

# Morphological differentiation and follow-up of pancreatic cystic neoplasms using endoscopic ultrasound

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## ABSTRACT

Endoscopic ultrasound (EUS) is a key modality for the evaluation of suspected pancreatic cystic neoplasms (PCNs), as the entire pancreatic gland can be demonstrated with high spatial resolution from the stomach and duodenum. Detailed information can be acquired about the internal contents of the cyst(s) [septum, capsule, mural nodules (MNs)], its relation with the main pancreatic duct (MPD), and any parenchymal changes in the underlying gland. PCNs comprise true cysts and pseudocysts. True cysts can be neoplastic or nonneoplastic. Here, we describe serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN) as prototype neoplastic cysts, along with nonneoplastic lymphoepithelial cysts (LECs).

**Key words:** Endoscopic ultrasound (EUS), intraductal papillary mucinous neoplasm (IPMN), mucinous cystic, serous cystic

## INTRODUCTION

Pancreatic cystic neoplasms (PCNs) are being detected with increasing frequency, primarily as a result of increased physician awareness and widespread availability of cross-sectional imaging in concert with technological improvements.<sup>[1]</sup> PCNs comprise a potpourri of lesions types including intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasm (SCN), lymphoepithelial cyst (LEC), epidermoid cysts, and cystic degeneration of solid tumors. The most important issues that the endosonographer faces are ensuring appropriate patient treatment while avoiding overtreatment and undue patient anxiety, and selecting patients who would benefit from surgery.<sup>[2,3]</sup>

The diagnostic accuracy of EUS morphology to differentiate between cystic lesions of the pancreas ranges from 51% to 90%.<sup>[4]</sup> One study<sup>[5]</sup> found that 20% of resected PCNs are benign, even in a tertiary hospital, indicating the challenge involved in accurately diagnosing PCN.

Being less invasive as well as having imaging from anatomical proximity to the pancreas with high resolution renders EUS as an ideal tool for diagnosing PCN.<sup>[6]</sup> Recent improvements in EUS hardware and software have provided new options for image enhancement. Contrast-enhancement and elastography are novel modalities that might improve

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the detection and characterization of suspected lesions.<sup>[7,8]</sup> Here, we review the application of EUS morphology for the differentiation and follow-up of PCNs.

**CLASSIFICATION**

Figure 1 shows the classification of PCNs, which consist of true cysts covered with the epithelium and pseudocysts that are not.

True cysts can be neoplastic or nonneoplastic. Neoplastic true cysts include SCN, MCN, and IPMN types of neoplasms. Nonneoplastic cysts comprise cystic fibrosis, and retention, lymphoepithelial, and epidermoid cysts.

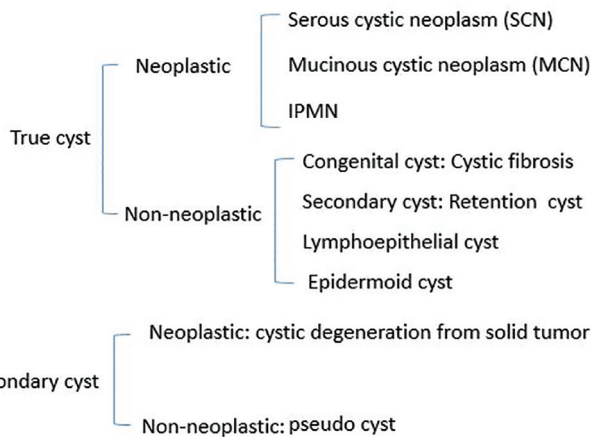
Secondary cysts can be classified as cystic degeneration from solid tumors and nonneoplastic pseudocysts.

