American Gastroenterological Association Institute Guidelines for Management of Asymptomatic Neoplastic Pancreatic Cysts

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the management of pancreatic cystic neoplasms. 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 can be invasive and expensive.

A key component of pancreatic cyst clinical management 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 future. Appropriately timed surgical resection can reduce mortality from pancreatic cystadenocarcinoma. However, surgical resection for pancreatic cysts is associated with significant rates of morbidity and mortality. Ideally, the clinician would have highly effective methods to identify patients most likely to benefit from surgery. A major challenge is that commonly employed diagnostic tools such as computerized tomography (CT), MRI and endoscopic ultrasound (EUS) with fine needle aspiration (FNA) cytology have suboptimal sensitivities and specificities to identify the highest risk patients. These guidelines pertain 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 neoplastic lesions such as solid papillary neoplasms, cystic degeneration of neuroendocrine tumors, and main duct intraductal papillary mucinous neoplasms (IPMN) without side-branch involvement.
Several previous guidelines have provided recommendations regarding management of pancreatic cysts. However, none have pursued a systematic evaluation of the available evidence. This guideline employs the GRADE criteria (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 under study, the Intervention or investigation under consideration, the Comparator against which that intervention or investigation is assessed and the Outcome 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 that have asymptomatic pancreatic cysts identified by radiology and 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 is described on a four-point scale from high to very low. A very low quality of evidence indicates great uncertainty regarding the 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 are derived from case series. Often these reports were retrospective, usually there was major unexplained heterogeneity between studies, with outcomes assessment that was indirect assuming reduced mortality from pancreatic cystadenocarcinoma as the key outcome. A reasonable argument can be advanced that no recommendations regarding the management of pancreatic cysts can be made, as the evidence pertaining to the available approaches is so weak. Further, as discussed below, it is unclear that the benefits of surveillance outweigh the risks for most patients. However, given the serious outcome of some pancreatic cysts and the need for clinical
guidance on how to manage this complex problem it is important to develop guidelines employing the limited evidence that is available.

In addition to reviewing evidence quality, 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 while a “weak” (also called “conditional” 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 patients, before starting any pancreatic cyst surveillance program, should have a clear understanding of programmatic risks and benefits

This is a “motherhood statement” that does not require the application of the GRADE system (3). Discussing 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 have surveillance. Patients that have a limited life expectancy are unlikely to benefit, and surveillance may also be inappropriate for patients who are not surgical candidates because of age or severe comorbidities.

DO NOT CITE OR REFERENCE
2. The AGA suggests that pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct should be offered an MRI surveillance in one year and then every two years for a total of five years if there is no change in size or characteristics. *Weak 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 over 70 years old. Pancreatic cystadenocarcinoma is rare. Using SEER database statistics, we estimate that the risk that a cyst seen incidentally on MRI has a 17 in 100,000 chance to be an invasive malignancy. The overall risk that an incidental pancreatic cyst is malignant is therefore very low. Provided a radiologist experienced in the accurate assessment of pancreatic cystic lesions reports no concerning features then it should be safe to follow the great majority of patients. MRI does not expose the patient to radiation and therefore is the preferred surveillance modality over CT. Also, MRI is less invasive than EUS. The follow up interval of one and then 2 years is not based on any evidence but was felt to be reasonable given the small absolute risk of malignancy. The recommendation was weak as some patients may need closer follow up if there are other issues such as a first degree relative with pancreatic cancer or there were equivocal findings on MRI.

3. The AGA recommends that pancreatic cysts ≥ 3 cm and/or cysts with higher risk features such as a dilated main pancreatic duct or associated solid component should have EUS/FNA. *Strong recommendation, very low quality evidence*

A systematic review of the literature suggests that cyst size ≥ 3cm, dilated pancreatic duct and the presence of a solid component are factors associated with increased risk of malignancy. Supporting evidence is indirect, utilizing selected cases of surgically resected IPMN where cyst histology is more fully characterized than pre-operative imaging alone would allow. We conducted a review of the
literature for the accuracy of the features for unselected cysts (2) and found that size $\geq$ 3cm increased the risk of malignancy approximately 3x and the presence of a solid nodule increased the risk of malignancy approximately 8x (2). There was no statistically significant association of 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 as there was unexplained variation between studies and the population evaluated was highly selected involving patients undergoing pancreatic resection. A relative increase in malignancy risk of 8x is substantial, but given the very low baseline risk the absolute effect is modest. Nevertheless we felt these features should trigger further investigations to characterize the risk of malignancy more accurately. Systematic review data would suggest this is best achieved by EUS and FNA with a sensitivity of approximately 60% and a specificity of 90%.

4. The AGA suggests patients without concerning EUS/FNA results should be offered MRI surveillance after one year and then every two years to ensure no change in risk of malignancy.

