Curr Treat Options Gastro (2019) 17:457–469
DOI 10.1007/s11938-019-00260-3

Gastroenterology for Geriatric Patients (S Katz and A Afzali, Section Editors)

Pancreatic Cysts in the Elderly

Luis F. Lara, MD[*]
Anjuli Luthra, MD
Darwin L. Conwell, MD, MS
Somashekar G. Krishna, MD, MPH

Address
[*]Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, 395 W 12th Avenue, Room 226, Columbus, OH, 43210, USA
Email: Luis.Lara@osumc.edu

Published online: 9 November 2019

This article is part of the Topical Collection on *Gastroenterology for Geriatric Patients*

Keywords Pancreatic cysts · Mucinous cysts · Cyst diagnosis · Cyst management · Cyst treatment

Abbreviations *PCL* Pancreatic cystic lesions · *CT* Computed tomography · *MRI* Magnetic resonance imaging · *PDAC* pancreatic ductal adenocarcinoma · *IPMN* Intraductal papillary mucinous neoplasm · *MCN* Mucinous cystic neoplasm · *MRCP* Magnetic resonance cholangiopancreatography · *CEA* Carcinoembryonic antigen · *NGS* Next-generation sequencing · *KRAS* Kirsten rat sarcoma viral oncogene homolog · *GNAS* Guanine nucleotide binding protein, alpha stimulating · *SMAD4* Drosophila protein, mothers against decapentaplegic (Mad), and the Caenorhabditis elegans protein (Sma) homolog 4 · *VHL* von Hippel-Lindau · *y/o* Years old

Abstract

Purpose of review Incidental pancreatic cysts are common, and management strategies continue to evolve. This review summarizes diagnostic and management recommendations in older patients with these lesions based on guidelines and best clinical evidence.
Recent findings Diagnosis of cyst type has been enhanced with improved imaging and cyst fluid analysis and visualization. Recent outcome studies indicate that certain cyst types should be followed independent of patient age as long as certain criteria which are reviewed are met.
Summary Differentiation of pancreatic cyst type is important as this dictates the need for long-term follow-up. Because most cyst-related neoplasia occurs in older patients, surveillance should continue within certain guidelines.

Introduction

Pancreatic cystic lesions (PCLs) are common, and usually asymptomatic. They are incidental in 1 to 3% of computed tomography (CT) examinations, and up to 15-20% MRI [1••, 2, 3]. They are more frequent with age approaching a prevalence of 8% in older adults, which is generally defined as being ≥ 65 years of age (www.pewsocialtrends.org) [4]. An autopsy study showed an incidence of PCLs of 24% indicating that they are many times asymptomatic [5]. The concern for malignant transformation, and lack of data on the natural history, led to variability for diagnosis and management. Recent guidelines have helped establish somewhat of a standard of care, which includes long-term observation rather than surgical intervention.

There is a need to improve identification of the cysts which have a higher malignant potential which are the mucinous pancreatic cystic lesions, and to a lesser extent, cystic degeneration of neuroendocrine tumors and other pancreas malignancies which are much less frequent [6••]. Progression towards malignancy follows a low-grade-to-high-grade neoplasia sequence, sometimes accompanied by symptoms that include abdominal pain, nausea or vomiting, weight loss, jaundice, and acute pancreatitis, as well as worrisome features of the cyst itself which can be identified using different diagnostic tools discussed below. This progression usually takes years and also occurs as patients get older, so mucinous cystic neoplasms in particular can be equated to the "polyps" of the pancreas which can be targeted for close follow-up and resection; thus, the window of opportunity for potential curative resection and prevention of invasive malignancy spans a broad period [7]. The susceptibility for malignancy associated with PCLs in older patients is a reason to maintain surveillance, but it is also appropriate to discuss when to discontinue it.

Types of pancreas cysts

Solid-pseudopapillary neoplasms are rare, usually unilocular, indolent, slow-growing, and large at time of diagnosis, and affect females at an average age of 25 [8, 9]. Most patients undergo curative resection at time of diagnosis and do not require long-term follow-up, so they do not represent a concern with older age.

Serous cystadenomas are also more common in females. They are primarily in the body and tail of the pancreas and are diagnosed at a median age of 60. The characteristic central stellate scar on CT scan can be diagnostic but is only found in about 30% of cases [10]. As long as patients are asymptomatic, they require no intervention or follow-up because of their lack of malignant potential [11].

MCN almost exclusively affect females between the ages of 30 and 50, are unilocular, usually in the body and tail of the pancreas, with a reported rate of neoplasia of 12–29% and presence of carcinoma in situ of 5% [11]. Symptoms, size, and morphology are used to determine resection which usually occurs around age 50. This is usually curative, so follow-up in the elderly is typically not required.

IPMN are diagnosed at an older age, and malignant transformation generally occurs at an even older age, which indicates that for the most part this PCL is a concern of the elderly, and will be the focus of this review.

