

## Cystic Neoplasms of the Pancreas: Where Do We Stand?

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### Abstract

Pancreatic cysts are becoming increasingly recognized in clinical practice. Despite our improved awareness and understanding of these lesions, making a correct diagnosis and determining their malignant potential remains challenging. We aim to provide an overview of pancreatic cysts including classification, diagnosis, and recommendations for treatment and surveillance in recent consensus guidelines.

**Keywords:** Pancreas; Cyst; Malignancy; Surveillance

### Introduction

Pancreatic cysts are frequently encountered in clinical practice with increasing utilization of cross-sectional abdominal imaging. The reported prevalence of pancreatic cysts range from 2.4% to 14% based on studies of magnetic resonance imaging (MRI) and computed tomography (CT) [1-3]. They are often discovered incidentally in an asymptomatic individual on routine imaging, although less commonly, can manifest with obstructive symptoms such as abdominal pain, weight loss, jaundice and recurrent pancreatitis [4]. Some pancreatic cysts carry malignant potential, triggering significant anxiety for patients and clinicians. In addition, current diagnostic modalities are imperfect in determining their absolute risk of malignancy. However, a growing body of literature suggests that the majority of these lesions are at low risk of malignant transformation, and more recent guidelines advocate watchful waiting rather than upfront surgical resection for low-risk lesions [5,6].

The purpose of this article is to provide an overview of various types of pancreatic cysts and the evolution of guidelines over the last decade on the surveillance and management of pancreatic cysts with malignant potential.

### Classification of Pancreatic Cysts

Pancreatic cysts with malignant potential include mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN), cystic neuroendocrine tumour (NET) and solid pseudopapillary tumor (SPT). These cysts can be classified as mucinous and non-mucinous lesions based on the production of mucin (Table 1). This distinction is clinically important, as mucinous cysts are associated with an increased risk of pancreatic adenocarcinoma, whereas non-mucinous cysts, if premalignant, progress to non-adenomatous malignancy which has a vastly different prognostic implication. On the other hand, pseudocysts, serous cystadenoma and lymphangioma are considered benign. CT, MRI and endoscopic ultrasound (EUS) with or without fine needle

aspiration (FNA) for cytology and the measurement of tumor markers are the current mainstay diagnostic tools to classify these cysts and estimate their malignant potential.

### Pancreatic Cysts with Malignant Potential

#### Mucinous cysts

**Intraductal papillary mucinous neoplasm (IPMN):** IPMNs occur more commonly in males in their sixth decade of life [7]. Half the lesions are located in the head of the pancreas [8]. IPMNs are often detected incidentally on imaging but can manifest with abdominal pain, weight loss and steatorrhea. Jaundice and new onset diabetes are often concerning findings of an already developed malignant transformation of these lesions. Acute pancreatitis due to the obstruction of the pancreatic duct by mucus plugs is reported to occur in 15% of patients [8]. Histological features that characterize IPMN are intraductal dysplastic epithelium resembling colorectal villous adenomas with resultant aberrant mucin production [9]. It is classified as either a main duct (MD-IPMN, Figure 1a-1c), side branch (BD-IPMN, Figure 2a-2c) or mixed IPMN depending on the origin/site of involvement of the lesion. IPMNs can occur at multiple locations within the pancreas, and up to 41% of BD-IPMNs are multi-focal in nature [10]. Histological subtypes with varying natural history and progression have been described: 1) gastric, the most common subtype in BD-IPMN with a low malignant potential, 2) intestinal, the most common variant in MD-IPMN with a significant malignant potential, 3) pancreatobiliary, which is uncommon and has a propensity to behave aggressively, and 4) oncocytic, which is generally benign. When an IPMN progresses to invasive carcinoma, it manifests as either 1) tubular type which shares similar histological and biological characteristics with ductal adenocarcinoma, or 2) colloid type with mucin production, which is usually associated with a more favorable prognosis. An adenoma-to-carcinoma sequence is believed to account for the slow growth of tumors arising from IPMN [11]. An endoscopic appearance of “fish mouth

<b>Malignant/premalignant cysts</b>	Mucinous cysts	Mucinous cystic neoplasm (MCN)
		Intraductal papillary mucinous neoplasm (IPMN)
	Non-mucinous cysts	Solid pseudopapillary tumour (SPT)
		Cystic neuroendocrine tumour (NET)
<b>Benign cysts</b>	Pseudocysts	
	Serous cystadenoma (SCA)	
	Lymphangioma, lymphoepithelial cyst, mesenteric cyst, 'simple' cyst	

