct type, branch duct type, and mixed type. The mixed type involves the main duct and the branch duct, based on imaging studies with or without histology. Main duct intraductal papillary mucinous neoplasm causes dilation of the main pancreatic duct of more than 5 mm without other identified causes. Branch duct intraductal papillary mucinous neoplasms have a lower risk of malignancy, ranging between 12% and 47%, while main duct intraductal papillary mucinous neoplasms and mixed type have a higher risk of being malignant, ranging from 38% to 68%.[22]

Serous cystic neoplasms are most frequent in women between the ages of 50 and 60, exhibit a honeycomb appearance on imaging (many tiny cysts surrounding a central stellate scar with calcification), and have a negligible chance of becoming malignant.[22,23] There are 4 distinct morphological patterns: microcystic, macrocystic, mixed microcystic and macrocystic, and solid.[23,24]

Solid pseudopapillary tumors are large solid, cystic, or mixed solid-cystic tumors that primarily affect young women. Although their malignant potential has not been well investigated, these are certainly malignant tumors with both local and metastatic potential, and surgical excision is recommended.[25]

Other lesions with a cystic appearance include pancreatic adenocarcinomas with a cystic component and cystic pancreatic endocrine neoplasm.[7,26]

PCL CANCER RISK

Determining the cancer risk of PCLs should be approached in 2 steps. First, determine whether the cyst is neoplastic. Next, look for clinical and imaging signs that have been linked to an elevated risk of cancer and are described as "high-risk" or "worrisome" characteristics.[6]

High-risk clinical features include obstructive jaundice without other explanation, recurrent pancreatitis due to a PCL, a significantly elevated serum carbohydrate antigen 19-9 level, or, if cytology is obtained, the presence of cells demonstrating high-grade dysplasia or neoplasia, and new-onset or worsening diabetes. Worrisome characteristics include main pancreatic duct dilation greater than or equal to 5 mm, cyst size greater than or equal to 3 cm, and the presence of a solid component or mural nodule in the PCL.[6,7,9,10] Of the PCLs with malignant potential, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms are the most commonly observed in clinical practice.

Table 2[6,7] lists the high-risk and worrisome traits for presumed intraductal papillary mucinous neoplasms. When 1 or more of these characteristics are present, the patient should be referred to a center of excellence for additional examination and treatment by a multidisciplinary expert group.

DIAGNOSIS

PCLs are frequently seen on cross-sectional imaging of the abdomen in asymptomatic patients. If a PCL is an incidental finding, dedicated magnetic resonance cholangiopancreatography with dynamic magnetic resonance imaging is the test of choice and should be