**TRUE CYSTS — NEOPLASMS**

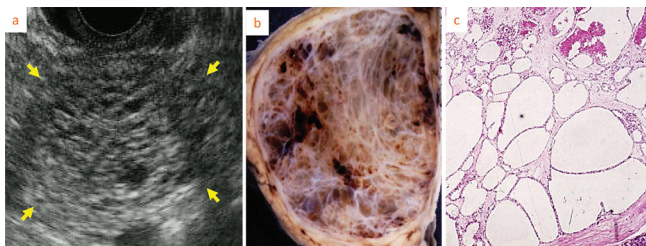
*Serous cystic neoplasms*

**Characteristics**

SCNs are cystic tumors formed by glycogen-rich epithelial cells that produce serous fluid. The



**Figure 1.** Classification of pancreatic cystic neoplasms



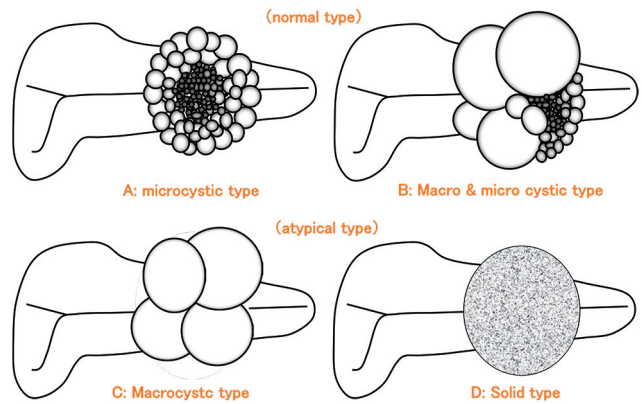
**Figure 3.** Microcystic type serous cystic neoplasms (SCNs). EUS image (arrow) shows honeycomb-like appearance caused microcyst accumulation

epithelial cells are cuboidal with clear cytoplasm.<sup>[9]</sup> One characteristic feature of SCN is a rich vascular formation referred to as a RecN-epithelial network located immediately below the epithelium.

SCNs have typical<sup>[1,10]</sup> honeycomb-like microcystic [Figures 2a and 3], or mixed macrocystic and microcystic morphology [Figures 2b and 4], with an aggregation of large- and small-cyst architectures. Morphologic variants include macrocystic type SCN with only larger cysts [Figure 2c],<sup>[1,10]</sup> and the solid type SCN [Figures 2d and 5]<sup>[10]</sup> with macroscopically unrecognizable microcysts. Thus, SCN comprises neoplasms with various gross and microscopic findings. Around 10% of SCNs are unilocular without an obvious microcystic component.<sup>[11]</sup>

**Imaging features**

A microcystic honeycomb structure is the typical structure of SCN. Low-resolution imaging modalities such as percutaneous ultrasound cannot define the internal



**Figure 2.** Classification of serous cystic neoplasms (SCNs)



**Figure 4.** Macrocystic type and microcystic type serous cystic neoplasms (SCNs)

microcystic structures, and only show a solid, echo-poor mass, unlike EUS.<sup>[12]</sup> Contrast-enhanced EUS can further clarify microcyst structures.<sup>[13]</sup> The septum and wall are usually thin, and typical microcystic SCN with calcification of a central fibrosis scar can be clearly visualized on EUS images.<sup>[14,15]</sup> The macrocystic type without a microcystic component requires differentiation from solid type SCN, MCN, or branch type IPMN. Solid type SCN needs to be differentiated from neuroendocrine neoplasms (NENs), which can be accomplished using EUS-FNA.<sup>[16,17]</sup>

### Treatment strategies

Malignant pancreatic SCNs are very rare, as the malignant potential is thought to be only 1-2%.<sup>[12,18]</sup> Therefore, as a reasonable strategy for lesions that can be diagnosed as SCN by an imaging modality would be surveillance imaging.<sup>[1]</sup> Considering the possibility of rare malignant SCN, a cautious follow-up should be advised.

### Mucinous cystic neoplasms

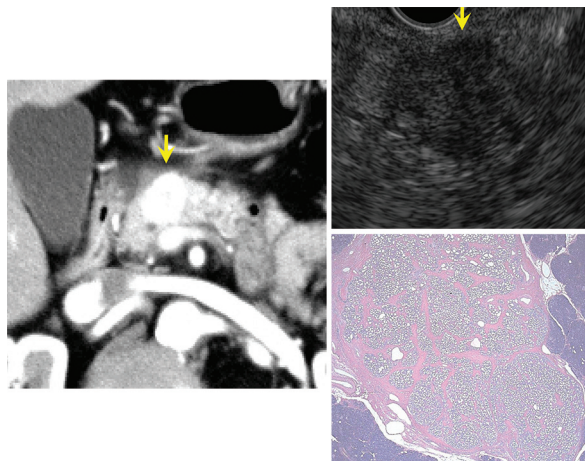
#### Characteristics

MCNs arise almost exclusively (>95%) in women (age range: 40-50 years), typically in the body and tail of the pancreas.<sup>[15,19]</sup> Estrogen receptor-positive and progesterone receptor-positive ovarian type stroma

