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AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

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This article has an accompanying continuing medical education activity on page e12. Learning Objective: At the conclusion of this exercise, the learner will understand the approach to counseling patients regarding the optimal method and frequency of radiologic imaging, indications for invasive tests like endoscopic ultrasonography (EUS) and surgery, select patients for follow-up after surgery, decide the duration of such follow-up, and decide when to stop surveillance for those with and without surgery.

See related Commentaries (pages 685-692); Clinical Decision Tool and Technical Review (pages 823-824); and related Commentary by RP Harris in the April issue of *Annals of Internal Medicine*.

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the management of pancreatic cysts. The guideline was developed by the AGA's Clinical Practice Guideline Committee and approved by the AGA Governing Board.

The incidental identification of pancreatic cysts is common with the growing use of sophisticated abdominal imaging techniques. Approximately 15% of patients undergoing abdominal magnetic resonance imaging (MRI) for other indications harbor unsuspected pancreatic cysts. Once detected, these cysts can trigger significant anxiety for patients and their physicians. Immediate as well as surveillance evaluations and resulting interventions can be invasive, expensive, and harmful.

A key component of clinical management of pancreatic cysts is a reliable strategy to identify the small minority of cysts with early invasive cancer or high-grade dysplasia (HGD) and to predict those that will develop them in the future. Appropriately timed surgical resection can reduce mortality from pancreatic adenocarcinoma. However, surgical resection for pancreatic cysts is associated with significant rates of morbidity and some mortality. Ideally, the clinician would have highly effective methods to identify patients most likely to benefit from surgery. A major challenge is that commonly used diagnostic tools such as computed tomography, MRI, and endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) cytology have suboptimal sensitivities and specificities to identify patients at highest risk.

These guidelines pertain only to asymptomatic pancreatic neoplastic cysts. We did not evaluate the impact of symptoms on the management of cysts, and this guideline also does not consider some neoplastic lesions such as solid papillary neoplasms, cystic degeneration of adenocarcinomas, neuroendocrine tumors, and main duct intraductal papillary mucinous neoplasms (IPMNs) without side branch involvement, because identification of these neoplasms may be less challenging and the accepted approach is surgical resection if the patient is a suitable candidate.

Several previous guidelines have provided recommendations regarding management of pancreatic cysts. However, none have pursued a systematic evaluation of the available evidence. This guideline uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[1] This approach breaks down the management of patients with a specific disorder into a series of statements phrased in the PICO format that defines the population (P) under study, the intervention or investigation (I) under consideration, the comparator (C) against which that intervention or investigation is assessed, and the outcome (O) worthy of evaluation.[1] It is important to emphasize that the outcomes in these statements should be focused on what is relevant to patients. In the case of pancreatic cysts, all statements refer to adult patients who have asymptomatic pancreatic cysts identified by radiology; if a comparator is not stated, then it is implied that the management strategy is being compared against "do nothing."

Both the quality of the available evidence and the strength of the recommendation are provided for each PICO statement. The quality of the evidence supporting the PICO statement is described on a 4-point scale from high to very low. A very low quality of evidence indicates great uncertainty regarding the

Abbreviations used in this paper: **AGA, American Gastroenterological Association; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; MRI, magnetic resonance imaging; PICO, population, intervention, comparison, and outcome.**

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estimate of effect. The evidence for the management of pancreatic cysts is summarized in the technical review[2] that accompanies this guideline. All the evidence related to the management of pancreatic cysts is graded as very low quality. Nearly all data were derived from case series. Often these reports were retrospective, with major unexplained heterogeneity between studies, and did not directly evaluate reduced mortality from pancreatic adenocarcinoma as the key outcome. A reasonable argument can be advanced that no recommendations regarding the management of pancreatic cysts can be made because the evidence pertaining to the available approaches is so conditional. Further, as discussed in the following text, it is unclear that the benefits of surveillance outweigh the risks for most patients. However, given the serious outcome of a minority of pancreatic cysts and the need for clinical guidance on how to manage this complex problem, it is important to develop guidelines using the limited evidence that is available.

In addition to reviewing the quality of the evidence, a strength of recommendation for each statement is made that considers, as a whole, the quality of the evidence, the risks and benefits of the strategy, the values and preferences of patients, and the cost (financial and otherwise) of the approach being recommended. A "strong" recommendation supports a clinical decision that should apply to most patients most of the time, whereas a "conditional" (also called "weak" in some settings) recommendation implies that the decision is more nuanced and a significant number of patients could have a different approach.

Issues Related to the Conduct of Surveillance

1. The AGA recommends that before starting any pancreatic cyst surveillance program, patients should have a clear understanding of programmatic risks and benefits.

This is a "motherhood statement" that does not require application of the GRADE system.[3] Discussing the risks and benefits of a management strategy with the patient is good clinical practice for nearly all diseases and interventions. In the context of this guideline, it is important to emphasize that surveillance may not be appropriate for, or desired by, some patients. Certain patients may have a higher tolerance of risk. When the probability of a cyst becoming malignant is explained to them, they may elect not to undergo surveillance. Patients who have a limited life expectancy are unlikely to benefit, and surveillance is inappropriate for patients who are not surgical candidates because of age or severe comorbidities.