They are the most common mucinous neoplasms of the pancreas from the main and side branches, or both, and the branch duct (BD-IPMN) type is the one most frequently encountered. Studies indicate male predominance, with a mean age of presentation of 65 years, and usually involve the head of the pancreas, but they are frequently multifocal [12–15]. Four histological

subtypes, gastric, intestinal, pancreatobiliary, and oncocytic, have been described and are associated with degrees of aggresiveness [1••].

The incidence of malignancy in IPMN varies from 14–48% and is higher for main duct IPMN. Invasive malignancy has been reported between 6–38%, but is 89% when high-risk features such as jaundice, abnormal cytology, and cyst mural nodules are present [16, 17•, 18]. These numbers likely reflect a referral bias because there are likely many patients with undiagnosed and asymptomatic PCLs, including IPMN, who will never develop pancreas malignancy.

Guidelines

A comprehensive review of the guidelines is beyond the purpose of this manuscript but they are mentioned in the context of surveillance strategies, and summarized in Table 1. While some guidelines include most pancreas cyst types, they generally bias towards mucinous cystic lesions of the pancreas because of their potential for malignancy, and focus on size, abnormal fluid cytopathology, and morphological anomalies of the cyst such as mural nodules, the presence of papillary projections, and wall thickening as indicators of malignancy. Surgical resection of most mucinous neoplasms used to be common, but subsequent knowledge about the natural history, and considerations regarding morbidity associated with surgery changed this approach [21••]. Studies using the Sendai guidelines reported a sensitivity of 100% for predicting high-grade dysplasia and pancreas ductal adenocarcinoma (PDAC) for BD-IPMN, but specificity was low, between 23–31% [22, 23]. .The Fukuoka consensus recommended different surveillance intervals based on IPMN size, cyst characteristics, and incorporated the results of cyst fluid obtained by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) [12]. Comparisons between this and the Sendai guidelines showed similar clinical performance [12, 17•, 24]. The American Gastroenterological Association (AGA) focused on low-risk cysts, anticipating that most mixed and main duct IPMN would undergo surgery [7]. These guidelines recommended discontinuing follow-up after 5 years of cyst stability which has caused concern. This guideline was developed as a general recommendation for all cysts, not just BD-IPMN, and was meant as a general guide for practitioners of all specialties who may encounter them, and thus may have been misunderstood. The AGA guidelines were not superior to the first Fukuoka guidelines in predicting advanced neoplasia in one study [25]. In another study, AGA guidelines were shown to have a low sensitivity of 62% and specificity of 79%, but more importantly, 45% of high-risk IPMN would have been missed applying them [26••]. Worrisome features and malignancy may occur in IPMN well after the 5-year surveillance period, and with an average life span of 78.6 years in the USA (www.cdc.gov/nchs), and 85 years in Japan (www.who.int) the AGA guidelines are impractical for long-term mucinous cyst surveillance [27].

The revised Fukuoka guidelines incorporated high-risk features including a growth rate > 5 mm every 2 years, but recommended caution about using cyst size alone as a major indication for surgery [1••]. A recent study indicated that the presence of an enhanced mural nodule had a sensitivity of 95%, and specificity of 87% for invasive carcinoma using these revised criteria [28]. The American College of Gastroenterology guidelines focused on MRI and

Table 1. Summary of current guidelines on cyst diagnosis, surveillance, and management

	Revised Fukuoka [1••]	ACG [19•]	ACR [20]	AGA [7]	EU [6••]
All pancreatic cysts included		+	+	+	+
Mucinous cysts only	+				
Defined high-risk features[a]	+	+		+	
Defined worrisome features[b]	+	+			
Cyst growth rate	+	+	+		+
Cyst size cut-off for resection					> 40 mm
Main duct IPMN resection	≥ 10 mm				≥ 10 mm
Serum CA 19-9	+	+			+
MDB review		+			
Post-resection recommendations		+			+
Stop surveillance recommendation	Not fit	> 75 y/o or not fit	Stable > 10 years or > 80 y/o	Stable > 5 years	Not fit

High-risk features: symptoms, jaundice, solid component, cyst mural nodule, main pancreas duct dilation > 5 mm
[a]Worrisome features: cyst size ≥ 3 cm, cyst growth rate > 2 mm/year, acute pancreatitis, thickened cyst walls, pancreas atrophy, abnormal cytology
[b]*ACG* American College of Gastroenterology, *ACR* American College of Radiology, *AGA* American Gastroenterological Association, *EU* European evidence-based guidelines on pancreatic cystic neoplasms, *MDB* Multidisciplinary Board, *y/o* years old
+: mentioned in the guideline

endoscopic ultrasound (EUS) intervals according to cyst size, and incorporated EUS ± FNA in most of the evaluation pathways [19•]. The American College of Radiology (ACR) recommendations for management of incidental pancreas cysts focused on frequency of repeat imaging and when to proceed with EUS + FNA according to cyst size [20]. The most recent European evidence-based guidelines gave recommendations for all types of PCLs, and included relative and absolute indications for surgery which may predict the presence of advanced carcinoma [6••, 29]. The guidelines have limitations regarding their ability to establish a diagnosis, and predict malignant transformation or the presence of cancer, so management needs to be personalized as discussed below [30].