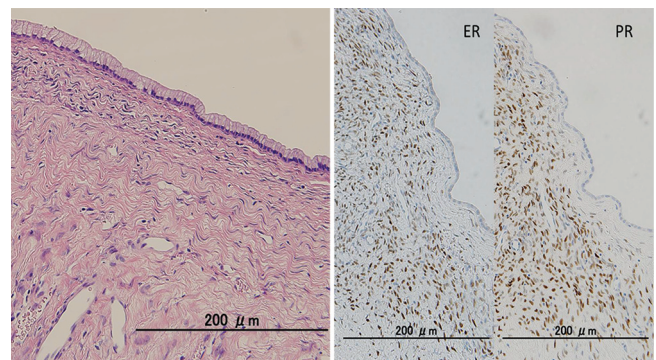
(OTS) is characteristic [Figure 6]. New data suggest that the proliferative effect of estrogen and progesterone hormones plays an important contributory role in the development of MCN, which is consistent with the female gender restriction of MCN.<sup>[20]</sup> MCN predominantly manifests as unilocular or multilocular cystic lesions, usually with mucinous contents. The epithelial lining of MCN usually takes the form of a single layer of cuboidal to columnar cells with minimal variation in nuclear size and shape. Unlike SCN, MCN can be malignant.<sup>[15]</sup>

### Imaging features

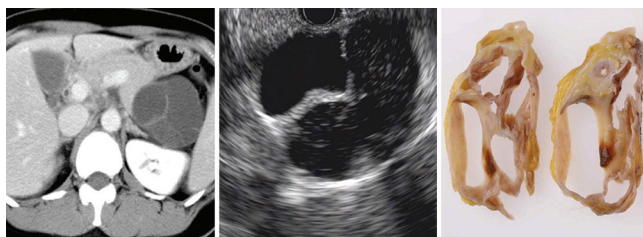
MCNs usually present as macrocystic lesions with a rounded morphology, an irregular septum, thick wall and complex content that can be particulate, viscous and dense due to mucin and hemorrhage [Figure 7]. Ovarian type stroma is a defining feature of MCN<sup>[17]</sup> that assumes the form of bland spindle cells forming a compact layer immediately beneath the epithelium. Cysts in cysts [Figure 8]<sup>[21]</sup> appearance is characteristic of MCN, and EUS can detect even small cysts within cysts. MCN does not communicate with the pancreatic ductal system although a recent Japanese multicenter study<sup>[21]</sup> found that 18.1% of MCNs had a luminal connection with the pancreatic ductal system.



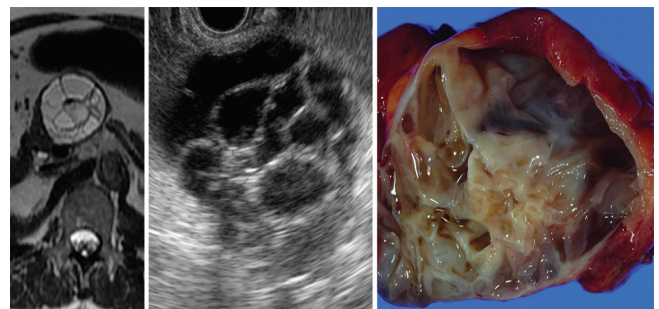
**Figure 5.** Solid type serous cystic neoplasm (SCN). Enhancement is intense on CT. Honeycomb-like appearance is undetectable by EUS but pathological microscopic findings show small microcystic appearance



**Figure 6.** Ovarian type stroma (OTS) immediately below the epithelium detected by microscopy is estrogen-receptor and progesterone-receptor positive



**Figure 7.** Image of MCN adenoma shows round macrocystic lesion with thickened wall and septum



**Figure 8.** Image of MCN adenoma shows cysts within cysts

Although mural cysts are characteristic of MCN, they can be misdiagnosed by computed tomography (CT) as mural nodules (MNs). Thus, mural cysts determined by CT should be confirmed by EUS [Figure 9].

