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# American Gastroenterological Association Technical Review on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

James M. Scheiman,[1] Joo Ha Hwang,[2] and Paul Moayyedi[3]

[1]Department of Internal Medicine and Gastroenterology, University of Michigan Medical School, Ann Arbor, Michigan; [2]Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, Washington; and [3]Division of Gastroenterology, Hamilton Health Sciences, Farncombe Family Digestive Health Research Institute, McMaster University Hamilton, Ontario, Canada

**See related Commentaries (pages 685-692); Guideline and Clinical Decision Tool (pages 819-823); and related Commentary by RP Harris in the April issue of *Annals of Internal Medicine*.**

Pancreatic cysts are being identified with increasing frequency as a result of the escalating use of cross-sectional imaging, typically for unrelated reasons.[1,2] The incidence of pancreatic cysts in the US population is estimated to be between 3% and 15%, with increasing prevalence with age.[3] Identification of a cystic lesion in the pancreas creates anxiety for both patients and clinicians related to the potential specter of a deadly malignancy. Historically, non-neoplastic inflammatory pancreatic pseudocysts were believed to be the most common pancreatic cysts; however, as imaging has become more sensitive, smaller, neoplastic cysts are more frequently detected. The finding of a pancreatic abnormality with potential association with malignancy is an increasing source of referral to specialists and an important driver of resource utilization, particularly in the United States. Imaging studies vary widely in their quality and interpretation, fueling the need for additional investigation. This technical review discusses the challenges in evaluating pancreatic cysts and critically examines the existing data set for evidence-based medical decision making.

Although the concern for current or future malignancy is justified, a rational, evidence-based, cost-effective approach to care of the patient with a pancreatic cyst remains poorly defined. Despite the high prevalence of these lesions, investigators have recently questioned just how frequently a clinically relevant adverse outcome occurs, that is, the development of a life-threatening malignancy. This is a critical consideration given the cost of repeat imaging, performance of invasive procedures such as endoscopic ultrasonography (EUS) with or without fine-needle aspiration (FNA), and consideration of a major pancreatic resection with the substantial attendant morbidity and mortality, particularly in the aging population with a high rate of prevalent cysts. In a recent analysis, investigators using the Surveillance, Epidemiology, and End Results (SEER) database estimated an annual prevalence of 1137 mucin-producing pancreatic adenocarcinomas with a concurrent prevalence of nearly 3.5 million cysts in the same population, concluding that malignant transformation is a very rare event.[4] In this clinical context, the American Gastroenterological Association has commissioned an evidence-based review of the diagnosis and management of pancreatic cysts.

## Differential Diagnosis

Cystic lesions of the pancreas have a broad differential diagnosis. In general, they can be categorized into non-neoplastic (eg, pseudocysts) and neoplastic cystic lesions. The latter group, often referred to as cystic neoplasms of the pancreas, can be broadly subcategorized into those that produce a mucin-rich fluid (ie, mucin-producing cystic neoplasms) and those that do not. This distinction is important, because an increased risk of pancreatic adenocarcinoma has been attributed to all of the mucin-producing variants, which include branch duct intraductal papillary mucinous neoplasm (IPMN), main duct IPMN, and mixed IPMN (which has features of branch duct and main duct IPMN). The classic example of a cystic neoplasm that is not mucin producing, to which an increased risk of cancer is not attributed, is a serous cystadenoma. Papillary cystic neoplasms (eg, solid pseudopapillary tumors of the pancreas) and cystic pancreatic neuroendocrine tumors are additional examples of cystic neoplasms of the pancreas. There are many challenges associated with achieving an accurate diagnosis and, arguably more importantly, identifying reliable and reproducible methods to stratify risk of cancer for these patients, making clinical decision making difficult. Several groups, including an international consensus panel, have proposed management recommendations (including algorithms) for patients with suspected cystic neoplasms of the pancreas.[5,6] These are commonly used in clinical practice; however, these are consensus guidelines and not

***Abbreviations used in this paper:*** **CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; ERCP, endoscopic retrograde pancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LR, likelihood ratio; MCN, mucinous cystic neoplasm; MeSH, Medical Subject Heading; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; OR, odds ratio; PICO, population, intervention, comparison, and outcome; SEER, Surveillance, Epidemiology, and End Results.**


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necessarily evidence based. Following a basic description of the different types of cystic neoplasms, we provide results from our evidence-based systematic literature review, which was designed to assess the strength of the evidence for specific focused clinical questions commonly encountered in the management of patients with pancreatic cysts. The purpose of this report is to assess the existing evidence to address specific clinical questions related to the evaluation and management of pancreatic cysts with a focus on indeterminate cysts.