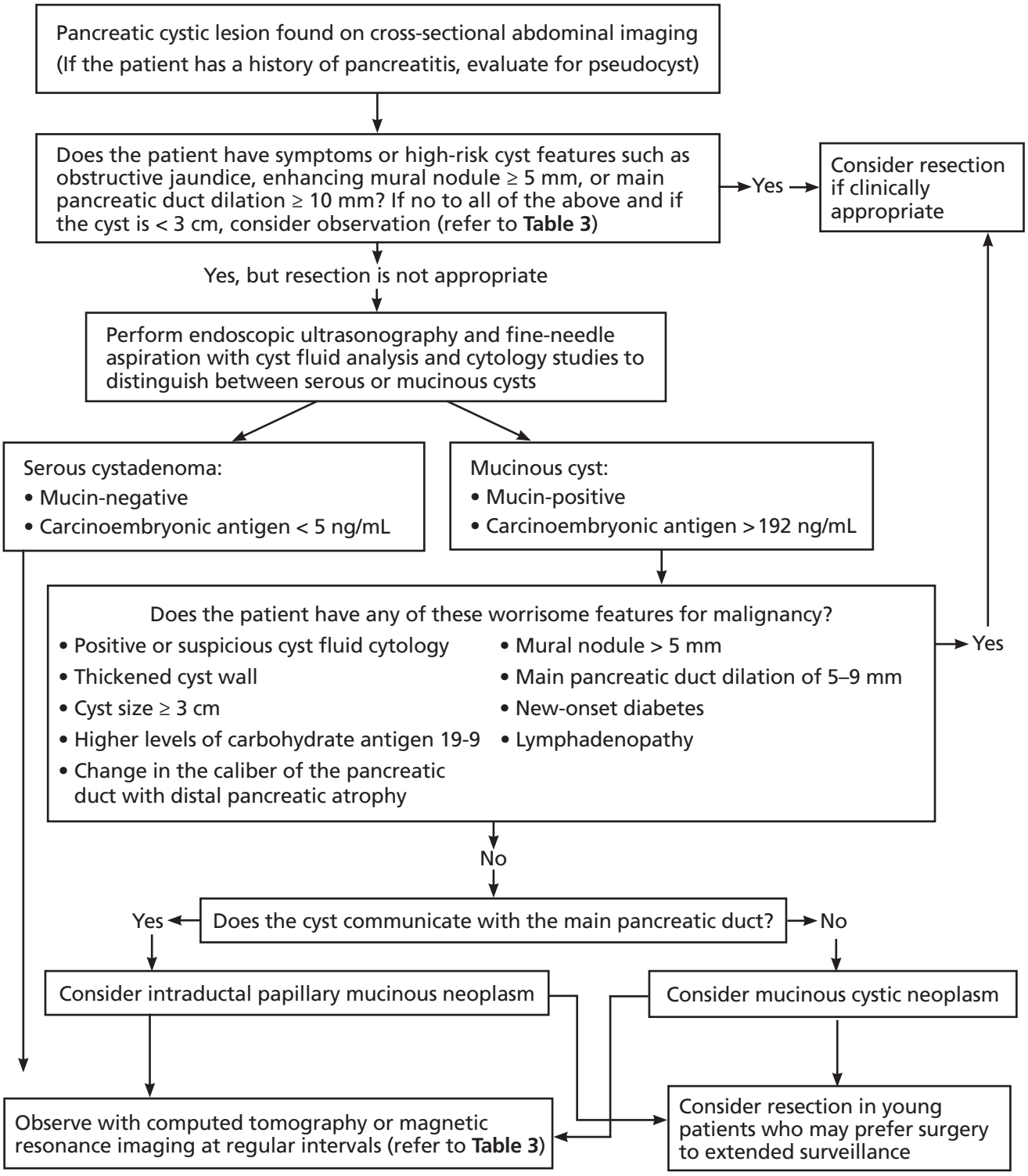

Figure 1. Strategy to evaluate and manage pancreatic cystic lesions.

TABLE 3
Approach to surveillance of pancreatic cystic neoplasms based on the different society guidelines

Cyst size	IAP[6] (Kyoto), 2023	ACG,[7] 2018	AGA,[9] 2015	ACR,[8] 2017	European consensus,[10] 2018[a]
< 1 cm	CT/MRI or EUS in 6 months and then every 18 months if stable	MRI every 2 years for 4 years	MRI in 1 year, then every 2 years for 5 years Stop if no significant change in the characteristics of the cyst after 5 years of surveillance	MRI/CT every 1 year for cysts 1.5 cm to < 2 cm and every 6 months for cysts 2.0–2.5 cm for 4 times, then lengthen the interval Stop after stability over 10 years	Surveillance every 6 months for 2 times with MRI with or without EUS or CA19-9 If stable, lifelong surveillance is recommended with annual MRI/EUS or CA19-9
1–2 cm		MRI every 1 year for 3 years then every 2 years for 4 years			
2–3 cm	CT/MRI or EUS every 6 months for 2 times and then every 12 months if stable	MRI/EUS every 6 months–1 year for 3 years then every year for 4 years		For cysts ≥ 2.5 cm, MRI/CT every 6 months for 4 times, and if stable over initial 2 years, MRI/CT yearly for 2 times, then every 2 years for 3 times, then stop if stable over 10 years	
> 3 cm	CT/MRI or EUS every 6 months	MRI/EUS every 6 months for 3 years then every year for 4 years	Pursue EUS-FNA	For patients age ≥ 80, imaging every 2 years for 2 times, and stop if cyst is stable	

[a]European consensus = European Study Group on Cystic Tumours of the Pancreas, United European Gastroenterology, European Pancreatic Club, European-African Hepato-Pancreato-Biliary Association, European Digestive Surgery, and the European Society of Gastrointestinal Endoscopy.