- Guidelines generally bias towards mucinous neoplasms which have the highest malignant risk.
- They do recommend surveillance intervals which practitioners should incorporate to their practice.
- Malignant cyst transformation usually occurs at an older age and after years of surveillance so in adequate patients surveillance should be continued.

Diagnosis

A comprehensive and multi-specialty approach should be standard. This includes consideration of the patient's family, personal, and clinical history; cross-

sectional imaging studies; cyst fluid analysis; and cytopathology. Differentiating between malignant, mucinous, and non-mucinous cystic lesions is the most important aspect as this dictates the need for long-term follow-up.

Dedicated pancreas enhanced CT and MRI establish an accurate diagnosis of cystic lesions > 60% of the time, and both are comparable at establishing malignancy, > 70% [1••]. Gadolinium-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) has better contrast resolution of characteristics such as septations, nodules, and ductal communication, and avoids radiation exposure which is a concern as patient's are subjected to repeated follow-up x-ray studies [20].

- EUS alone is not better than CT or MRI to establish the cyst type
- EUS-guided FNA enhances the ability to differentiate cyst types and determine the presence of malignancy

EUS alone is not more accurate than CT or MRI in establishing the PCL type, but EUS-guided FNA and cyst fluid carcinoembryonic antigen (CEA) has a diagnostic accuracy of 80% at a cut-off of ≥ 192 ng/ml for differentiating mucinous and non-mucinous cysts. A low CEA does not exclude a mucinous neoplasm, and the CEA cannot establish the presence of malignancy [31, 32]. The revised Fukuoka guidelines recommend an endoscopic ultrasound in the presence of worrisome features including cyst size ≥ 3 cm, the presence of an enhancing mural nodule > 5 mm, thickened cyst wall, main pancreas duct size between 5 and 9 mm, change in the main pancreatic duct caliber, lymphadenopathy, elevated serum carbohydrate antigen 19–9, and cyst growth of more than 5 mm over 2 years [1••]. Patients with features more significant than this should be considered for surgical resection.

Some of the findings need to be interpreted with caution because morphological anomalies determined by EUS such as cyst size and even the presence of a mural nodule may not be able to predict advanced neoplasia with confidence, with reported sensitivity of between 32 and 74% and specificity of 49 to 91% which, in part, reflects operator and equipment variability [31]. EUS-FNA cytopathology has a reported sensitivity of 25 to 88%, and specificity of > 95% for malignancy [33].

The cyst fluid can also undergo genetic mutational analysis.

Mucinous cystic neoplasms follow a dysplasia to carcinoma sequence, which occurs over time, and allows for longitudinal follow-up. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations occur in over 80% of IPMNs, followed by *GNAS* mutations in 65%, and 97% when combined [34]. While these two mutations are more likely to be present in the setting of dysplasia, they are unable to establish the presence of high-grade dysplasia or malignancy with confidence, so they may be most useful to confirm the presence of a mucinous cyst [35•]. Studies of cyst fluid DNA analysis have shown variable concordance with histopathology on surgical specimens and may not be superior to CEA and *KRAS* [36]. Next-generation sequencing to differentiate a mucinous from non-mucinous cyst has a sensitivity of 86–90% and specificity of 75–100% and may improve the ability to diagnose advanced neoplasia [26••, 37]. While TP53, PIK3CA, PTEN, CDKN2A, and SMAD4

mutations are more common in advanced neoplasia, they lack sensitivity as not all advanced neoplasia express these mutations [35•, 38]. Despite the limitations, DNA analysis can be helpful in clinical decision-making, including proceeding with surgery as recommended by Singhi, et al. and others [26••, 34, 39].

A recent publication showed that endoscopic ultrasound-guided needle-based confocal laser endomicroscopy (EUS-nCLE) was much more sensitive, specific, and accurate for determining if a cyst was mucinous or not compared to CEA or cytology [40•]. Image patterns obtained by EUS-nCLE were also accurate to differentiate cystic neuroendocrine tumor, solid-pseudopapillary neoplasm, and serous cystadenoma, as well as suggesting malignant transformation of IPMN particularly, so this technology merits further consideration. The incidence of adverse events was 4.9%, mostly post-procedure associated mild acute pancreatitis, a concern for any procedure that invades the pancreas.

Table 2 describes molecular and EUS-nCLE characteristics of different cyst types.

Risk of malignancy due to pancreatic cystic lesion in the elderly

Patients with an IPMN over the age of 65 are a higher risk group for malignancy. Generally, main duct IPMN should be considered for resection at any age group, with an alternative for close follow-up if < 9 mm in size. Predicting malignancy in BD-IPMN is more difficult, but there is some guidance regarding the risk of malignant transformation, patient survival, and other factors to consider for continuation of surveillance [41].

