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# Endoscopic ultrasound guided fine-needle aspiration and biopsy of pancreatic cysts

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ABSTRACT

Pancreatic cystic lesions (PCLs) are often incidentally found on cross-sectional imaging. Long strides have been made in the past decade with improved quality and optics of cross-sectional imaging and endoscopic ultrasound (EUS), but a singular reliable test to appropriately characterize and risk-stratify PCLs has still eluded us. EUS allows high-resolution imaging of the pancreatic parenchyma and the ductal system, for assessment of PCL characteristics, with features concerning for malignancy and additionally provides an opportunity to sample the cyst to obtain fluid or cells for further diagnostic testing. This presents new sets of challenges, which include devising suitable equipment or needles and techniques for reliable and safe tissue acquisition, as well as provision of an adequate cytology or tissue sample to the pathologist, in order to arrive at an accurate diagnosis. This article will review the current role of EUS in the diagnosis and characterization of PCLs, with a focus on available strategies and pitfalls of cytology, cyst-fluid biomarkers, and biopsy acquisition techniques; and future directions to increase the yield and accuracy.



## 1. Introduction

Pancreatic cystic lesions (PCLs) are being diagnosed more frequently, mainly attributed to increasing use of cross-sectional imaging, with their prevalence being about 1%-3% [1]. Unfortunately, imaging alone is not sufficient to distinguish nonmucinous cysts, which are usually benign, from mucinous cysts, which carry a risk of malignancy. Although the overall risk of malignancy is still considered low [2-4], these are often a cause of anxiety for patients and their families, especially since the prognosis of pancreatic adenocarcinoma remains dismally low despite aggressive multimodal therapy. Given the lack of adequate knowledge about the natural history of PCLs, even detection of small asymptomatic cysts often leads to a detailed work-up culminating in surgery.

### 1.1. Consensus and guidelines: where do we stand?

The management of PCLs is multidisciplinary, and several guidelines exist which advise physicians as to appropriate management. The oldest of these are the “Sendai” guidelines, published in 2006 by the International Association of Pancreatology [5], which advocated for resection for all mucinous cystic neoplasms (MCN), main duct intraductal papillary mucinous neoplasms (MD-IPMN), mixed main and branch-duct IPMN (Mixed-IPMN), or any other cyst with suspicious features, including symptomatic cysts, mural nodule, cyst size ≥3 cm, main pancreatic duct (MPD) ≥ 6 mm or positive cytology. On the other hand, it recommended imaging surveillance for smaller branch-duct IPMNs (BD-IPMN). These criteria were highly sensitive (close to 100%), but lacked robust specificity (approximately 20%-30%), and hence were revised in 2010 (“Fukuoka” guidelines) [6], which maintained a resection strategy for MCN, MD-IPMN, Mixed-IPMN, but restricted the resection criteria for BD-IPMN to include patients with obstructive jaundice owing to BD-IPMN in the head of pancreas, dilated MPD ≥ 10 mm, or enhancing mural nodule. The guidelines also relaxed the surveillance guidelines for BD-IPMNs smaller than 3 cm and recommended close observation of ≥ 3 cm BD-IPMNs. The guidelines suggested endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) for any cyst with suspicious features, including non-enhancing nodule, thick cyst wall, MPD between 5 and 9 mm, or an abrupt caliber change in MPD with distal atrophy, and lymphadenopathy. These guidelines improved the specificity, albeit at the cost of sensitivity, and carried forward the major pitfall from Sendai of assuming the correct diagnosis of MCN or

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IPMN based on clinical, laboratory, and imaging findings, before following their algorithm.

More recently, the American Gastroenterological Association (AGA) released their guideline [7], which supported surgical resection for MD-IPMN, Mixed-IPMN, and MCN, but recommended a uniform algorithm for all other cysts, including beginning work-up with a magnetic resonance imaging and upon identification of 2 or more suspicious features (cyst $>$ 3 cm, dilated MPD, or mural nodule) proceeding with EUS-FNA and surgery if positive cytology, else surveillance. Unfortunately, the AGA guidelines are also not infallible, with moderate sensitivity and specificity, and a risk of missing an unacceptably high number of advanced lesions, while unnecessarily surveying other lesions, which are known to be benign (like serous cystadenoma, SCA). The main reason for this pitfall is that cross-sectional imaging alone cannot reliably distinguish cysts with neoplastic potential (MCN, IPMN) from benign cysts. The same is true for EUS as well, since morphological features like cyst size, MPD diameter, or mural nodule are not accurate predictors of malignancy, as acknowledged by AGA in their technical review [8], and are also operator dependent [9], thus adding to the challenges.

EUS when coupled with FNA for cytology and cyst-fluid ancillary studies including tumor markers and genetic mutations overcome these limitations of imaging and may even provide up to 100% specificity [10]. However, this opens up new sets of challenges, which include devising suitable equipment or needles and techniques for safe tissue acquisition, as well as provision of adequate cytology to the pathologist, in order to arrive at an accurate diagnosis. This article will review the current role of EUS in the diagnosis and characterization of PCLs, with a focus on available strategies and pitfalls of cytology, cyst-fluid biomarkers and biopsy acquisition techniques; and future directions to increase the yield and accuracy.

