



How many pancreatic cysts are out there and how to best manage them?

Victor Ciofoaia, Nadim G. Haddad, Jill P. Smith

Department of Medicine, Gastroenterology, Georgetown University, Washington DC, USA

Correspondence to: Jill P. Smith. Department of Medicine, Gastroenterology, Georgetown University, Washington DC, USA.

Email: jps261@georgetown.edu.

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The finding of an incidental asymptomatic cyst in the pancreas with routine radiographic imaging makes both patients and physicians question, “What level of ‘risk’ is acceptable for either surveillance or for an invasive intervention?” and “What price should be paid for the only approach we have to cure pancreatic cancer—early detection and adequate resection?” This topic has been the focus of several recent reviews (1-3). This issue has become clinically relevant over the last few decades since more pancreatic cysts are diagnosed with each higher quality magnetic resonance imaging (MRI) performed in an aging population (4,5). While there are international and professional societies management guidelines to help plan immediate and long term sequences of various invasive and non-invasive interventions (6-8) the evidence supporting many recommendations is weak (9), debated (10,11) and following these recommendations can be expensive (5), reflecting the incomplete knowledge currently available on their natural history and the still evolving diagnostic and interventional tools available to describe their etiology, natural course and malignant potential. High quality studies are needed to help refine and perfect future guidelines.

In this regard the study by Kromrey *et al.* (12) entitled, “Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study”, adds to the pancreatic cystic lesion knowledge base a prospective population cohort study with another answer to an apparently very simple question: how many pancreatic cysts can one anticipate finding on an MRI performed in the general asymptomatic population and do

they pose a risk for development of pancreatic cancer?

The answer is unfortunately very often not straight forward. The evaluation and surveillance of high-risk pancreatic lesions and individuals in multidisciplinary pancreatic cysts programs is emerging as a comprehensively way to evaluate and risk stratify the significance of each findings for a given patient, leading in many cases to less invasive and more confident decisions and to better answers for the frequently raised question: what can one physician tell an asymptomatic patient who while having an MRI for an unrelated indication is told there is a “small cyst” in the pancreas? The involvement of a gastroenterologist, radiologist, surgeon, oncologist and geneticist is needed to better answer this and the underlying question: what is the etiology of the cyst and what is the risk of malignancy? (13).

In this study by Kromrey *et al.* (12), an asymptomatic population cohort had two MRIs performed 5 years apart, leading to an unexpectedly high 49.1% prevalence of pancreatic cystic lesions and new incidence of lesions of 12.9%. To put this high number in perspective of previous studies, the American Gastroenterological Association (AGA) based its recommendations (7) on an averaged prevalence of pancreatic cystic lesions of 15% in the general population and the broad range reported in various asymptomatic or high risk populations from 2.4% to 38.8% (*Table 1*). Factors such as the patient’s age and history of pancreatic disease increase the prevalence, number and size of pancreatic cysts, paralleling the various types of pancreatic cysts met in clinical practice, as does the diagnostic modality. The best noninvasive diagnostic

Table 1 Recent large studies of pancreatic cysts lesions

Study	Population	Findings
2018 Kromrey <i>et al.</i> (12)	1,077 asymptomatic patients who agreed to have an MRI, 676 underwent a 5-year follow-up MRI	49.1% PCL prevalence 12.9% 5-year PCL incidence Mean cyst size 5.2 mm Only 0.7% larger than 2 cm Only 5.1% between 1–2 cm Of the 26 Patients with PCL >1 cm, 14 decreased in size and 11 remained in the same size category
2017 Lawrence <i>et al.</i> (14)	Retrospective review of 2,472 Patients with PCL (1995–2016). Comparison of more than 5-years follow-up with less than 5-years follow-up PCL features.	The >5-year follow-up group experienced a greater frequency of cyst growth (44% vs. 20%; P<0.0001); 69% had demonstrated radiographic stability at the 5-year time point Cyst size stability at the 5-year time point did not preclude future growth, cross-over to resection, or carcinoma development Patients who were stable at 5 years had a nearly 3-fold higher risk of developing cancer
2017 Yoen <i>et al.</i> (15)	Retrospective review of 95 PCLs diagnosed on CT during 2003–2004, followed for more than 5 years	42.9% enlarged, only 5 cysts increased to >3 cm at the end of observation No cysts <15 mm and without PD change showed a significant change within 3 years
2017 Kim <i>et al.</i> (16)	Cohort of 553 unilocular PCLs less than 3 cm, diagnosed 11/2003–12/2014 on CT or MRI, followed for 6 to 129 months	23.1% enlarged 76.1% did not change 9.1% enlarged to >3 cm
2017 Kayal. <i>et al.</i> (17)	Retrospective review of 2,423 presumed branch duct IPMNs with more than 4 years of follow-up either by CT, MRI or EUS, between 2001–2013	No difference in cyst size or CEA comparing those that progressed compared to those that did not progress 55.7% progressed: 46.6% enlarged, 7.6% enlarged and developed worrisome features, and 1.5% developed worrisome features only Of the PCL that enlarged, 70.4% did so within the first 5 years, and 21 (29.6%) grew after 5 years No patient had adenocarcinoma
2016 Chang <i>et al.</i> (18)	Retrospective data review of 21,745 asymptomatic individuals underwent abdominal CT as a health screening examination between 2003 and 2013	2.2% prevalence, increasing with age (13.5% in their 80s) PCL size 8.0±7.2 mm Multiple cysts 10.5% 8 operated cases: 1.8% (7 IPMN, 1.5%; 1, SCN)