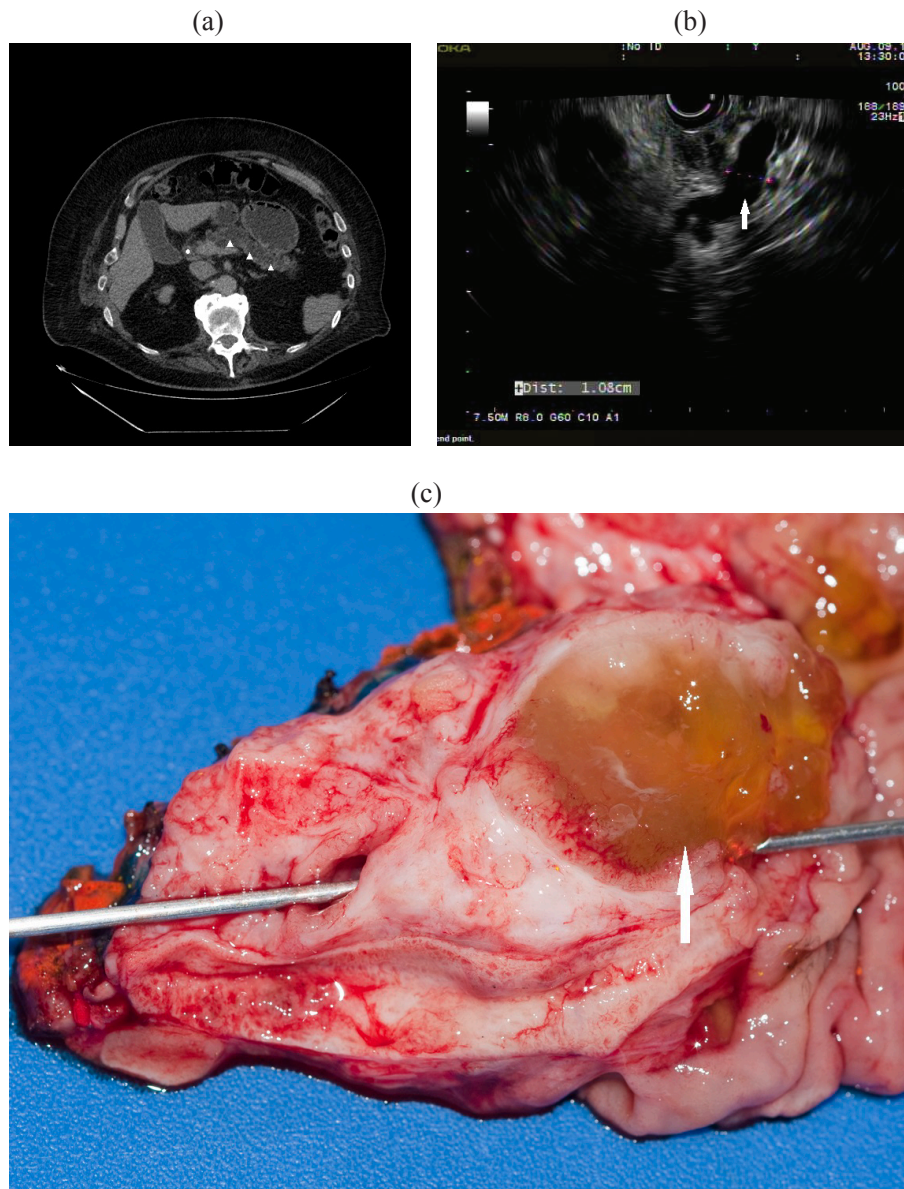
**Table 1:** Classification of pancreatic cysts.

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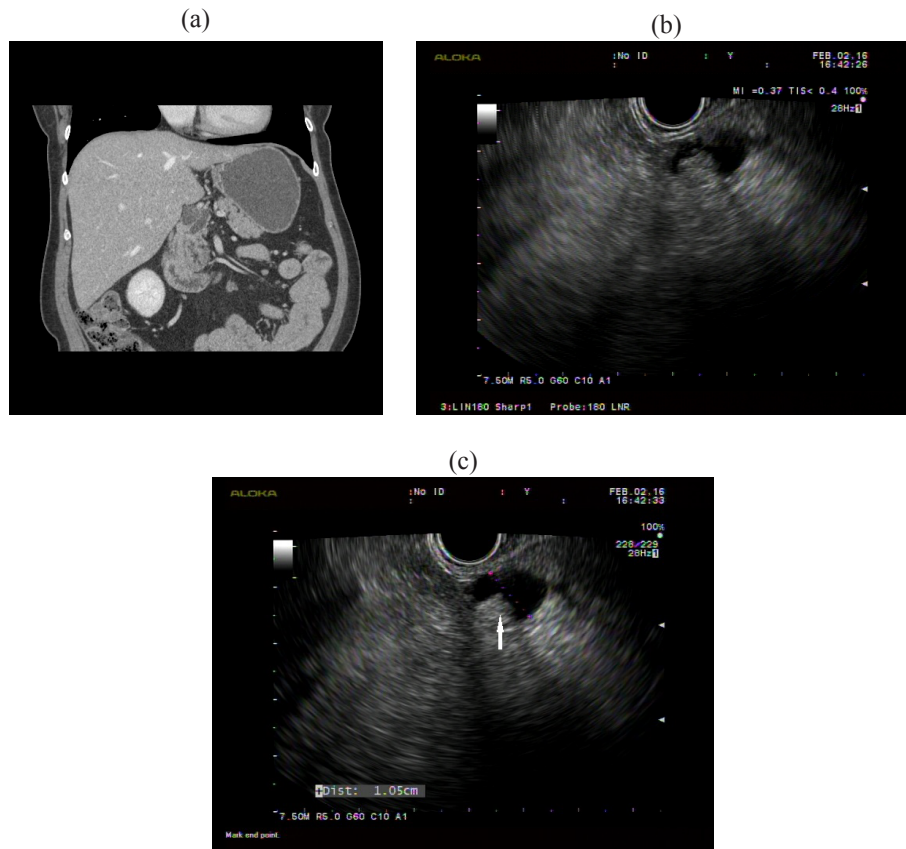
**Figure 1:** a) CT scan showing a diffuse cystic dilatation of the main pancreatic duct. b) EUS demonstrates a dilated, ectatic main pancreatic duct measuring 1cm in diameter in the body of the pancreas. c) Gross specimen of a resected MD-IPMN showing a dilated main pancreatic duct filled with mucin.