Because cyst cavities are independent and do not communicate with individual cysts in MCN, differences in the echogenicity of individual cysts contents can be visualized by EUS. Peripheral calcification along the thick wall has been found in 10-25% of the patients.

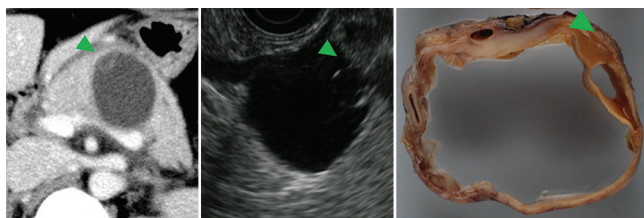
**Treatment strategies**

A Japanese multicenter study<sup>[21]</sup> found that the frequency of invasive and noninvasive carcinoma arising from MCN is 3.8% and 13.4%, respectively. Resection is considered the choice of treatment for most MCNs because of their malignant potential, when patients have low or acceptable operative risk. This aggressive approach is supported by the 2012 consensus guidelines of the International Association of Pancreatology.<sup>[22]</sup>

*Intraductal papillary mucinous neoplasms*

More IPMN cysts are being recognized as neoplasms. A large, retrospective study of resected pancreatic cystic lesions found that IPMNs were the most commonly resected types of cysts, accounting for about 2% of resections.<sup>[23]</sup> IPMNs are classified as main duct (MD)-IPMNs, branch duct (BD)-IPMNs arising from branches, or mixed IPMNs arising in both the MD and the side branches.

Not only do MD-IPMNs and BD-IPMNs morphologically differ, but they also have different histological gastric (70%), intestinal (20%), pancreatobiliary (<10%) and oncocytic (<5%) subtypes with varying degrees of risk of malignancy and aggressiveness.<sup>[24]</sup> The term “incipient IPMN” has been recently proposed to describe cysts between 0.5 cm and 1 cm in diameter, lined with a gastric type mucinous epithelium.<sup>[25]</sup>