PCL, pancreatic cystic lesion; IPMN, intraductal papillary mucinous neoplasms; SCN, serous cystic neoplasm; PD, pancreatic duct.

modality remains the MRI (19), with endoscopic ultrasound increasing the diagnostic yield over CT and MRI by 36% and respectively 54% in one study (20).

The description of the small subcentimeter incidental pancreatic cysts is one of the strengths of the Kromrey *et al.* study. Of the study's asymptomatic 1,077 subjects

who accepted to undergo an MRI, 676 received a 5-year follow-up MRI, with 12.9% newly detected pancreatic cysts and an increase in the number and/or maximum cyst size in 57.1% of the subjects who were found to already have pancreatic cystic lesions on the index MRI. However, these were mostly small cysts, with a mean cyst size 5.2 mm.

The almost “1 in 2” 49.1% prevalence is strikingly different from the 2.4% pancreatic cysts prevalence resulted from a prior similar prospective study with only a slightly different study population (21) of 2,803 consecutive asymptomatic patients who underwent an abdominal MRI at a preventive medical examination, where the median cyst size was 8 mm (range, 2–54 mm) with only 6% of these cysts larger than 2 cm. Another multicenter study (22) that looked at higher risk patients with a strong family history of pancreatic cancer or a predisposing germline mutation that screened 225 asymptomatic adults using computed tomography, magnetic resonance imaging and endoscopic ultrasonography found out that the overall prevalence of a focal pancreatic abnormality in any of the 3 screening tests was 42.6%, with most of the pancreatic mass lesions detected small (mean size 0.55 cm, range, 0.2–3.9 cm), cystic (96%), with patients presenting with multiple lesions (60.7% of those with a cyst). The robust AGA technical review (7) identified 7 studies that reported based on MRI the prevalence of pancreatic cysts to range from 2% to 38%, with an overall prevalence of 15% (95% CI, 7–24%). These are all MRI based studies; the prevalence (23) of pancreatic cysts on autopsies was up to 30% in the 80–89 years old age group and on CT imaging as low as 2.6% (24,25). In the current study, 57% of the patients with pancreatic cysts had an increase in size in 5 years (12) and other studies also suggested that pancreatic cysts still continue to grow 2.2 years later (26) with 11% of them showing delayed growth even after an initial 1-year period of stability. As in other studies, the prevalence of pancreatic cystic lesions was noted to increase with age.

In this observational study by Kromrey *et al.*, important information regarding the cohort is not included in the results that may potentially be important. Of the 1,077 subjects who received MRI/magnetic resonance cholangiopancreatography (MRCP) in this study only 676 received the follow-up in 5 years. It would be of importance to know details of the 401 subjects that did not follow up; and several questions could help clarify the lack of return: (I) how many of these subjects had cysts; (II) what was the size of cyst detected on their baseline scan; and (III) did the subjects follow-up with additional evaluations (i.e., EUS, or imaging earlier than the 5 years) because of either patient concern or high risk features on the initial MRI? Although we are provided with the mean cyst size in *Table 1* of this manuscript, a range in size is provided. Standard recommendations and further evaluation are based upon

high risk criteria (27) on imaging including cyst size (≥ 3 cm). We are not provided information on whether those with larger cysts (if there were any) underwent surgery.