papilla” due to excessive mucin extruding from a patulous papilla is pathognomonic of MD-IPMN. Pancreatogram during endoscopic retrograde cholangiopancreatogram (ERCP) can demonstrate diffuse or segmental pancreatic duct dilation with intraductal filling defects due to mucin or intraductal tumor growth, although ERCP is no longer recommended with the availability of non-invasive imaging such as MRCP and EUS. EUS features of IPMN include dilated pancreatic duct, cysts communicating with the pancreatic duct and/or mural nodules. Differentiating BD-IPMN from MCN on morphological appearance alone can sometimes be difficult, particularly in the absence of a visible communication between the cyst and the pancreatic duct.

The risk of malignant transformation is higher with MD-IPMN compared to BD-IPMN. MD-IPMN carries the risk of *in situ* malignancy of 57% to 92% in resected specimen, compared to less than

20% in BD-IPMN [12-16]. The surveillance and management of IPMN will be further discussed under the section “evolution of guidelines on pancreatic cysts”.

**Mucinous cystic neoplasm (MCN):** MCN occurs almost exclusively in women (>98%) with a peak incidence in the fifth decade [7,17-19] and a predilection for the distal pancreas [7]. Although both IPMN and MCN are mucinous lesions, MCN is histologically distinguished from IPMN by the presence of ovarian stroma underlying the mucinous columnar cyst epithelium [20]. On EUS, MCNs appear as thin-walled, septated fluid-filled cavities. They rarely exhibit any communication with the pancreatic duct, and are associated with peripheral calcification in up to 15% of cases [19]. What also distinguishes MCNs from BD-IPMNs is that MCNs are more common among middle-aged women and are more often located in the distal pancreas, whereas BD-IPMNs



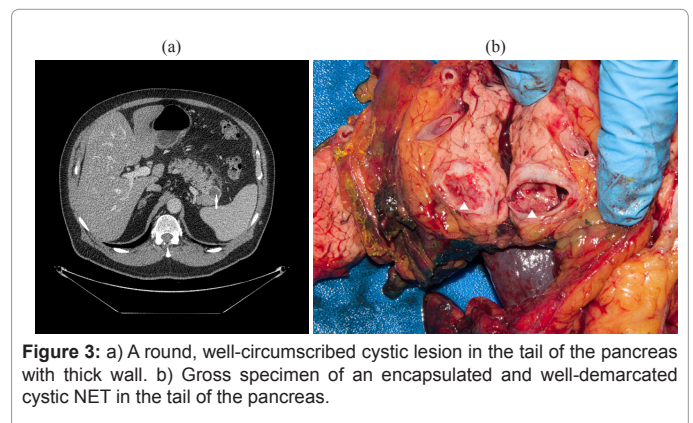
**Figure 2:** a) CT scan showing a small cystic lesion in the head of the pancreas communicating with the pancreatic duct. b) EUS showing a small, unilocular cyst communicating with the pancreatic duct. c) EUS image of the cyst containing a mural nodule.

are more common in older men and are more frequently located in the proximal pancreas [21].

A series of 163 patients with resected MCN reported the risk of malignancy to be 17.5% [6] but the risk is thought to be less than that of MD-IPMN [20]. The surveillance and management of MCN will be further discussed under the section “evolution of guidelines on pancreatic cysts”.

