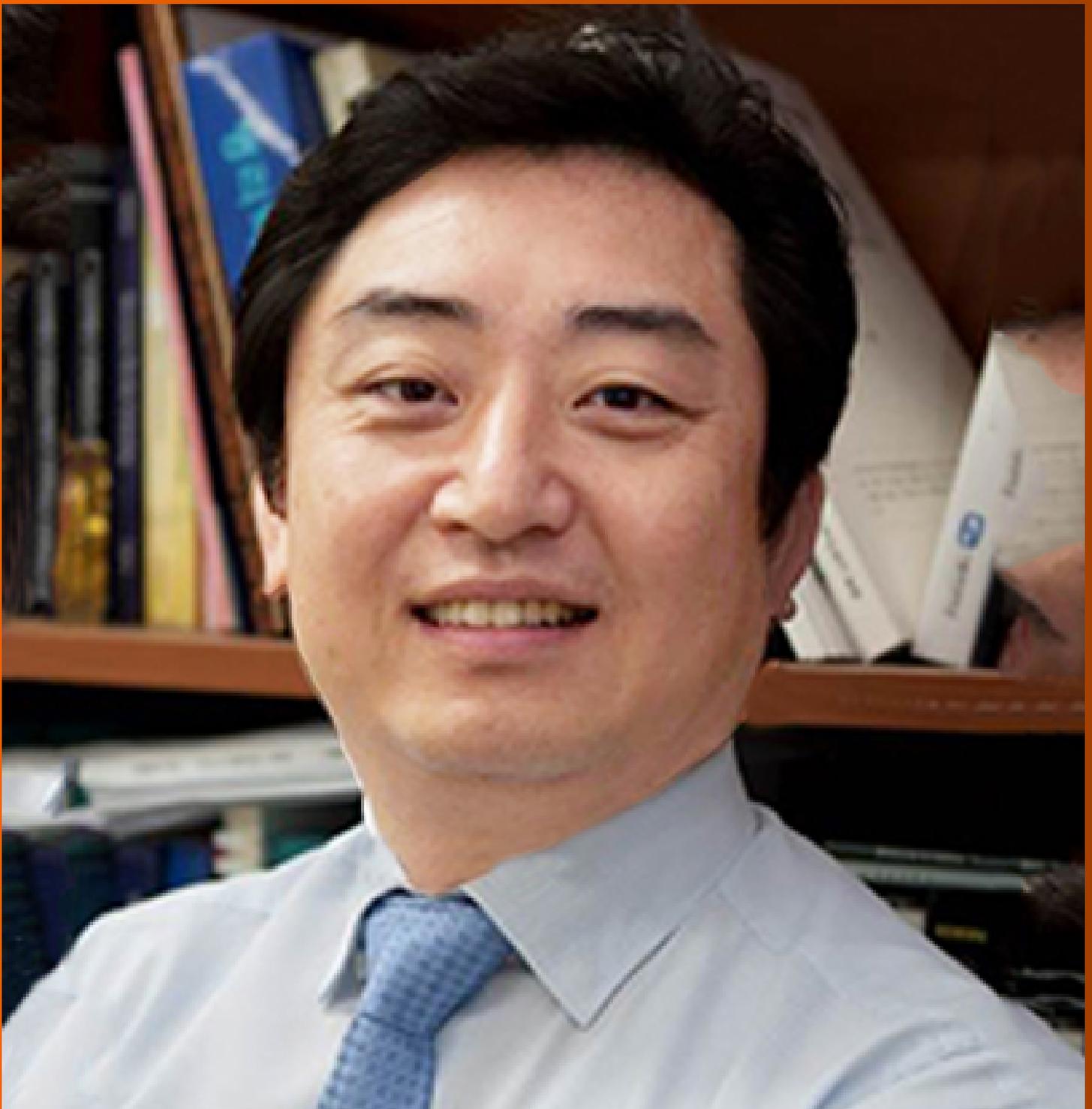


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## Similarities and differences in guidelines for the management of pancreatic cysts

Gandhi Lanke, Jeffrey H Lee

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### Abstract

Accurate diagnosis of Pancreatic cysts (PC) is key in the management. The knowledge of indications for surgery, the role of endoscopic ultrasound-guided fine needle aspiration, cyst fluid analysis, imaging, and surveillance of PC are all important in the diagnosis and management of PC. Currently, there are many guidelines for the management of PC. The optimal use of these guidelines with a patient-centered approach helps diagnose early cancer and prevent the spread of cancer.