The presence of jaundice, an enhancing mural nodule ≥ 5 mm, main pancreas duct > 10 mm, and positive EUS-FNA cytology strongly indicates

Table 2. Molecular and endomicroscopy findings of selected pancreatic cysts

	BD-IPMN	M-IPMN	MCN	SCA	SPN
KRAS	+++	++	+++	-	-
GRAS	++	+++	+	-	-
TP53, PIK3CA, PTEN, CDKN2A, SMAD4	Advanced neoplasia*	Advanced neoplasia*	Advanced neosplasia*	-	-
VHL	-	-	-	+++	-
CTNNB1	-	-	-	-	+
EUS-nCLE	Papillary fronds	Papillary fronds	Epithelial bands with inflammatory cells	Fern pattern vascularity	Trabecular pattern

BD-IPMN, branch-duct intraductal papillary neoplasm; *M-IPMN*, main duct IPMN; *MCB*, mucinous cystic neoplasm; *SCA*, serous cystadenoma; *SPN*, solid-pseudopapillary neoplasm; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *GNAS*, guanine nucleotide binding protein, alpha stimulating; *TP53*, tumor protein p53; *PIK3CA*, phosphoinositide 3-kinase, catalytic, alpha polypeptide; *PTEN*, phosphatase and tensin; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *SMAD4*, drosophila protein, mothers against decapentaplegic (Mad) and the Caenorhabditis elegans protein (Sma) homolog 4; *VHL*, von Hippel-Lindau; *CTNNB1*, catenin beta 1; *EUS-nCLE*, endoscopic ultrasound-guided needle-based confocal laser endomicroscopy

+: less likely to be present; +++ more likely to be present; *advanced neoplasia: mural nodule, dilated main pancreas duct > 9 mm, jaundice, growth >5 mm/2 years

malignancy and patients should undergo surgery if the patient is a candidate [1••, 4, 19].

Only the opinion based ACR guidelines have age based recommendations. These include stopping surveillance for incidental cysts < 15 mm if stable over 10 years in patients between 65 and 79 years of age. Discontinuing surveillance after 10 years for stable BD-IPMN between 20 and 25 mm for any age group was also recommended, but EUS + FNA was suggested for larger or faster growing lesions. The recommendation was to stop surveillance at age 80, except for patients with a new diagnosis of an incidental PCL close to this age group, where discontinuation of surveillance was recommended if cyst stability was confirmed on two MRIs over a 2-year span [20].

Studies show that cysts grow slowly, over years [41, 42]. While this alone does not necessarily indicate malignant transformation, rate of growth and other cyst changes can trigger more invasive testing such as EUS + FNA, and even surgery. Rate of growth of BD-IPMN > 2 mm increases the likelihood of high-risk features in the cyst regardless of age and should be managed accordingly [1••, 43•, 44].

A comprehensive medical history is important, and needs to be updated frequently. Studies indicated that subjects with IPMN and a family history of PDAC in first, and even second-degree relatives had a risk of developing IPMN associated PDAC of 11 to 17%, compared with 2 to 3% when there was no family history [45, 46].

- A family history of PDAC should be obtained and updated because studies show increased risk of malignant transformation in subjects with IPMN and a family history of PDAC.

The impact of a Markov model for management of asymptomatic MCN and BD-IPMN (assuming that main duct IPMN would undergo surgery) was developed utilizing 3 strategies [47]. Strategy 1 was watch and wait. The 2nd strategy was surgical resection as long as they were operative candidates. This was determined by a self-developed surgical risk score that consisted of age, surgical risk based on ASA score, size of the lesion, and its location. In strategy 3 all patients underwent endoscopic ultrasound, and EUS + FNA for cytology and to determine the CEA level. Surgical resection was the least expensive strategy, but was not favored even with the lowest surgical risk score regarding quality-adjusted life years. EUS + FNA was the most cost-effective most of the time. Interestingly, if the probability that the PCL was mucinous was low the watch and wait strategy was the most cost-effective. Not surprisingly, this approach also became the preferred strategy with increasing patient age, and in patients with a higher American Society of Anesthesiologists score probably reflecting age related comorbidities, and concerns about surgery. However, this study did not focus particularly on age.

Comorbidities are common with PCL, and especially IPMN as they occur in an older population, so the impact of these should also be considered when performing PCL surveillance. A large registry study used the Charlson Comorbidity Index (CCI) as a predictor of comorbidity associated mortality in a group of patients with a pancreas cyst, and estimated cancer mortality related to the PCL or another cause [48]. Patients were classified into four profiles: (1) Low-risk patient with low-