### Non-mucinous cysts

**Cystic neuroendocrine tumor (NET):** Cystic NETs are rare tumors which occur equally in men and women in the sixth and seventh decade of life (Figure 3a and 3b) [3]. They are frequently found in the body and tail of the pancreas [4] and are associated with multiple endocrine neoplasia type I (MEN-1) [22]. NETs can be classified as functional and non-functional (which constitutes the vast majority) tumors depending on the production of clinically significant circulating hormones [23]. At EUS, NETs usually appear as round, well-circumscribed, hypoechoic lesions often with a surrounding hyperechoic rim. Contrast administration at EUS can give the characteristic hypervascular pattern in NET [24], as is seen with other cross-sectional imaging studies. When there is a diagnostic uncertainty with morphology alone, EUS-FNA cytology may be helpful, showing minimal cytoplasm and monomorphic nuclei with “salt-and-pepper” chromatin [25]. Immunohistochemical (IHC) staining for chromogranin and synaptophysin is frequently seen [26] especially in cell block preparations. Surgery is recommended for NETs >2 cm

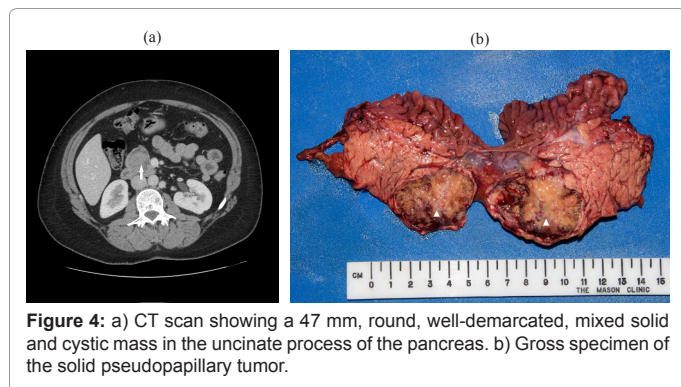


**Figure 3:** a) A round, well-circumscribed cystic lesion in the tail of the pancreas with thick wall. b) Gross specimen of an encapsulated and well-demarcated cystic NET in the tail of the pancreas.

in size [4], with an excellent short and long-term survival (1-year and 5-year survival of 97% and 87%, respectively) [22].

**Solid pseudo papillary tumor (SPT):** SPTs are rare, occur predominantly in young females in the third and fourth decade, and are usually found in the tail or body of the pancreas (Figure 4a and 4b) [27,28]. On abdominal imaging, SPTs appear as well-demarcated, heterogeneous and mixed solid/cystic lesions with areas of hemorrhage and necrosis. Histologically, SPTs are histologically characterized by small, uniform epithelial cells arranged as papillary structures with delicate fibrovascular cores [29]. Immunohistochemical staining is often positive for vimentin, CD10, CD56, alpha-1-antitrypsin, and





**Figure 4:** a) CT scan showing a 47 mm, round, well-demarcated, mixed solid and cystic mass in the uncinus process of the pancreas. b) Gross specimen of the solid pseudopapillary tumor.

usually neuron-specific enolase. Immunoreactivity for beta-catenin is present in almost all cases [30]. A recent multicenter study reported that EUS-FNA with or without immunochemistry preoperatively diagnosed SPT in 75% of 28 patients [31]. SPTs generally behave in an indolent fashion. However, given their malignant potential, surgical resection is recommended once the diagnosis has been confirmed. Following a complete resection with a clear margin, SPT is associated with an excellent prognosis, with the reported 5-year survival rate of 95% [32].

## Cysts without or Negligible Malignant Potential

### Serous cystadenoma

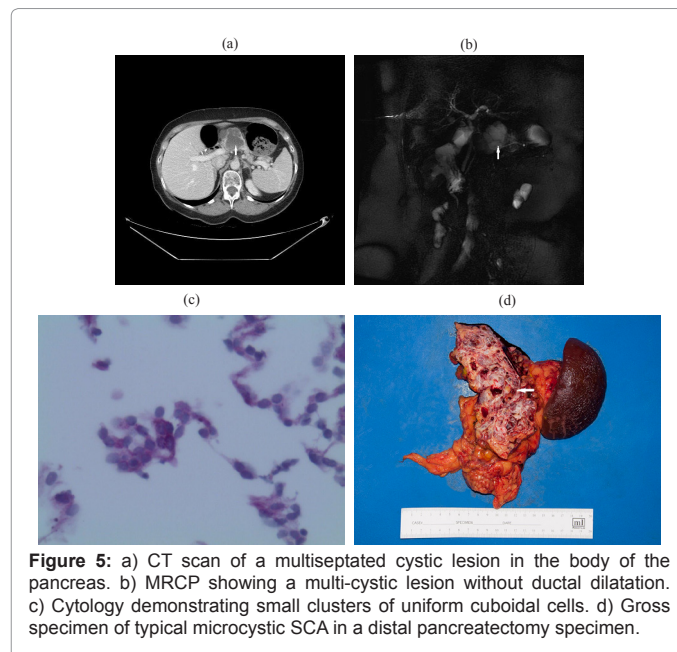
Serous cystadenomas (SCA) are slow-growing lesions with a predilection for females in the sixth decade of life (Figure 5a-5d) [3,33]. They are most commonly found in the body and tail of the pancreas [34] but can also involve the entire organ [7]. Up to 90% of patients with von Hippel-Lindau syndrome have been reported to develop SCA [34]. These lesions are macroscopically characterized by multiple, small cysts (typically less than 5 mm in size) arranged in a classic “honeycomb” pattern separated by thin septae and lined by cuboidal epithelial cells [35]. The honeycomb appearance secondary to the cluster of small cysts is often seen on EUS [36]. A central fibrous scar with calcification giving rise to a “sunburst” appearance, pathognomonic for SCA, is observed in up to 30% of cases on abdominal imaging [37].