**Key words:** Pancreatic cysts; Serous cystadenoma; Main pancreatic duct; Intraductal papillary mucinous neoplasm; Endoscopic ultrasound-guided fine needle aspiration; Carcinoembryonic antigen

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**Core tip:** The differentiation of mucinous and non-mucinous cysts is key in the effective management of pancreatic cysts. Thorough understanding of the absolute indications for surgery, the role of endoscopic ultrasound-guided fine needle aspiration, cyst fluid analysis, imaging, and the guidelines for surveillance are important in the diagnosis and treatment of pancreatic cysts. Patient-centered approach with a multidisciplinary team involving the surgeon, radiologist, pathologist, oncologist, and advanced endoscopist improves the management of pancreatic cysts.

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## INTRODUCTION

Pancreatic cysts (PC) are diagnosed more frequently with the widespread use of cross-sectional imaging, and most of them are found incidentally. The prevalence of PC varies with age and race and they are found approximately 3%-14% on routine computed tomography (CT) and Magnetic resonance imaging (MRI) for unrelated reasons<sup>[1,2]</sup>. They can be benign or neoplastic. Accurate determination of cyst categorization is key in the management. With the introduction of endoscopic ultrasound (EUS) and fine-needle aspiration (FNA), the accuracy of pancreatic cyst classification is improved. This review article focuses on the management of PC using different guidelines.

## PANCREATIC CYST CLASSIFICATION

The pathological classification of PC (Table 1) includes inflammatory fluid collections (IFCs), non-neoplastic PC, and pancreatic cystic neoplasms (PCNs). PC can also be associated with an underlying disorder such as Von Hippel-Lindau or polycystic kidney disease<sup>[3,4]</sup>. IFCs are usually as a result of a complication of acute pancreatitis. IFCs are categorized according to the revised Atlanta classification into acute peripancreatic fluid collections, pseudocysts, acute necrotic collections, and walled-off pancreatic necrosis<sup>[5]</sup>.

Non-neoplastic or benign PC include true cysts, retention cysts, mucinous non-neoplastic cysts, and lymphoepithelial cysts. They are typically seen after surgical resection of a pancreatic lesion that is suspected to be a pancreatic cystic neoplasm (PCN) preoperatively. According to World Health Organization histological classification, PCNs are classified into serous cystic tumors, mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs) and solid pseudopapillary neoplasms (SPN).

## HOW TO APPROACH PC

Serous cystic tumors are usually serous cystadenomas commonly seen in women over the age of 60 years and can arise anywhere in the pancreas<sup>[6]</sup>. Serous cystadenomas are classified into microcystic (composed of multiple small cystic spaces) and oligocystic (composed of fewer larger cystic spaces)<sup>[7,8]</sup>. Most of them are benign and malignant potential is low<sup>[9]</sup>. Serous cystadenomas are often found incidentally on imaging. Sometimes it is difficult to distinguish serous cystic neoplasms from mucinous neoplasms on imaging. EUS finding of honeycomb appearance with central calcification can be diagnostic (Figure 1)<sup>[10]</sup>. EUS-FNA with low carcinoembryonic antigen (CEA) in cyst fluid can help distinguish mucinous and serous cystic tumors<sup>[11]</sup>. Histologically, the cysts are lined by cuboidal epithelial cells with clear cytoplasm filled with glycogen<sup>[12]</sup>.