### Pseudocysts

Inflammatory pseudocysts historically were believed to represent up to 90% of all pancreatic cysts, but recent data obtained with high-resolution imaging showed a high prevalence of incidentally noted cysts among patients without a history or evidence of pancreatitis, suggesting that neoplastic cysts are likely far more common. The critical patient management issue is differentiating these non-neoplastic lesions from neoplastic lesions. When a cyst without an associated solid mass arises in a patient with known chronic pancreatitis, the clinical concern of a neoplasm is minimal. When patients present with unexplained pancreatitis for the first time with a cyst, or have only subtle changes of chronic pancreatitis on EUS alone, the clinician should consider whether the cyst may be a neoplasm and the lesion is the cause of the pancreatitis instead of assuming it is the consequence of pancreatitis. Review of imaging studies performed before the episode of pancreatitis, if available, may address this critical question.

### Serous Cystadenomas

Serous cystadenomas were originally termed "microcystic adenomas," referring to the small (<2 cm) cystic compartments that make up the tumors. The term "microcystic adenoma" is still used synonymously with serous cystadenomas but has recently been criticized because of reports of macrocystic variants.[7]

Serous cystadenomas occur more commonly in women, who typically present in their 60s. Lesions with serous morphology in a young woman or a man may therefore lead to diagnostic confusion. Although nearly always benign, malignant serous cystadenocarcinomas have rarely been described.[8] They can become symptomatic by increasing in size with "invasive features," leading to the recommendation by some surgical experts to remove them in younger patients. The low risk of malignancy should forestall the need for frequent surveillance. However, if the diagnosis is not confirmed, or if there is concern for local invasiveness, surveillance and management for these cysts remains controversial.

Serous cystadenomas are generally slow-growing tumors that are symptomatic in less than one-half of patients. The pathology of these tumors shows well-circumscribed masses enclosed in a fibrous capsule containing numerous small fluid-filled cysts arranged in a classic "honeycomb" pattern.[9] Fibrous bands within the lesions often converge centrally, forming a stellate scar that may calcify, giving a pathognomonic "sunburst" appearance on computed tomography (CT).[10]

### Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) represent nearly one-half of the tumors removed in contemporary surgical series. MCNs occur almost exclusively in women (>98%) and are generally diagnosed in patients in their 40s and 50s.[11,12] The patient may present with pain, an abdominal mass, or weight loss, but up to one-third of series report discovery by cross-sectional imaging for unrelated reasons. Ninety percent of cases occur in the pancreatic body or tail.[13]

MCNs are characterized by a thick fibrous capsule that encircles the cystic spaces. A characteristic spindle cell stroma containing epithelioid cells similar to ovarian stroma surrounds the tumor. The cyst lining is composed of mucin-producing duct-like cells frequently exhibiting a papillary architecture. However, the epithelial lining may be denuded, leading to misdiagnosis of a "pseudocyst" on limited tissue samples such as operative frozen sections.

The prognosis of MCNs is defined by the presence or absence of invasive adenocarcinoma. Cancer has been described in approximately one-third of operated tumors; these patients have a variable prognosis, with 5-year survival up to 60% after surgery for cancer to poor outcomes similar to those for ductal adenocarcinoma.[14] One explanation for the disparate findings may reflect sampling, because the invasive component may be only a small part of the lesion.

### IPMNs

IPMNs are also mucin-producing lesions, which characteristically communicate with the main pancreatic duct as their main point of distinction from MCNs. These increasingly recognized lesions are characterized by intraductal dysplastic epithelium resembling colorectal villous adenomas, with papillae covered by columnar epithelium and the occasional goblet cell with extensive mucin production. This category includes several previously used terms and was most commonly referred to as mucinous ductal ectasia in the past. These tumors always exhibit at least low-grade dysplasia and should be considered premalignant in all clinical situations.[14] However, the natural history with regard to progression to cancer is not well characterized. Gastric, intestinal, pancreatobiliary, and oncocytic subtypes of the papillary epithelium have been described with clinicopathological significance.[15]

IPMNs principally occur in men, with a mean age of diagnosis in the mid-60s. The lesions are frequently (50%) confined to the head; if symptomatic, a typical presenting complex is recurrent unexplained pancreatitis with ductal dilation or symptoms similar to those of chronic pancreatitis, typically without risk factors.[14] IPMNs may involve the main duct and/or side branches, and mixed variants can occur. Pure main duct IPMNs have a dilated main pancreatic duct without an associated "cystic" component, whereas branch duct IPMNs are composed of cysts that communicate with the main pancreatic duct. Identification of the