In contrast to the conventional microcystic SCA which can be readily identified on EUS, the oligocystic (macrocytic) variant can be difficult to differentiate from mucinous cysts based on morphology alone. In these circumstances, cyst fluid CEA level can be used to differentiate oligocystic SCAs from mucinous cysts, as SCAs typically have a cyst fluid CEA level of <5 ng/mL (95% specificity) [3]. The presence of intramural nodules, cyst wall thickening and/or dilated pancreatic duct should also raise the suspicion of a mucinous cyst rather than SCA [38,39].

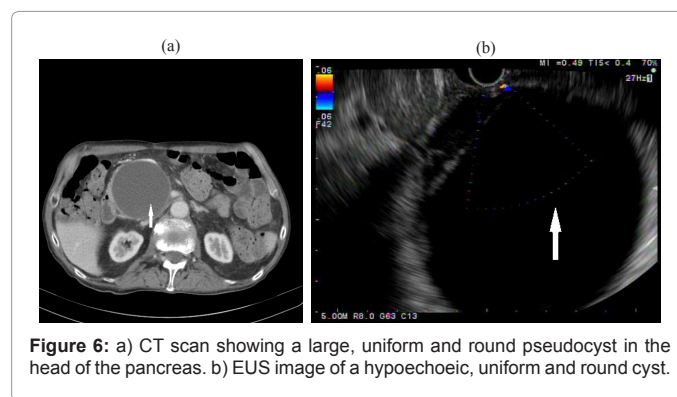
Malignant transformation of SCA is exceedingly rare [40], and there is no consensus with regard to the frequency and duration of surveillance. Various surveillance intervals for asymptomatic patients have been proposed, ranging from 6 months to 24 months [41-43]. Surgical resection can be recommended for symptomatic patients, cysts greater than 4 cm, and when there is uncertainty about the true nature of the cyst [42].

### Pseudocysts

Pseudocysts are typically associated with acute or chronic pancreatitis (Figure 6a and 6b) [44]. They are not true cysts, as its wall



**Figure 5:** a) CT scan of a multiseptated cystic lesion in the body of the pancreas. b) MRCP showing a multi-cystic lesion without ductal dilatation. c) Cytology demonstrating small clusters of uniform cuboidal cells. d) Gross specimen of typical microcystic SCA in a distal pancreatectomy specimen.



**Figure 6:** a) CT scan showing a large, uniform and round pseudocyst in the head of the pancreas. b) EUS image of a hypochoic, uniform and round cyst.

lacks an epithelial lining and is formed by fibrous and granulation tissue. The cavity is filled with fluid rich in pancreatic enzymes including amylase, and usually communicates with pancreatic duct. Recent history of acute pancreatitis and radiographic features of pancreatitis in the pancreatic parenchyma may point towards a diagnosis of pseudocyst. Asymptomatic pseudocysts do not require treatment, whereas symptomatic cysts may require either an endoscopic ultrasound-guided drainage or surgery.

## Evaluation of Pancreatic Cysts

The most fundamental task when evaluating a pancreatic cyst is to determine its malignant potential and make an appropriate recommendation to patients whether surveillance or surgical resection is warranted. It is critical to consider all the available information in the clinical context of each individual patient. For example, a MD-IPMN even with high-risk stigmata in the head of the pancreas in an 85-year-old patient, with medical comorbidities, may not confer any survival benefit from Whipple operation given the significant risk associated with surgery. Conversely, a MCN in the tail of the pancreas which has been growing steadily over the last 5 years in an otherwise healthy 45-year-old patient should warrant a distal pancreatectomy, which has substantially lower morbidity and mortality than a pancreatoduodenectomy.