The authors expand in their discussion regarding the potential cancer risk in pancreatic cystic lesions and early detection and resection of premalignant lesions is important. However, only three subjects in their 2,333 participants died from pancreatic cancer. Only one of the three subjects with pancreatic cancer had a follow up MRCP; however, we are not told whether any of these three subjects had cysts at baseline. Literature supports that about 85% of those with pancreatic cancer arise from non-cystic lesions called pancreatic intraepithelial neoplasia (PanINs).

Lastly, it is unclear why the 5-year follow-up surveillance time period was chosen. According to the majority of pancreatic cyst guidelines published, most recommend follow-up imaging for cysts without high risk potential within 1 year. Perhaps simple pancreatic cysts in the general population that are incidentally found may be similar to those who have incidental hepatic cysts (8) and renal cysts (28).

The clinical management of pancreatic cystic lesions is currently based on the AGA guideline (29) for incidental asymptomatic cysts and the Sendai guidelines 2006 (30) and their 2012 and 2017 revision—the Fukuoka guidelines (6,27)—for mucinous cystic neoplasms and intraductal papillary mucinous neoplasms, the small percentage of the pancreatic cystic lesions with an established malignant potential. The AGA guidelines recommend MRI surveillance after 1 year and then every 2 years for a total of 5 years for patients with pancreatic cysts without high risk features (size less than 3 cm, without a solid component or a dilated pancreatic duct), with EUS-FNA (endoscopic ultrasound with fine needle aspiration) pursued if one high risk feature is present and surgery recommended if there are two high risk features. Many studies show that stopping surveillance after 5 years (as recommended by AGA) would miss some cysts that may progress to cancer (14).

The American College of Radiology Incidental Findings in a 2017 expert based white paper (19) expands the follow-up period to 10 years, considering the patient's age (up to 80 years of age, when surveillance should be stopped if the patient is not a surgical candidate), the pancreatic cyst size and growth and incorporating EUS with FNA as an intervention for higher risk lesions and intervals as short as 6 months for follow-up MRIs. The recommendation to expand the surveillance period to 10 years is based on the finding that even after 5 years of stability pancreatic cysts

can still increase in size (14).

The international Fukuoka guideline risk stratify pancreatic cysts based on “high-risk stigmata”(obstructive symptomatology such as jaundice, enhancing mural nodules larger than 5 mm, main pancreatic duct size more than 10 mm) and “worrisome” features (cyst size more than 3 cm, enhancing mural nodule less than 5 mm, thickened enhanced cyst walls, main pancreatic duct size 5–9 mm, abrupt change in the main pancreatic duct diameter with distal pancreatic atrophy, lymphadenopathy, elevated CA19-9 levels, rapid rate of cyst growth more than 5 mm/2 years). Symptomatic cysts (which are not covered by the AGA guideline) or the presence of high risk stigmata should be evaluated clinically for surgical resection, while the presence of worrisome features should be followed for further risk stratification by EUS-FNA, with inconclusive features on EUS-FNA triggering based on cyst size surveillance with EUS alternating with MRI every 3–6 months for cysts larger than 2 cm and the recommendation to consider surgery in young and fit patients instead of prolonged surveillance. In an attempt to increase the yield of EUS exams, there is an evolving role for contrast enhanced harmonic EUS that can demonstrate the presence of blood supply in the mural nodule (31,32), cyst and pancreatic duct lavage (33) and of 19G through the FNA needle cyst wall puncture and micro biopsy (34).

Current research is focusing on risk stratification of the pancreatic cystic lesions (35), molecular and genetic markers of cyst (36) and the role of integrated molecular pathology (37). The AGA recently released a new whitepaper on the role of EUS/FNA for theranostics (38). Others are focusing their attention on developing a “liquid biopsy” (39) using circulating DNA. Circulating miRNAs and metabolites are also promising non-invasive biomarkers that are currently being developed for early detection of pancreatic cancer (40–43).

Despite these shortcomings of this additional study in healthy asymptomatic subjects with incidental pancreatic cysts, the authors conclude that a restrictive follow-up approach can be followed and that screening the general population with imaging for pancreatic cysts to reduce risk of malignancy is not recommended. Based upon the recommendations from the current study and all the prior studies listed (*Table 1*), researchers can perhaps now stop doing large cohort expensive studies on asymptomatic incidental cysts and turn their attention to factors besides radiographic findings that may identify a cyst-bearing patient at risk for cancer.

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