*Weak 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. An alternative strategy of pancreatic resection in lieu of surveillance is associated with surgical morbidity and mortality that we felt to exceed any benefits. The recommendation is weak as the group recognized that the quality of evidence is very low and there may be some patients where surgery is appropriate even if all criteria are not met.
5. The AGA suggests that significant change in cyst characteristics including the development of a solid component and/or increasing pancreatic duct size are indications for EUS/FNA. *Weak recommendation, very low quality evidence*

Our review (2) suggested that increase in size of the cyst was not a statistically significant risk factor for malignancy. There are insufficient data on increasing size of pancreatic duct or the development of a nodule in a cyst that previously did not exhibit this feature so we cautiously recommend reassessing patients that have these features during follow-up with EUS/FNA. This is a weak recommendation given the very low quality of evidence underpinning supporting the statement.

*When can pancreatic cyst surveillance be discontinued?*

6. The AGA recommends discontinuation of pancreatic cyst surveillance if there has been no significant change in cyst characteristics after five years of surveillance or if the patient is no longer a surgical candidate. *Strong recommendation, very low quality evidence*

Our review of the literature (2) suggested that the risk of malignant transformation of pancreatic cysts is approximately 0.4% per year. This estimate considers all cysts, including those that change over time. The cancer risk in cysts without significant change over a five year period is likely to be lower, although there are no data that specifically compare cancer rates in stable versus unstable cysts. The small risk of malignant progression in stable cysts is likely outweighed by the costs of surveillance including the risks of surgery. We gave this a strong recommendation as available data suggest this approach will apply to most patients. The clinician may elect to continue surveillance.
for longer in a minority of patients, if there are other factors such as those with a strong family history of pancreatic cancer or equivocal changes in cysts that possess high risk features.

**When to offer surgery for pancreatic cysts**

<table>
<thead>
<tr>
<th>7. The AGA suggests that patients with both solid nodule and a dilated pancreatic duct and/or concerning features on EUS and FNA should be offered surgery to reduce the risk of mortality from mucinous cyst-adenocarcinoma. <strong>Weak recommendation, very low quality evidence</strong></th>
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<td>Positive cytology on EUS-guided FNA has the highest specificity for diagnosing malignancy and if there are a combination of high-risk features on imaging then this is likely to increase the risk of malignancy even further. Similarly if a ≥ 3cm cyst has both a solid nodule and a dilated pancreatic duct (confirmed on both EUS and MRI) then 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 but 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 (&gt; 95%). Despite the low overall risk of malignancy, such a high test specificity will best identify patients who will have malignant disease at resection. In the technical review (2) accompanying these guidelines, we evaluated all surgical case series of cystic pancreatic neoplasms. Overall 15% patients harbored invasive malignancy.</td>
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<td>These data would suggest the benefits of surgery outweigh the risks in this selected population. Normally we would have given this a strong recommendation. To do so assumes most patients will</td>
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benefit from the surgery; our review (2) estimated the overall 5 year survival of patients with invasive
cancer was 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 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 that truly benefit from surgery is unclear even in this high-risk group. Any benefit
also has to be taken in context with an overall post-operative mortality of 2% and major morbidity of
30% from our review of the literature (2). It is for these reasons that we only gave a weak
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 on outcomes of all pancreatic surgery demonstrated the lower immediate post-
operative mortality as well as long term mortality for patients operated 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 SEER database, which reflects all pancreatic surgeries in the US, reports a 6.6% post-
operative mortality. In comparison, the 2% post-operative 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 have MRI surveillance of any remaining pancreas every 2 years. Weak 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 had a 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 recommends that pancreatic cyst patients without high grade dysplasia or malignancy at surgical resection should not be offered any further surveillance. Strong recommendation, very low quality evidence.

There are no case series that report outcomes in this group. However it seems very likely that if the patient did not have HGD or invasive malignancy in any cyst that was resected then they are likely not to have any field defect that predisposes them to malignancy. Continued surveillance in this group is extremely unlikely to be cost effective.
Summary

Pancreatic cysts are common and increase with age but mucinous cyst-adenocarcinoma development in these cysts is extremely rare. The management strategy for pancreatic cysts aims either 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 above 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 as they advocate less frequent follow up and a higher threshold before offering surgery. However, consistent utilization should decrease inadvertent harm to patients and reduce the costs of health care delivery.
References


Figure: Algorithm summarizing the AGA guideline on the management of pancreatic cysts.
Cyst seen on imaging

> 3cm and/or +ve features on MRI

No

Repeat MRI in 1 year and then biennially to year five

Yes

> 3cm and/or +ve features on MRI at any point during 5 year surveillance

Yes

Repeat MRI in 1 year and then biennially to year five

No

Concerning cytology and/or both features +ve

No

Interval change so that one/or both features +ve at any point during 5 year ...

No

Repeat EUS+FNA

Yes

Repeat MRI in 1 year and then biennially to year five

Yes

Consider surgery

+ve feature = dilated main pancreatic duct or solid nodule

Stop surveillance