### Clinical presentation

Although the majority of patients have a small cyst and are asymptomatic, some may report symptoms related to the lesion itself or pancreatitis secondary to the lesion. Symptoms which suggest rapid tumor growth and invasive malignancy include jaundice, weight loss, abdominal pain, steatorrhea and new onset or worsening diabetes. Symptoms of recurrent pancreatitis may point towards the diagnosis of IPMN. The age of onset, gender and co-existing conditions (particularly in the setting of NET and MCN) also need to be taken into account as pancreatic cysts have various predilections for age, gender and the location within the pancreas (Table 2).

### CT and MRI

High-resolution CT is widely utilized for an initial characterization of a pancreatic cyst. MRI has an advantage of determining communication between the cyst and the pancreatic duct as well as lack of radiation exposure, particularly when a patient requires frequent surveillance [45]. Clinicians should obtain any available previous abdominal imaging to determine how long the lesion has been present and whether there has been any significant change in the size and appearance of the lesion. Despite the advances in the

quality of abdominal imaging, CT and MRI have variable accuracy of determining premalignant cysts, even when the operator certainty is high (Figure 7) [46].

### EUS

Compared to CT and MRI, EUS has an advantage of providing a dynamic image and access to the lesion for tissue acquisition via FNA of cyst fluid and a solid component within the cyst. Nevertheless, EUS morphology alone is not perfect for predicting malignant potential and the nature of the cyst (with the exception of microscopic SCA which has a typical honeycomb appearance) with a reported diagnostic accuracy of 51% in differentiating mucinous from non-mucinous cysts [47]. In addition, there is significant interobserver disagreement even in expert hands [48].

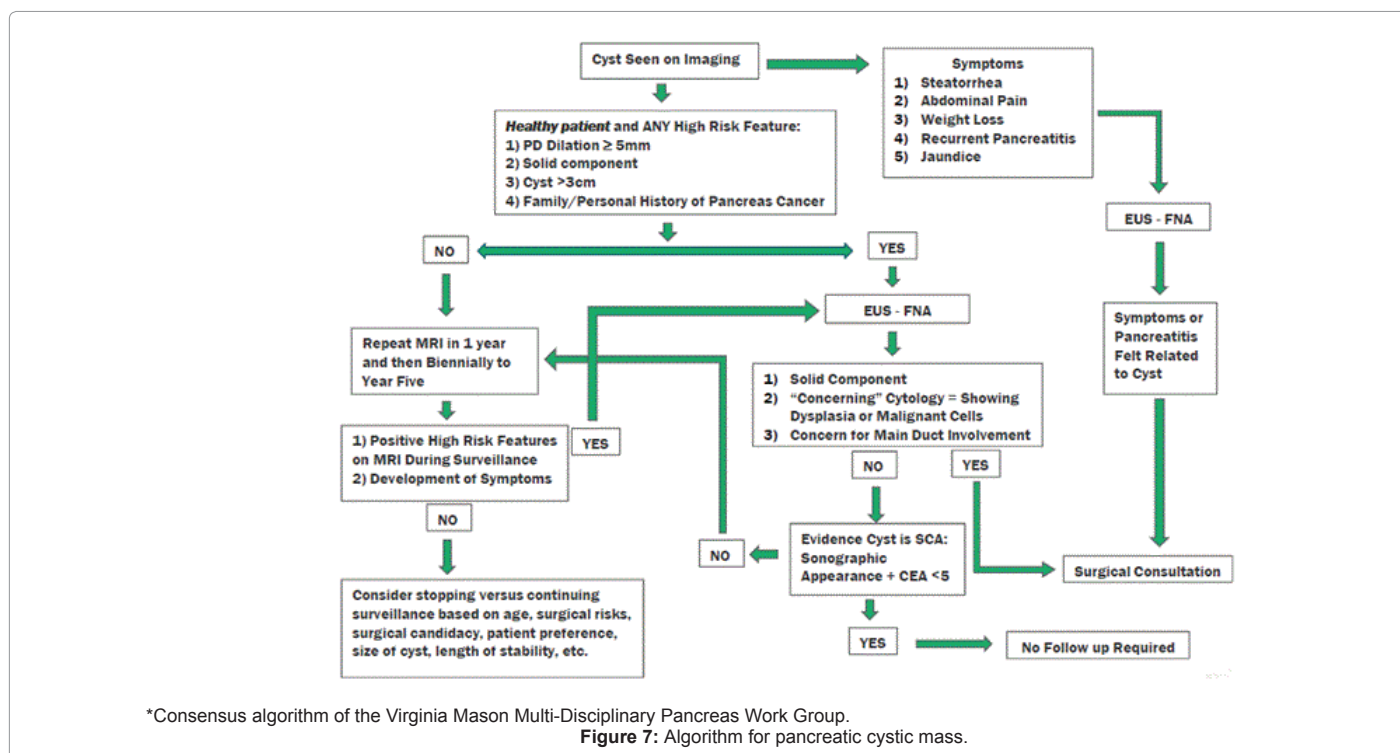
### EUS-FNA for cytology, CEA and amylase