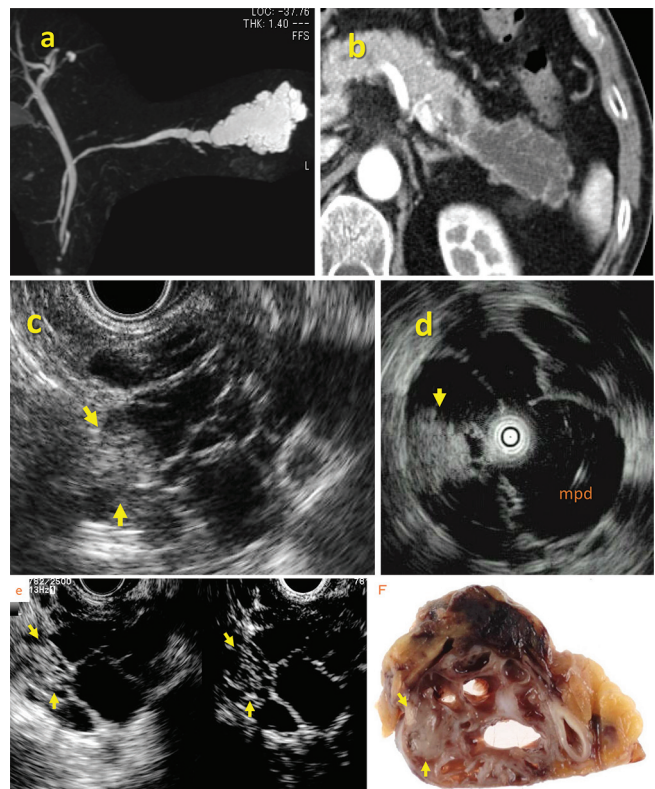


**Figure 9.** Mural cyst of MCN adenoma. Apparent mural nodule in CT image appearing as a mural cyst in EUS image is MCN

**Imaging features of branch duct and mixed type intraductal papillary mucinous neoplasm [Figure 10]**

A key feature of IPMN is dilation of a BD or MD due to proliferative papillary tumors, or large amounts of secreted intraductal mucin. Accordingly, the size of IPMN depends on the diameter of the dilated BD, MD, and MNs. The diameter of dilated ducts can be measured by either Multi-Detectors CT (MDCT) or magnetic resonance cholangiopancreatography (MRCP) but only EUS can accurately define the size of MNs. The presence of MNs is considered to be the most reliable indicator of whether an IPMN tumor is benign or malignant.<sup>[26-28]</sup> However, a cutoff diameter for differentiating benign from malignant nodules has been controversial, and ranges between 5 mm and 10 mm.

The revised international guidelines 2012<sup>[29]</sup> recommend that cysts with worrisome features should undergo a detailed evaluation by EUS. A notable change from previous guidelines is that side-branch dilation of  $\geq 3$  cm in BD-IPMN, which was previously an indication for surgery,<sup>[30]</sup> is now considered a worrisome feature. These lesions should be carefully assessed for MNs using EUS. In all of these situations, EUS is a



**Figure 10.** Branch duct (BD) type IPMN (noninvasive carcinoma). Hyperechoic mass (arrow) in dilated branch is evident on EUS and IDUS images. Contrast agents show blood flow signals in mass indicating mural nodules

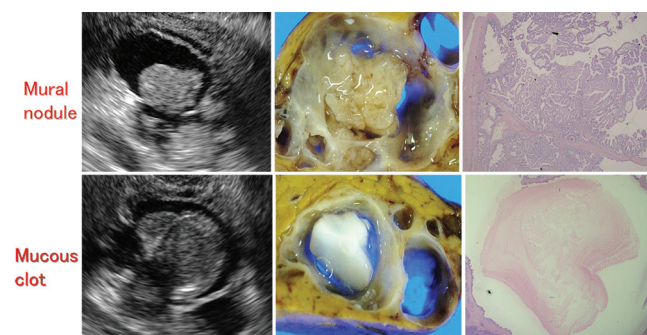
key modality for the risk stratification and classification of IPMN lesions.

Protein plaques can be differentiated by their characteristic annular hyperechoic appearance with a low echoic central part [Figure 11], whereas mucin is difficult to discriminate from MNs by B-mode imaging. Caution is required in this regard because the misdiagnosis of mucin as a nodule will lead to overdiagnosis of malignancy. The use of ultrasound contrast agents such as Sonazoid® can rule out MNs if there is an absence of blood flow signals in the intracystic structures.<sup>[31]</sup>

### Imaging features of main duct type intraductal papillary mucinous neoplasms [Figure 12]

MD IPMNs are defined by segmental or diffuse MD dilation to >5 mm, without BD dilation >5 mm. An MD diameter  $\geq 10$  mm is considered to be high-risk stigmata, according to the International Consensus Guidelines,<sup>[29]</sup> and resection is recommended in such situations. The entire pancreatic duct until the ampulla of Vater should be observed to rule out upstream ductal dilation due to chronic pancreatitis or obstruction by a pancreatic ductal adenocarcinoma (PDAC).

Large papillary projections in a dilated MD can be evaluated using CT or MRCP but EUS might be the most suitable modality for visualizing smaller nodules. MD IPMN has a tendency of superficial intraductal extension. Hence, accurate preoperative assessment of the longitudinal extent of the disease is important to decide whether pancreatectomy should be total or partial. Intraductal ultrasound (IDUS) and peroral pancreatoscopy (POPS) are other useful modalities for determining the extent of intraductal superficial lesions.



**Figure 11.** Upper and lower panels show mural nodule (adenoma) and mucous clot, respectively

### Protocol for follow up of patients with intraductal papillary mucinous neoplasm

When both high-risk stigmata and worrisome features are absent, MNs are undetectable by EUS, lesions are localized in the BD, and cytology findings of pancreatic juice are negative, the revised international guidelines specify a follow-up protocol using CT/magnetic resonance imaging (MRI) and EUS depending on whether a cyst is 1-2 cm or 2-3 cm in diameter.<sup>[29]</sup>

A large natural history study of BD-IPMN from Japan,<sup>[32]</sup> based on a nationwide survey, found an 18% rate of disease progression, and stable disease in 82% of the 349 patients without MNs at initial diagnosis, over a mean observation period of 3.7 years. The rate of IPMC occurrence in these patients was 2.5%.