2. The AGA suggests that patients with pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct undergo MRI for surveillance in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics. *(Conditional recommendation, Very low quality evidence)*

The incidence of pancreatic cysts in the US population increases with age and may be as common as 25% in those older than 70 years. Pancreatic mucinous cystadenocarcinoma and pancreatic ductal carcinoma are rare. Using Surveillance, Epidemiology, and End Results database statistics, we estimate that a cyst seen incidentally on MRI has a 10 in 100,000 chance of being a mucinous invasive malignancy and a 17 in 100,000 chance of being a ductal cancer. The overall risk that an incidental pancreatic cyst is malignant is therefore very low. If a radiologist experienced in the accurate assessment of pancreatic cystic lesions reports no concerning features, then it should be safe to follow up the great majority of patients. MRI is the preferred surveillance imaging modality over computed tomography because MRI does not expose the patient to radiation and better demonstrates the structural relationship between the pancreatic duct and associated cyst. Also, MRI is less invasive than EUS. The follow-up interval of 1 and then 2 years is not based on any evidence but is believed to be reasonable given the small absolute risk of malignancy.

3. The AGA suggests that pancreatic cysts with at least 2 high-risk features, such as size ≥3 cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with EUS-FNA. (*Conditional recommendation, Very low quality evidence)*

A systematic review of the literature suggests that cyst size $\geq$3 cm, a dilated main pancreatic duct, and the presence of a solid component are factors associated with increased risk of malignancy. Supporting evidence is indirect, using selected cases of surgically resected IPMN where cyst histology is more fully characterized than preoperative imaging alone would allow. We conducted a review of the literature for the accuracy of the features of unselected cysts[2] and found that size $\geq$3 cm increased the risk of malignancy approximately 3 times and the presence of a solid component increased the risk of malignancy approximately 8 times.[2] There was no statistically significant association of a dilated pancreatic duct with malignancy in our review, but we included this as a risk factor given the systematic review findings with resected IPMNs. The quality of the evidence was graded as very low because there was unexplained variation between studies and the population evaluated was highly selected, involving patients undergoing pancreatic resection. A relative increase in risk of malignancy of 8 times is substantial; however, given the very low baseline risk, the absolute effect is modest. Nevertheless, we believe that if 2 of these features are present, the risk of malignancy is likely to be even higher and this should trigger further investigations to characterize the risk of malignancy more accurately. Systematic review of the data suggests this is best achieved by EUS and FNA, with a sensitivity of approximately 60% and a specificity of 90%. This is a conditional recommendation in view of the very low quality of the evidence. Some clinicians and patients may elect to evaluate the cyst with just one high-risk feature present, such as a solid component if this is particularly prominent.

4. The AGA suggests that patients without concerning EUS-FNA results should undergo MRI surveillance after 1 year and then every 2 years to ensure no change in risk of malignancy. *(Conditional recommendation, Very low quality evidence)*

The sensitivity of EUS and FNA is modest, but this is more than counterbalanced by the low prevalence of malignancy in pancreatic cystic lesions. The negative predictive value of unremarkable EUS-FNA results, although not 100%, is high, with a very low associated risk of malignancy. However, there may be a minority of patients in whom surgery is appropriate or surveillance with MRI earlier than 1 year should be performed, even if all criteria are not met. The recommendation is conditional because the group recognizes that the quality of evidence is very low.

5. The AGA suggests that significant changes in the characteristics of the cyst, including the development of a solid component, increasing size of the pancreatic duct, and/or diameter ≥3 cm, are indications for EUS-FNA. *(Conditional recommendation, Very low quality evidence)*

The technical review[2] suggests that an increase in the size of the cyst is not a statistically significant risk factor for malignancy. There are insufficient data on increasing size of the pancreatic duct or the development of a solid component in a cyst that previously did not exhibit this feature, so we cautiously recommend reassessing patients who have these features during follow-up with EUS-FNA. This is a conditional recommendation given the very low quality of evidence underpinning the statement.

When Can Pancreatic Cyst Surveillance Be Discontinued?

6. The AGA suggests against continued surveillance of pancreatic cysts if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate. *(Conditional recommendation, Very low quality evidence)*

The review of the literature[2] suggests that the risk of malignant transformation of pancreatic cysts is approximately 0.24% per year. This estimate considers all cysts, including those that change over time. The risk of cancer in cysts without a significant change over a 5-year period is likely to be lower, although there are no data that specifically compare rates of cancer in stable cysts versus cysts that change over time. The small risk of malignant progression in stable cysts is likely outweighed by the costs of surveillance and the risks of surgery. We gave this a conditional recommendation because some patients may elect to continue surveillance for longer after discussion with their clinician if there are other factors, such as a strong family history of pancreatic cancer or equivocal changes in cysts that possess high-risk features.