EUS-FNA cytology for the detection of malignancy within pancreatic cysts has an excellent specificity above 90% but is fraught with a low sensitivity of less than 50% [47,49]. Similarly, in regard to the distinction of mucinous from non-mucinous lesions with FNA cytology, studies have demonstrated a low sensitivity of 35% to 43%

	IPMN	MCN	SPT	NET	SCA
<b>Age</b>	6 <sup>th</sup> - 7 <sup>th</sup> decade	5 <sup>th</sup> - 6 <sup>th</sup> decade	2 <sup>nd</sup> - 3 <sup>rd</sup> decade	3 <sup>rd</sup> - 6 <sup>th</sup> decade	7 <sup>th</sup> decade
<b>Gender</b>	M>F	F>M	F>M	M=F	F>M
<b>Location</b>	Head>body/tail	Body/tail>head	Body/tail>head	Body/tail>head	Body/tail>head
<b>CEA</b>	Increased	Increased	N/A	low	low
<b>Amylase</b>	Increased	Variable	N/A	low	low
<b>Cytology</b>	Acellular with background mucin, mucinous epithelial cells with papillary projections may be seen	Acellular with background mucin, mucinous epithelial cells may be seen	Branching papillae with myxoid stroma that reacts to vimentin on cell block	Round nuclei what stain positive for chromogranin and synaptophysin on cell block	Acellular, small glycogen staining cuboidal cells may be seen in the background

IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm; SPT: Solid Pseudopapillary Tumor; NET: Neuroendocrine Tumor; SCA: Serous Cystadenoma

Table 2: Comparison of pancreatic cysts.



and specificity of 83% to 96% [47,49,50]. The poor sensitivity may be attributed to frequent sampling error, sporadic distribution of malignant cells in the cyst, contamination of the specimen due to gastrointestinal tissue and subjective cytopathologist interpretation.

At present, carcinoembryonic antigen (CEA) is the most commonly used cystic fluid tumor marker for the evaluation of a pancreatic cyst. A seminal paper by Brugge et al. [47] reported that CEA cut-off of 192 ng/mL has a sensitivity of 73% and specificity of 84% for differentiating mucinous from non-mucinous cysts. An appropriate cut-off for CEA level has been a contentious issue. Higher CEA levels tend to exhibit superior specificity and lower sensitivity for the detection of mucinous cysts. A CEA level of >800 ng/mL is associated with 98% specificity, 48% sensitivity, and 79% accuracy in differentiating MCN from SCA or PC [51]. Disadvantages of cyst fluid CEA are that there is no correlation with the degree of dysplasia [52], and it does not help in distinguishing between MCN and IPMN [53].

Cyst fluid amylase has been used in the hope of differentiating cysts communicating with the pancreatic duct (pseudocyst and IPMN) from those without any communication with the duct (MCN and SCA). A level of <250 U/L has a 44% sensitivity and 98% specificity for SCA and MCN, and can be used to exclude pseudocysts [51]. Nonetheless, an amylase level should be interpreted with caution as high levels can still be detected in MCNs and SCAs.

In summary, although EUS-FNA is often performed as part of the diagnostic work-up of pancreatic cysts, it may not provide additional diagnostic information unless cytology is positive for malignancy or CEA level is at the extremes of the scale. EUS-FNA should therefore be used with caution and in certain circumstances, for instance, when a macrocystic variant of SCA cannot be distinguished morphologically from MCN and IPMN. This selective approach for the use of EUS-FNA is advocated by the 2012 Fukuoka consensus guideline [5]. On the other hand, when there is a convincing morphological feature to support a diagnosis, such as honeycomb appearance that occurs in microcystic SCA, EUS-FNA is not indicated.

### Novel diagnostic modalities in development

**Molecular markers and integrated molecular pathology:** Several studies have demonstrated that malignant pancreatic cysts are associated with a higher number of molecular alterations [54,55], particularly in the KRAS and GNAS oncogenes. However, molecular analysis is often not readily available in clinical practice, and a single genetic marker alone cannot reliably determine malignancy risk. More recently, the utility of combining a panel of molecular markers with clinical features has been investigated [56]. In this study of 130 patients with resected pancreatic cysts, their composite molecular/clinical marker provided a sensitivity of 89% and a specificity of 69% for determining the need for surgery.

**Confocal laser endomicroscopy:** Confocal laser endomicroscopy (nCLE) is an emerging technique where a submillimeter probe is inserted through a 19-gauge needle into the cystic cavity under EUS-guidance to obtain real-time imaging of the villous structures and superficial vascular pattern of pancreatic cyst epithelium. A recent study reported a sensitivity of 69%, specificity 100%, PPV 100% and NPV 82% for the detection of SCA [57].