The recently reported rates of PDAC concomitant with IPMN range from 2.0% to 9.3%. Hence, patients with IPMN should be regarded as being at a high risk of developing PDAC.

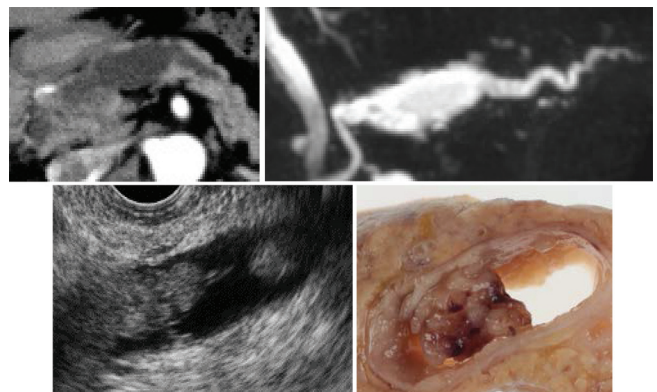
These observations highlight the importance not only of evaluating IPMN lesions but also of carefully observing the entire pancreas during follow-up EUS studies to avoid overlooking PDAC. Regular EUS evaluations can allow early detection of PDAC in such situations.

## TRUE CYSTS — NONNEOPLASMS

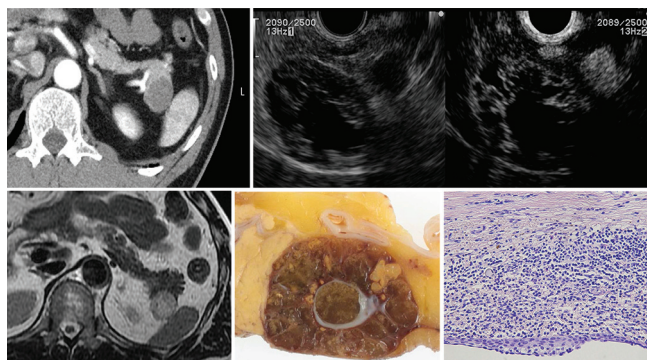
### *Lymphoepithelial cysts [Figure 13]*

#### Characteristics

LECs are rare, benign lesions characterized by mature squamous epithelium with surrounding nonneoplastic lymphoid elements.<sup>[33-35]</sup> They are more common in men, tend to occur predominantly as extrapancreatic



**Figure 12.** MD type IPMN (noninvasive carcinoma). Mural nodule is detectable inside MPD



**Figure 13.** Lymphoepithelial cysts

lesions, and are well-demarcated from surrounding pancreatic parenchyma [Figure 13].<sup>[36-38]</sup>

### Imaging features

LECs can be unilocular (40%) or multilocular (60%), well-circumscribed, and sharply distinct from the adjacent pancreas. They can resemble extrapancreatic lesions. The cyst wall is usually 1-3 mm thick, and the cysts contain cheesy keratinaceous debris. On EUS, LECs have a thin septum and wall, a clear margin, and contain viscous echogenic keratin.

### Treatment strategy

Malignant transformation has not been described, and a conservative follow-up strategy is recommended.

### Secondary cysts

#### Cystic degeneration of solid tumors

Solid pseudopapillary tumors,<sup>[39-40]</sup> cystic neuroendocrine neoplasms of the pancreas,<sup>[41-44]</sup> acinar cell neoplasms,<sup>[45]</sup> and pancreatic adenocarcinomas (adenosquamous and/or anaplastic carcinoma)<sup>[46]</sup> can occasionally appear as cystic masses.

## SUMMARY

We have reviewed the key EUS features of pancreatic cystic lesions. B-mode EUS alone cannot be used to diagnose pancreatic cystic lesions and thus, contrast-enhanced ultrasound, CT, and MRI are required to supplement the EUS findings of such lesions.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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