risk cyst, (2) Low-risk patient with high-risk cyst, (3) High-risk patient with low-risk cyst, and (4) high-risk patient with high-risk cyst. Cyst size ≥ 3 cm, main duct dilation, and a CCI ≥ 3 constituted the high-risk cyst, and high-risk patient cohort, respectively. There were 1800 asymptomatic PCLs, and 43 (2.8%) PDAC-related deaths over the study period of 5.7 years. Median time to diagnosis of PDAC was 0.6 years, and 79% were due to malignant cyst degeneration. In the other 21% PDAC occurred at a site separate from the PCL so deemed unrelated. Low-risk cyst characteristics had a 5-year mortality due to PDAC of 0.1% in the low-risk patient group, and 0.3% in the high-risk patient group. High-risk cyst characteristics had a 5-year PDAC mortality of 7.2% in the low-risk patients, and 6.5% in the high-risk patient group. Mortality from non-PDAC causes was 8.1 to 10.7% in the low-risk cohort according to low or high-risk cyst characteristics, respectively. Mortality from other causes beyond PDAC was 38.8 to 46% in high-risk patients according to they had low- or high-risk cyst characteristics, respectively. This study demonstrated that risk of death was unrelated to PDAC the majority of the time, even with high-risk feature pancreatic cysts, underscoring that mortality-associated comorbidities are more significant than having the PCL. This needs to be considered when subjecting patients to invasive diagnostics such as EUS, as well as the morbidity- and mortality-associated with surgical resection. While the high-risk cyst features were limited to cross-sectional imaging findings of cyst size and the presence of main pancreas duct dilation in this cohort, and did not include EUS + FNA findings, another long-term study of patients with PCLs evaluated by EUS reported a < 1% risk of pancreas cancer in cysts with low-risk features [27].

- Mortality from malignant transformation of pancreatic cysts is low even in subjects with high-risk cyst features.
- Most patients will require follow-up only.

Treatment

For now, surgical resection is the only curative intervention for mucinous cystic lesions. The region with the highest risk of neoplasia should be resected first [1••]. Unfortunately, morbidity is 40%, and surgical mortality rate at high-volume centers is around 2% [49]. Disease may recur so long-term follow-up with MRI/MRCP is recommended for IPMN [50].

EUS-guided cyst ablation utilizing ethanol with or without paclitaxel achieves resolution in 33 to 79% of patients with remarkably low related adverse events in expert hands [31]. .The lack of complete cyst obliteration, need for continued monitoring, potential for neoplastic progression, difficulty to detect neoplasia by EUS after treatment, and the possibility of increased adverse events with less experienced endoscopists are concerns. However, this may become an option for patients who have a higher risk mucinous pancreas cyst and are not good surgical candidates. The results of a EUS-guided cyst ablation study with paclitaxel and gemcitabine using enhanced patient selection criteria are awaited (CHARM II, ClinicalTrials.gov Identifier: NCT03085004).

Patient evaluation

The majority of the patients are seen in the Pancreas Clinic at The Ohio State University Wexner Medical Center (OSUWMC), where mechanisms are in place to expedite consultations for patients with concerning clinical presentation such as jaundice, weight loss, or significant imaging findings. The complete medical history, and imaging review with a staff radiologist, is performed. The Pancreas Clinic Coordinator organizes this pre-visit. At OSUWMC a Multidisciplinary Board (MDB) consists of gastroenterologists, pancreatologists, endoscopists, pancreas surgeons, specialty radiologists, and others who meet once a week. Case presentations lead to discussions and a consensus on treatment strategies, including surveillance, more invasive diagnostic testing, proceeding with surgery, and discontinuing surveillance. This multidisciplinary approach has been recommended for patients with pancreas disease [51, 52].

For asymptomatic PCLs < 10 mm without worrisome features a follow-up in Pancreas Clinic and by MRI/MRCP is recommended in 1 year, and if stable, it is repeated in 2 years. PCLs 10–20 mm are discussed in the MDB and EUS is almost always recommended. Cyst fluid is sent for CEA and lipase levels, next-generation sequencing, and nCLE. Serous cystadenomas are not followed unless the patient exhibits symptoms. Symptomatic patients will undergo the above regardless of cyst size and will see a pancreas surgeon in consultation. Cyst growth > 2 mm per year, and with worrisome features will undergo repeat MRI/MRCP and/or repeat EUS at shorter intervals, usually 3 to 6 months, and may be referred to pancreas surgery consultation. Cyst fluid samples with genetic mutations will also undergo surgery evaluation regardless of symptoms. For patients between 65 and 75 years of age the protocol is individualized, but generally applied as described if the patient is able to undergo surgery and has a life expectancy of over 5 years. After 75 years, re-evaluation of cyst and patient characteristics, including a family history of PDAC, occurs in the MDB, and discontinuing surveillance may be recommended. A follow-up consensus recommendations is conveyed to the patient and referring physicians (see Fig. 1).

Discussion

The incidental finding of PCLs is likely going to increase at least numerically as a reflection of the population growth. A comprehensive history is important to determine potential etiologies, and a family history of pancreas neoplasia for risk stratification. It is important to adequately classify PCLs, and particularly determine if they are non-mucinous, mucinous, or cystic degeneration of neoplasia. Adoption of reporting standards for findings on cross-sectional imaging and by EUS will help improve identification of high-risk features which should guide management. The use of advanced diagnostic strategies including genetic analysis, EUS-nCLE, and contrast-enhanced endoscopic ultrasound where available should become more common to help guide management. Their use will need to be weighed against procedural risks including acute pancreatitis, and the costs and anxiety associated with surveillance.