**Through-the-needle biopsy of the cyst wall:** The use of a small micro forceps (the Moray micro forceps, US Endoscopy) which can be advanced through a 19-gauge needle to obtain biopsies of the cyst wall under EUS guidance has been reported [57]. This new technique allows

targeted tissue sampling under EUS guidance and may potentially provide an improved diagnostic yield for cytology [58].

### Evolution of Guidelines

According to the initial Sendai consensus guideline in 2006, the presence of symptoms, size >3 cm, mural nodules, dilated MPD and positive cytology are considered as indications for upfront resection whereas smaller cysts without any high risk features can be observed with imaging over various interval periods [59]. On the other hand, a revised 2012 Fukuoka consensus guideline divides imaging characteristics as either “high risk” (solid enhancing components, dilated pancreatic duct of more than 10 mm and obstructive jaundice) which are absolute indications for resection, and “worrisome” (cyst size  $\geq$  3 cm, thickened walls and pancreatic duct dilatation of 5 mm to 9 mm), for which further evaluation by EUS is suggested [5].

In the revised guideline, cyst size  $\geq$  3 cm is no longer an absolute indication for surgery. This change in criteria was based on the fact that 75% of patients who underwent surgery for presumed BD-IPMN after meeting the 2006 criteria did not have invasive cancer or high-grade dysplasia [60,61], and could have been safely observed instead. Additionally, there is a growing body of literature to suggest that malignant transformation of pancreatic cysts is uncommon. Studies, ranging in number from 82 to 287 patients, show stability in 82% to 94% of cysts, with malignancy being found in 0% to 2.6% of the patients with IPMN over median follow-up periods of 32 months to 59 months [62-64].

On the other hand, the guidelines have also raised concerns for missing high-risk lesions. According to a recent study of 194 patients with pancreatic cysts, the 2006 guideline had 91.7% sensitivity, 21.5% specificity, 21% PPV and 91.9% NPV for identifying advanced neoplasia whereas the 2012 guideline was associated with 55.6% sensitivity, 73% specificity, 32% PPV and 87.9% NPV [65]. All 22 patients with invasive cancer were identified by the guidelines as high-risk patients, but 5 of 14 patients with high-grade dysplasia were classified as low-risk and hence missed.

The most recent guidelines from the AGA in 2015 [6] advocates an even more conservative approach by recommending: 1) surgery for an asymptomatic patient only if a cyst has 2 of the 3 concerning features (size >3 cm, nodule, or duct dilation) and EUS shows malignancy, 2) surveillance intervals of 2 years, regardless of the size of the cyst, as opposed to the 2012 guideline which recommends various interval for surveillance depending on the size of the cyst, and 3) discontinuation of surveillance after 5 years if no significant change or after resection of the cyst, or if the patient is no longer an appropriate surgical candidate, whereas the 2012 guidelines are undecided about the cessation of surveillance.

Whilst these recommendations spark more controversies surrounding the management of pancreatic cysts, one needs to acknowledge that the AGA guideline pertains to all cysts including undifferentiated and asymptomatic cysts, whereas the previous two guidelines are relevant to mucinous cysts. Furthermore, in their systematic analysis, the overall rate of conversion to invasive cancer for all pancreatic cysts in general is approximately 0.24% per year, which adds to a body of literature that the risk of conversion to malignancy for pancreatic cysts is low. Nevertheless, some important questions remain to be answered. Is stopping surveillance after 5 years justified? A recent report found that the risk of malignancy is rare after 5 years [66], but the risk of concomitant pancreatic adenocarcinoma is reported to be significant in cases of multi-focal IPMN [67]. Long-term data are



needed to clarify whether it is safe to stop surveillance in patients with IPMN given this potential 'field-effect'. Another factor that deserves an attention is the cyst growth rate. A size increase of >2 mm per annum has been shown to correlate with an increased potential for malignancy over 3 years to 5 years [68], which has not been mentioned in the guidelines to date. Lastly, patients with hereditary cancer syndromes (Peutz-Jeghers syndrome, familial breast-ovarian cancer) and/or a family history of pancreatic cancer have an increased likelihood of having pancreatic cystic lesions detected at routine imaging [69] and may need to be incorporated in the guidelines.

In summary, the current guidelines are in line with growing evidence that the vast majority of pancreatic cysts are benign. However, the guidelines which are based on weak evidence from retrospective data are not absolute, and treatment decisions should be individualized.

## Summary and Conclusion

Although much remains to be learned about the natural history of pancreatic cysts, it is becoming more apparent that only a small minority of such lesions progress to cancer. Given the limitations of current diagnostic modalities, the management of patients with pancreatic cysts should be individualized, incorporating guideline recommendations along with sound clinical judgment. Further work is needed to develop reliable molecular markers and novel diagnostic tools to predict the malignant potential of pancreatic cysts.

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