The risk of malignant transformation to cystadenocarcinoma is approximately 0.2-3%<sup>[12,13]</sup>. Surgery should be reserved for symptomatic (jaundice, extrinsic organ compression) patients and when in doubt close follow up with multidisciplinary team approach is advocated<sup>[14,15]</sup>. Size > 4 cm alone should not be an indication for surgery, although some authors advocate it<sup>[16,17]</sup>. There is no consensus on guidelines for follow up in terms of imaging. Many authors recommend yearly CT/MRI although currently, it is uncertain about how long the patient needs follow up. Overall, conservative management is recommended for serous cystic tumors and the algorithm for management of serous cystic tumors is shown in Figure 2.

MCNs are found commonly in women over the age of 40 years and can occur in the body or tail of the pancreas (Figure 3)<sup>[8]</sup>. They secrete mucin, demonstrate ovarian like stroma, exhibit cellular atypia and do not communicate with the main pancreatic duct<sup>[8]</sup>. MCNs have the risk of malignant potential. MCNs are classified according to the grade of dysplasia into low, intermediate, high grade, or invasive carcinoma<sup>[18]</sup>. The prevalence of invasive carcinoma in MCNs is approximately 12% and most patients are young at presentation, which would require long term surveillance<sup>[19]</sup>. The current treatment recommendation for MCNs is surgical resection<sup>[20]</sup>. Also, MCNs do not require surveillance after surgical resection unless there is invasive cancer<sup>[21]</sup>. Some authors do not recommend surgery for MCNs < 3 cm without mural nodules or elevated tumor markers<sup>[22]</sup>. The algorithm for the management of MCNs is shown in Figure 2.

SPNs predominantly affect young females and are generally located in the tail of the pancreas (Figure 4A)<sup>[23]</sup>. They appear as solid and cystic components with areas of

**Table 1 Pathological classification of most common pancreatic cysts**

<b>Inflammatory fluid collections</b>
Acute peripancreatic fluid collections
Pseudocysts
Acute necrotic collections
Walled-off pancreatic necrosis
<b>Non-neoplastic</b>
True cysts
Mucinous non-neoplastic cysts
Lymphoepithelial cysts
<b>Pancreatic cystic neoplasms</b>
Serous cystic neoplasms
Mucinous cystic neoplasm
Intrapapillary mucinous neoplasm
Solid papillary neoplasm

hemorrhage, calcification, and a rim of the fibrous capsule<sup>[24]</sup>. They have malignant potential. Surgery is the treatment of choice and R<sub>0</sub> resection is curative<sup>[25]</sup>. The algorithm for the management of SPNs is shown in [Figure 2](#).

IPMNs are mucin-producing papillary neoplasms of the pancreatic duct that exhibit variable cellular atypia with dilation of the pancreatic ducts and are more common over the age of 60 years<sup>[26]</sup>. Based on the involvement of the pancreatic duct, they are classified into branch duct, main duct (MD-IPMN), or mixed type of IPMN ([Figure 4B-D](#)) respectively<sup>[27]</sup>. IPMNs have malignant potential and according to the grade of dysplasia they are classified into mild dysplasia, moderate dysplasia, high-grade dysplasia, or invasive carcinoma<sup>[27]</sup>.

## SIMILARITIES AND DIFFERENCES OF VARIOUS GUIDELINES IN THE MANAGEMENT OF PC: WHICH PC CAN BE OBSERVED AND HOW LONG DO THEY NEED SURVEILLANCE?

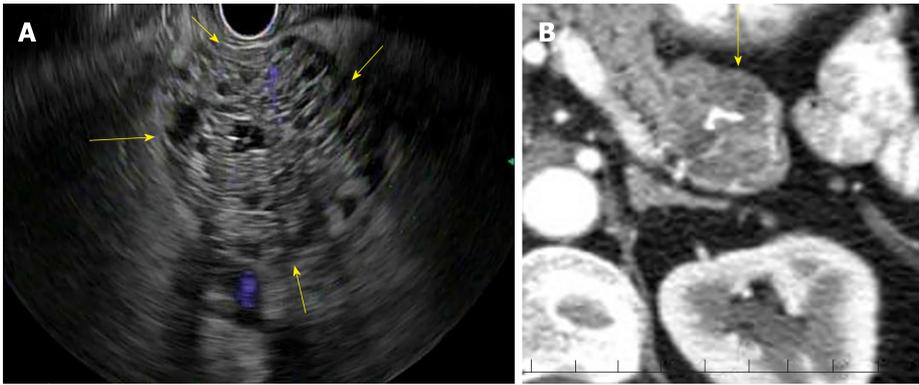
### **European guidelines<sup>[28]</sup>**