### 1.2. EUS-based diagnosis and characterization of PCLs

Although PCLs are often incidentally found on cross-sectional imaging, EUS enables assessment of cyst size, features concerning for malignancy (eg, mural or solid nodule and duct dilation), and extent and vascular invasion, and an opportunity to sample the cyst to obtain fluid or cells for further diagnostic testing. In fact, for diagnosis of pancreatic neoplasms less than 2 cm in size in patients with clinical symptoms suggestive of malignancy but a negative computed tomography (CT) scan, EUS-FNA is reportedly superior to multidetector CT [11].

#### 1.2.1. Standard EUS examination of PCLs

EUS is a minimally invasive and relatively safe procedure, which allows high-resolution imaging of the pancreatic parenchyma and the ductal system. The choice of initial equipment (radial vs linear) may depend on patient characteristics, indication of procedure and operator preference, but a linear echoendoscope offers both a diagnostic and therapeutic platform, since it allows for FNA without changing equipment. The examination of the pancreas is generally started via a transgastric approach, which allows detailed evaluation of the body and tail of pancreas. In thin patients, the genu of pancreas can also be evaluated via transgastric approach. Then the echoendoscope is advanced past the pylorus for transduodenal examination of the head from the bulb and the uncinate process from the second part of duodenum.

A pancreatic cyst is identified as an anechoic, usually well-defined and round lesion within the parenchyma or as an exophytic growth, and does not demonstrate any vascularity on EUS Doppler flow (Figure 1A). EUS allows determination of size, shape (lobular or smooth unilocular), and total number of cysts in the pancreas, which are important features to record for future surveillance. Other important features within the cyst, which should be observed include, cyst wall for thickness (thin or thick walled), septations, calcifications (central or peripheral), central scar, and solid nodules and masses. Nodules are recognized predictors of malignancy, and may appear as an isoechoic or a hyperechoic lesion attached to the wall of the cyst or entirely within the cyst. However, nodules may be difficult to differentiate from internal debris or mucus, which may appear as hypoechoic with an occasional hyperechoic rim. Upon patient movement or cyst movement with FNA needle, internal debris or mucus may move relative to the cyst wall and these may assist the endoscopist to differentiate these from nodules, which are usually fixed and nonmobile in relationship to the cyst wall. A study showed that mucus accounted for up to 65% of intracystic lesions, and EUS was remarkably better than CT at detecting epithelial nodules. The same study showed that education about echogenicity, edge, and rim features helped operators distinguish nodules from mucus with greater accuracy (79% vs 57%; $P = 0.004$) [12]. Additionally, EUS may allow identification of features of chronic pancreatitis, including parenchymal (lobularity, hyperechogenic foci and strands, atrophy and intraparenchymal calcifications) or ductal (including pancreatic duct size, contour, dilation of side branches, wall hyperechogenicity, or intraductal calcifications) features. Defining the relationship of the cyst to the MPD is vital to establish main-duct vs branch-duct versus isolated pancreatic cysts (Figure 1B and C). This may, however, be challenging. Peripancreatic, celiac, and portal lymphadenopathy is specifically looked for, during evaluation of pancreatic cysts.

Despite the ability to obtain high-resolution images of pancreas, morphological features alone on EUS are still poor predictors of PCL type, and presence of high-risk stigmata [8], and these features have high interobserver discordance [9]. The utility of EUS is greatly enhanced owing to its capability of obtaining cyst-fluid for cytology (Figure 1D) and various biomarkers, and additionally allowing novel techniques for biopsy and cyst-wall cell acquisition.

#### 1.2.2. Cyst-fluid cytology

The cyst-fluid can be assessed for their physical characteristics immediately after aspiration (color, turbidity, and presence of blood), but additionally can be sent for cytological examination. However, studies have noted cytology yield to be usually suboptimal, with a pooled sensitivity of 63% and specificity of 88%, owing to the low amount and quality of aspirated epithelial cells in cyst fluid [13], and hence have marginal utility in surgical decision-making. Investigators have devised a modified cytological system that includes atypical epithelial cells, which are a cluster of cells with increased nuclear:cytoplasmic ratio and enlarged irregular nuclei, and identified high-grade dysplasia and malignancy with higher sensitivity (72%) and specificity (85%) [14,15]. However, owing to high interobserver discordance, adoption and generalizability of this modified cytological system using atypical epithelial cells has been limited [16], and hence the overall yield, accuracy and clinical utility of cytology still remains unsatisfactory.

#### 1.2.3. Cyst fluid biomarkers

(1) *Carcinoembryonic antigen (CEA)*: CEA level of $>$ 192 ng/mL was established by the Cooperative Pancreas Study [17] as the cut-off level to distinguish mucinous from nonmucinous cysts, albeit with a sensitivity of 73%, and diagnostic accuracy of just 80%. A large US multicenter study reported suboptimal accuracy of CEA in differentiation of mucinous and nonmucinous PCLs, and would misdiagnose 39% of MCN cases [18]. It further limits decision-making since low CEA levels does not exclude a