When to Offer Surgery for Pancreatic Cysts

7. The AGA suggests that patients with both a solid component and a dilated pancreatic duct and/or concerning features on EUS and FNA should undergo surgery to reduce the risk of mortality from carcinoma. *(Conditional recommendation, Very low quality evidence)*

Positive cytology on EUS-guided FNA has the highest specificity for diagnosing malignancy; if there is a combination of high-risk features on imaging, then this is likely to increase the risk of malignancy even further. Similarly, if a cyst has both a solid component and a dilated pancreatic duct (confirmed on both EUS and MRI), the specificity for malignancy is likely to be high even in the absence of positive cytology. It is important to emphasize that there are no data on the impact of multiple high-risk features on the risk of malignancy; however, in many areas of medicine, multiple risk factors have at least an additive effect in increasing the risk of disease being present. The specificity of this approach is likely to be high (>95%). Despite the low overall risk of malignancy, such a high test specificity will best identify patients who will have malignant disease at resection. Molecular techniques to evaluate pancreatic cysts remain an emerging area of research, and the diagnostic utility of these tests is uncertain. In the technical review[2] accompanying these guidelines, we evaluated all surgical case series of cystic pancreatic neoplasms. Overall, 15% of patients harbored invasive malignancy in a highly selected group of patients with pancreatic cysts.

These data would suggest that the benefits of surgery outweigh the risks in this selected population. Normally we would have given this a strong recommendation. To do so assumes that most patients will benefit from the surgery; our review[2] estimated that the overall 5-year survival of patients with invasive cancer is approximately 28%. In addition, this estimate may be prone to some lead and length time bias that, if present, would further reduce any surgical benefit. Surgery is likely to be most beneficial in cases of cyst resection for HGD, thereby preventing malignancy. Our review of the literature would suggest that approximately 17% of patients with IPMNs undergoing pancreatic resection have cysts that harbor HGD. The challenge in interpreting these data is that it is unclear how many of these would have progressed to invasive malignancy. It is clear from other cancers that not all HGD progresses, so the proportion of patients who truly benefit from surgery is unclear even in this high-risk group. Any benefit also has to be taken in context with an overall postoperative mortality of 2% and major morbidity of 30% from the review of the literature.[2] It is for these reasons that we only gave a conditional recommendation for surgery even in high-risk patients.

8. The AGA recommends that if surgery is considered for a pancreatic cyst, patients are referred to a center with demonstrated expertise in pancreatic surgery. *(Strong recommendation, very low quality evidence)*

A systematic review of outcomes of all pancreatic surgeries showed lower immediate postoperative mortality as well as long-term mortality for patients who undergo surgery in high-volume pancreatic centers. There are no direct data for pancreatic cyst surgery specifically, so the quality of the evidence is very low. The Surveillance, Epidemiology, and End Results database, which reflects all pancreatic surgeries in the United States, reports a 6.6% postoperative mortality. In comparison, the 2% postoperative mortality in our review is derived predominantly from centers of excellence, providing indirect evidence supporting this statement.

Surveillance After Surgery

9. The AGA suggests that patients with invasive cancer or dysplasia in a cyst that has been surgically resected should undergo MRI surveillance of any remaining pancreas every 2 years. *(Conditional recommendation, Very low quality evidence)*

We did not identify any evidence to support this statement. However, these patients may have a field defect in the pancreas that predisposes them to develop cancer. It therefore seems sensible to offer screening even after the cyst has been resected provided they have not undergone total pancreatectomy. Surveillance should continue as long as the patient remains a good candidate for surgery. MRI every 2 years may be a reasonable approach for these patients, in line with our recommendations for incidental pancreatic cysts. The clinician may elect to offer more frequent surveillance in the case of invasive cancer resection, particularly if there is concern that the lesion has not been fully resected.

10. The AGA suggests against routine surveillance of pancreatic cysts without high-grade dysplasia or malignancy at surgical resection. *(Conditional recommendation, Very low quality evidence)*

There are no case series that report outcomes in this group. However, it seems very likely that if patients do not have HGD or invasive malignancy in any cyst that was resected, then they are not likely to have any field defect that predisposes them to malignancy. Continued surveillance in this group is extremely unlikely to be cost-effective. This statement refers to those with no mixed duct IPMN and no strong family history of pancreatic cancer.

Summary

Pancreatic cysts are common and increase with age, but the development of invasive adenocarcinoma in these cysts is extremely rare. The management strategy for pancreatic cysts aims to prevent the development of invasive cancer and/or to resect invasive malignancy early when present. Current clinical practice is based on minimal evidence and relies almost exclusively on case series of frequent cross-sectional imaging with or without EUS and/or FNA cytology and surgery for concerning features. The preceding guidelines for asymptomatic mucinous cysts are different from all previously published guidelines in the following areas: 2-year interval for cyst of any size undergoing surveillance, stopping surveillance after 5 years if no change, surgery only if more than one concerning feature on MRI confirmed on EUS and only in centers with high volumes of pancreatic surgery, and no surveillance after surgery if no invasive cancer or dysplasia. Although based on extensive literature review and synthesis, these recommendations may result in significant controversy because they advocate less frequent follow-up and a higher threshold before offering EUS and/or surgery. However, consistent utilization should decrease inadvertent harm to patients and reduce the costs of health care delivery.

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Conflicts of interest
All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report. The authors disclose no conflicts.