Published guidelines differ in their appreciation of high-risk stigmata and follow-up intervals, but set reasonable standards. It is recommended that those taking care of patients with PCLs become acquainted with them, and high-

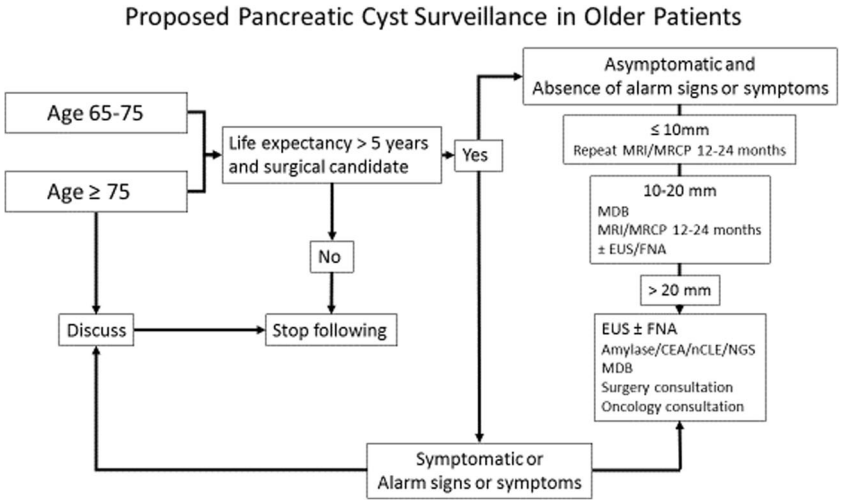

Fig. 1. A proposed algorithm for pancreatic cyst surveillance in older patients. Algorithm proposal for pancreatic cyst surveillance in older patients. Practitioners are cautioned to individualize care as much as possible. MRI magnetic resonance imaging, MRI/MRCP MRI with magnetic resonance cholangiopancreatography, EUS-FNA endoscopic ultrasound-guided fine-needle aspiration, MDB Multidisciplinary Board, CEA carcinoembryonic antigen, EUS-nCLE endoscopic ultrasound-guided needle-based confocal laser endomicroscopy, NGS next-generation gene sequencing.

volume centers should develop strategies along the lines of what has been discussed here. Ultimately, for most patients the clinical significance of having a pancreas cyst will relate to appropriate risk stratification including cyst malignant potential, the patient's current medical status, and life expectancy. The decision to observe, obtain more cyst fluid data by EUS-FNA or to resect must be individualized. Medical decision-making should not rely on a single criteria, and, except for the presence of high-risk stigmata in patients in good health, requires a comprehensive and multidisciplinary approach that should include the patient, patient's family, and potential for long-term survival. The physical and mental morbidity related to long-term follow-up, and the costs need to be studied further, especially since the available data indicates that the risk of dying as a result of malignant transformation of a PCL is low [53].

Members of the health care community are encouraged to remember the phrase *Primum non nocere* when making decisions about interventions and long-term follow-up. As most of the PCLs will be IPMN, in "younger" older patients, arbitrarily between 65 and 75, surveillance according to the recommendations discussed above can be performed. This is the age group with the highest incidence of PDAC, and appropriate for continued surveillance. For patients older than that surveillance should be tailored according to life expectancy and ability to undergo a major operation.

Endoscopic treatment of PCLs may change the paradigm of treatment in the future, so this recommendation will need to be revised as more information becomes available.

Conclusion

IPMN, especially of the branch duct type is the most common pancreatic cystic neoplasm. Guideline variability should be recognized but there are important

recommendations that must be considered in practice. Most PCLs can be followed by serial imaging, but there are enhanced diagnostics which should be considered as they may help differentiate a mucinous and non-mucinous cyst, or a malignant to a non-malignant cystic lesion, potentially saving the patient the morbidity, stress and concern, and treatment-related complications for a lesion that does not need to be followed or removed. For this reason, referral to a center with expertise on pancreas disease is recommended. The presence of comorbidities and life expectancy need to be incorporated into the medical decision-making regarding long-term follow-up and interventions.

Author contribution

Luis F. Lara, MD, and Somashekar G. Krishna, MD, MPH, studied concept and design and drafted, wrote, and reviewed manuscript. Anjuli Luthra, MD, and Darwin L. Conwell, MD, MS, studied concept design and wrote and reviewed the manuscript.

Funding informationLuis F. Lara: none. The companies mentioned in the funding (Covidien, Abbvie, Allergan) should go to conflict of interest for author Luis F. Lara

Compliance with ethical standards

Conflict of interest
Somashekar Krishna reports grant funding for a prospective study (currently recruiting patients) from Mauna Kea Technologies.
Luis Lara declares no conflict of interest.
Anjuli Luthra declares no conflict of interest.
Darwin L. Conwell declares no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Tanaka M, Fernandez-el Castillo C, Kamisawa T, et al. Revisions of the international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17:738–5.
Recent updated multidisciplinary guidelines on IPMN surveillance.
2. Zhang XM, Mitchell DG, Dohke M, et al. Pancreatic cysts: depiction on single-shot fast spin-echo MR Images. Radiology. 2002;223:547–53.
3. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol. 2008;191:802–7.
4. Brugge WR. Approach to cystic pancreatic lesions. Gastrointest Endosc Clin N Am. 2005;15:485–96.
5. Kimura W, Nagai H, Kuroda A, et al. Analysis of small cystic lesions of the pancreas. Int J Pancreatol. 1995;18:197–206.