ACG = American College of Gastroenterology; ACR = American College of Radiology; AGA = American Gastroenterological Association; CA = carbohydrate antigen; CT = computed tomography; EUS = endoscopic ultrasonography; FNA = fine-needle aspiration; IAP = International Association of Pancreatology; MRI = magnetic resonance imaging

performed to identify the cyst characteristics and any high-risk or worrisome characteristics.[6–8]

In patients who are unable to undergo magnetic resonance imaging, pancreatic-protocol computed tomography and endoscopic ultrasonography are suitable options.[7] If the diagnosis is ambiguous, or if the PCL has clinical or radiologic worrisome features, endoscopic ultrasonography can give further diagnostic information.[3] Fine-needle aspiration for cystic fluid cytology and biomarker analysis can provide information on amylase concentration, intracystic glucose level, carcinoembryonic antigen levels, or molecular markers.[7,27,28] Notably, while certain PCLs can be accurately diagnosed using cross-sectional imaging with or without endoscopic ultrasonography with fine-needle aspiration for cytology, surgical pathology is required for definitive histologic classification.[29]

Lately, remarkable progress has been made in the identification and validation of molecular cyst fluid biomarkers such as KRAS, GNAS, SPINK1, interleukin-1-beta, cancer antigen 72-4, vascular endothelial growth factor-A, vascular endothelial growth factor receptor 2, prostaglandin E2, and methylated DNA biomarkers.[30–35] These biomarkers play a pivotal role in aiding the diagnostic process, contributing to improved accuracy in assessing PCLs.

MANAGEMENT AND PROGNOSIS

PCLs that have the potential to become malignant are managed by active monitoring or surgical excision. PCLs with high-risk characteristics, and those with a known high risk of malignancy, such as main duct intraductal papillary mucinous neoplasms and solid pseudopapillary tumors, should be referred for surgical excision. Patients with PCLs who have symptoms such as pancreatitis, nausea and vomiting caused by intestinal obstruction, or abdominal discomfort should undergo surgical evaluation regardless of cancer risk.

Patients with asymptomatic cysts and those without high-risk characteristics can undergo active surveillance, as the likelihood of advanced neoplasia is low. Surveillance is not advised for people older than 85 or people with too many medical comorbidities to undergo surgery.[6,7,9,10] Simple cysts and asymptomatic pseudocysts don't require monitoring.[7,9] Depending on clinical symptoms, suspected PCL type, and the existence of high-risk traits, the monitoring period might range from 3 months to 2 years.[6,7,9,10]

Due to its exceptional resolution and ability to discern the main pancreatic duct effectively, magnetic resonance imaging and magnetic resonance cholangiopancreatography are used for surveillance. On the other hand, endoscopic ultrasonography is reserved for patients displaying concerning characteristics, in addition to fine-needle aspiration of cyst fluid for a precise diagnosis through biomarker analysis. However, for lesions with no worrisome features, a combination of history, examination, and radiologic characteristics may commonly define the type of PCL and assess the risk of malignant degeneration.[26] **Figure 1** outlines a strategy to evaluate and manage PCLs.

The duration of PCL surveillance is debatable, with most current guidelines recommending the surveillance interval based on radiologic PCL appearance and changes over time compared with previous imaging,[6,7,10] while some advocate stopping after 5 years if the PCL is stable and has not progressed.[9] If the patient is unwilling to undergo pancreatic surgery or is unfit for surgery, then asymptomatic PCL surveillance may be stopped as it is unlikely to impact clinical management or survival.[6,7,10]

Experts advocate maintaining surveillance till age 75 and individualizing follow-up between ages 76 and 85 (**Table 3**).[6–10] It is also advised to inform patients that they may require continued surveillance even after undergoing partial pancreatic resection, as recurrence may occur in the remnant pancreas.[6,7,35,36] Although it is difficult to find strong prospective evidence that surveillance reduces mortality, studies have shown that PCLs with the potential to become malignant can take years to develop, and that pancreatic cancers detected through surveillance were more frequently at an earlier stage in patients with intraductal papillary mucinous neoplasms.[7,36]

CONCLUSION

Pancreatic cysts are frequently found incidentally on cross-sectional imaging. The possibility of malignancy varies depending on the type of PCL. Magnetic resonance cholangiopancreatography with dynamic magnetic resonance imaging is the preferred test to identify cyst characteristics and high-risk or worrisome features. PCLs with malignant potential are treated by close surveillance or surgical excision. A multidisciplinary team should assess PCLs with high-risk characteristics and those with a known high risk of malignancy, such as main duct intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and solid pseudopapillary tumors.

Because advanced neoplasia is unlikely, active surveillance is appropriate for asymptomatic cysts and those that do not have any high-risk characteristics. Surgery should be performed to remove high-risk PCLs or those that progress while under surveillance. The overall prognosis is favorable, with early detection and active surveillance serving as the cornerstones of management.

DISCLOSURES

Dr. Stevens has disclosed teaching and speaking for Abbvie Pharmaceuticals. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: *Prabhleen Chahal, MD, FACG, FASGE, Department of Gastroenterology, Hepatology, and Nutrition, A31, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; chahalp@ccf.org*