6.•• European evidence-based guidelines on pancreatic cystic neoplasms. The European Study Group on Cystic Tumours of the Pancreas. Gut. 2018;67:789–80.

Most recently updated guidelines on all type of pancreatic cyst management.

7. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:819–22.
8. Estrella JS, Li L, Rashid A, et al. Solid pseudopapillary neoplasm of the pancreas: clinicopathologic and survival analyses of 64 cases from a single institution. Am J Surg Pathol. 2014;38:147–57.
9. Law JK, Ahmed A, Singh VK, et al. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? Pancreas. 2014;43:331–7.
10. Kimura W, Moriya T, Hirai I, et al. Multicenter study of serous cystic neoplasm of the Japan pancreas society. Pancreas. 2012;41:380–7.
11. Lee LS, Clancy T, Kadiyala V, et al. Interdisciplinary management of cystic neoplasms of the pancreas. Gastroenterol Res Pract. 2012;2012:513163.
12. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
13. Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007;246:644–51.
14. Waters JA, Schmidt CM, Pinchot JW, et al. CT vs MRCP: optimal classification of IPMN type and extent. J Gastrointest Surg. 2008;12:101–9.
15. Reid-Lombardo KM, St. Sauver J, Li Z, et al. Incidence, prevalence, and management of intraductal papillary mucinous neoplasm in Olmsted County, Minnesota, 1984-2005: a population study. Pancreas. 2008;37:139–44.
16. Sahora K, Mino-Kenudson M, Brugge W, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. Ann Surg. 2013;258(3):466–75.
17.• Goh BK, Tan DM, Thng CH, et al. Are the Sendai and Fukuoka consensus guidelines for cystic mucinous neoplasms of the pancreas useful in the initial triage of all suspected pancreatic cystic neoplasms? A single-institution experience with 317 surgically-treated patients. Ann Surg Oncol. 2014;21:1919–2.

A comparison trial of the effectiveness of the proposed guidelines in patients who ultimately had surgery.

18. Fritz S, Klauss M, Bergmann F, et al. Pancreatic main-duct involvement in branch-duct IPMNs. Ann Surg. 2014;260:848–56.
19.• Elta GH, Enestvedt BK, Sauer BG, et al. ACG Clinical Guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018;113:464–7.

A clinically appropriate guideline for all pancreatic cysts.

20. Megibow AJ, Baker ME, Morgan DE, et al. Management of incidental pancreatic cysts: a white paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2017;14:911–23.
21.•• Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17–3.

First proposed guidelines for cystic mucinous lesions of the pancreas.

22. Pelaez-Luna M, Chari ST, Smyrk TC, et al. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. Am J Gastroenterol. 2007;102:1759–64.
23. Tang RS, Weinberg B, Dawson DW, et al. Evaluation of the guidelines for management of pancreatic branch-duct intraductal papillary mucinous neoplasm. Clin Gastroenterol Hepatol. 2008;6:815–9.
24. Kaimakliotis P, Riff B, Pourmand K, et al. Sendai and Fukuoka consensus guidelines identify advanced neoplasia in patients with suspected mucinous cystic neoplasms of the pancreas. Clin Gastroenterol Hepatol. 2015;13:1808–15.
25. Ma GK, Goldberg DS, Thiruvengadam N, et al. Comparing American Gastroenterological Association pancreatic cyst management guidelines with Fukuoka consensus guidelines as predictors of advanced neoplasia in patients with suspected pancreatic cystic neoplasms. J Am Coll Surg. 2016;223:729–37.
26.•• Singhi AD, Zeh HJ, Brand RE, et al. American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinicopathological study of 225 patients with supporting molecular data. Gastrointest Endosc. 2016;83:1107–1.

A major study indicating the poor ability of the AGA guidelines in identifying high risk lesions.

27. Kwong WT, Hunt GC, Fehmi SM, et al. Low rates of malignancy and mortality in asymptomatic patients with suspected neoplastic pancreatic cysts beyond 5 years of surveillance. Clin Gastroenterol Hepatol. 2016;14:865–71.
28. Watanabe Y, Endo S, Nishihara K, et al. The validity of the surgical indication for intraductal papillary mucinous neoplasm of the pancreas advocated by the 2017 revised International Association of Pancreatology consensus guidelines. Surg Today. 2018;48:1011–9.
29. Pérez-Cuadrado-Robles E, Uribarri-González L, Borbath I, et al. Risk of advanced lesions in patients with branch-duct IPMN and relative indications for surgery according to European evidence-based guidelines. Dig Liver Dis. 2019;51:882–6.
30. Nguyen AH, Toste PA, Farrell JJ. Current recommendations for surveillance and surgery of intraductal papillary mucinous neoplasms may overlook some patients with cancer. J Gastrointest Surg. 2015;19:258–65.

31. Oh HC, Brugge WR. EUS-guided pancreatic cyst ablation: a critical review (with video). Gastrointest Endosc. 2013;77:526–33.
32. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102:2339–49.
33. Maker AV, Lee LS, Raut CP, et al. Cytology from pancreatic cysts has marginal utility in surgical decision-making. Ann Surg Oncol. 2008;15:3187–92.
34. Singhi AD, Nikiforova MN, McGrath K. DNA testing of pancreatic cystic fluid: is it ready for prime time? Lancet Gastroenterol Hepatol. 2017;2:63–72.
35.• Wu J, Matthaei H, Maitra A, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011;3:92ra6.
First study to report DNA mutation analysis and correlation with outcomes.
36. Sreenarasimhaiah J, Lara LF, Jazrawi SF, et al. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. JOP. 2009;10:163–8.
37. Jones M, Zheng Z, Wang J, et al. Impact of next-generation sequencing on the clinical diagnosis of pancreatic cysts. Gastrointest Endosc. 2016;83:140–8.
38. Garcia-Carracedo D, Chen ZM, Qiu W, et al. PIK3CA mutations in mucinous cystic neoplasms of the pancreas. Pancreas. 2014;43:245–9.
39. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a rare report of the PANDA study. Gastrointest Endosc. 2009;69:1095–102.
40.• Das A, Brugge W, Mishra G, et al. Managing incidental pancreatic cystic neoplasms with integrated molecular pathology is a cost-effective strategy. Endosc Int Open. 2015;3:E479–8.
A large surgical case series showing the benefits of confocal laser endomicroscopy for the evaluation of pancreatic cysts.
41. Krishna SG, Hart PA, Malli A, et al. Endoscopic ultrasound-guided confocal laser endomicroscopy increases accuracy of differentiation of pancreatic cystic lesions. Clin Gastroenterol Hepatol. 2019.
42. Maguchi H, Tanno S, Mizuno N, et al. Natural history of branch duct intraductal papillary mucinous neoplasms of the pancreas: a multicenter study in Japan. Pancreas. 2011;40:364–70.
43.• LaFemina J, Katabi N, Klimstra D, et al. Malignant progression in IPMN: a cohort analysis of patients initially selected for resection or observation. Ann Surg Oncol. 2013;20:440–.
A study indicating that cyst growth rate is associated with malignant transformation.
44. Kolb JM, Argiriadi P, Lee K, et al. Higher growth rate of branch duct intraductal papillary mucinous neoplasms associates with worrisome features. Clin Gastroenterol Hepatol. 2018;16:1481–7.
45. Akahoshi K, Ono H, Akasu M, et al. Rapid growth speed of cysts can predict malignant intraductal mucinous papillary neoplasms. J Surg Res. 2018;231:195–200.
46. Mukewar SS, Sharma A, Phillip N, et al. Risk of pancreatic cancer in patients with pancreatic cysts and family history of pancreatic cancer. Clin Gastroenterol Hepatol. 2018;16:1123–30.
47. Mandai K, Uno K, Yasuda K. Does a family history of pancreatic ductal adenocarcinoma and cyst size influence the follow-up strategy for intraductal papillary mucinous neoplasms of the pancreas? Pancreas. 2014;43:917–21.
48. Das A, Ngamruengphong S, Nagendra S, et al. Asymptomatic pancreatic cystic neoplasm: a cost-effectiveness analysis of different strategies of management. Gastrointest Endosc. 2009;70:690–9.
49. Kwok K, Chang J, Duan L, et al. Competing risks for mortality in patients with asymptomatic pancreatic cystic neoplasms: implications for clinical management. Am J Gastroenterol. 2017;112:1330–6.
50. Gaujoux S, Brennan MF, Gonen M, et al. Cystic lesions of the pancreas: changes in the presentation and management of 1424 patients at a single institution over a 15-year time period. J Am Coll Surg. 2011;212:590–600.
51. Spinelli K, Fromwiller T, Daniel R, et al. Cystic pancreatic neoplasms: observe or operate. Ann Surg. 2004;239:651–9.
52. Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. Ann Surg. 2015;261:21–9.
53. Lara LF, Takita M, Burdick JS, et al. A study of the clinical impact of a 20-minute secretin-stimulated endoscopic pancreas function test and performance according to clinical variables. Gastrointest Endosc. 2017;86:1048–55.
54. Scheiman JM, Hwang JH, Moayeddi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:824–48.
55. Roch AM, DeWitt JM, Al-Haddad MA, et al. Non operative management of main pancreatic duct-involved intraductal papillary mucinous neoplasm might be indicated in select patients. J Am Coll Surg. 2014;219:122–9.

Publisher's Note