MCNs size < 4 cm without symptoms or mural nodules can undergo surveillance every 6 mo during the 1<sup>st</sup> year using EUS/MRI or both<sup>[21,29]</sup>. They can be followed annually if no interval change in cyst size. Lifelong surveillance is advocated if they are fit for surgery. IPMNs cyst size < 4 cm or low-grade dysplasia can be followed with serum CA 19-9 level, EUS/MRI or both every 6 mo during the 1<sup>st</sup> year. Followed by every year if no interval change in cyst size until no longer fit for surgery<sup>[28]</sup>. After surgical resection of high-grade dysplasia or MD-IPMN, EUS/MRI is recommended every 6 mo for the 1<sup>st</sup> two years and yearly follow-up afterward. Low-grade dysplasia or remnant IPMN after surgical resection should be followed in the same manner as non-resected IPMN. Lifelong follow up after surgical resection is recommended if the patient is fit and willing to undergo surgery.

### **American College of Gastroenterology guidelines<sup>[30]</sup>**

The surveillance of IPMN/MCN is based on cyst size. Cyst size < 1 cm, MRI every 2 years for 4 years is recommended and lengthen the interval if cyst size is stable. Cyst size 1-2 cm, MRI every year for 3 years, followed by every 2 years for 4 years and lengthen the interval if cyst size is stable. Cyst size 2-3 cm, MRI/EUS every 6-12 mo for 3 years, followed by every year for 4 years and lengthen the interval once stable in size. Cyst size > 3 cm, MRI alternating with EUS every 6 mo for 3 years, followed by MRI alternating with EUS every year for 4 years and lengthen the interval once stable in size. Consider EUS-FNA if any increase in cyst size during follow up.

The risk of recurrence of IPMN after surgery varies based on the degree of dysplasia. EUS/MRI every 6 mo after surgical resection of IPMN-HGD is recommended. With low to intermediate grade dysplasia in the absence of PC in the remnant pancreas after surgical resection, MRI every 2 years is recommended. However, if IPMN or PC are present in the remnant pancreas after surgical resection, surveillance should be according to cyst size. Stop surveillance after surgical resection



**Figure 1 Endoscopic ultrasound (Honeycomb appearance).** A: Endoscopic ultrasound: Serous cystadenoma; B: Computed tomography: Serous Cystadenoma. Computed tomography: Portal venous phase showing calcification.

of MCN if no invasive cancer is present or no longer a surgical candidate.

### **American Gastroenterological Association guidelines<sup>[31]</sup>**

In asymptomatic pancreatic neoplastic cysts < 3 cm without a solid component or PD dilation, MRI is recommended in 1 year and every 2 years for 5 years. American Gastroenterology Association (AGA) recommends stopping surveillance when no longer fit for surgery or no change in cyst characteristics after 5 years of follow up.

### **Revised IAP 2017 Fukuoka guidelines<sup>[32]</sup>**

In revised IAP 2017 guidelines, for cyst size 1-2 cm, CT/MRI every 6 mo for a year, followed by every year for 2 years and lengthen the interval if stable. For cyst size 2-3 cm, EUS in 3-6 mo for 1 year. Increase the interval to 1 year with EUS/MRI as appropriate. For cyst size > 3 cm, close surveillance alternating MRI with EUS every 3-6 mo. In surgically resected IPMN, surveillance is recommended with cross-sectional imaging twice a year for patients with a family history of pancreatic ductal adenocarcinoma, surgical margin positive for HGD, and non-intestinal sub-type of IPMN. For all others, every 6-12 mo of cross-sectional imaging is recommended.

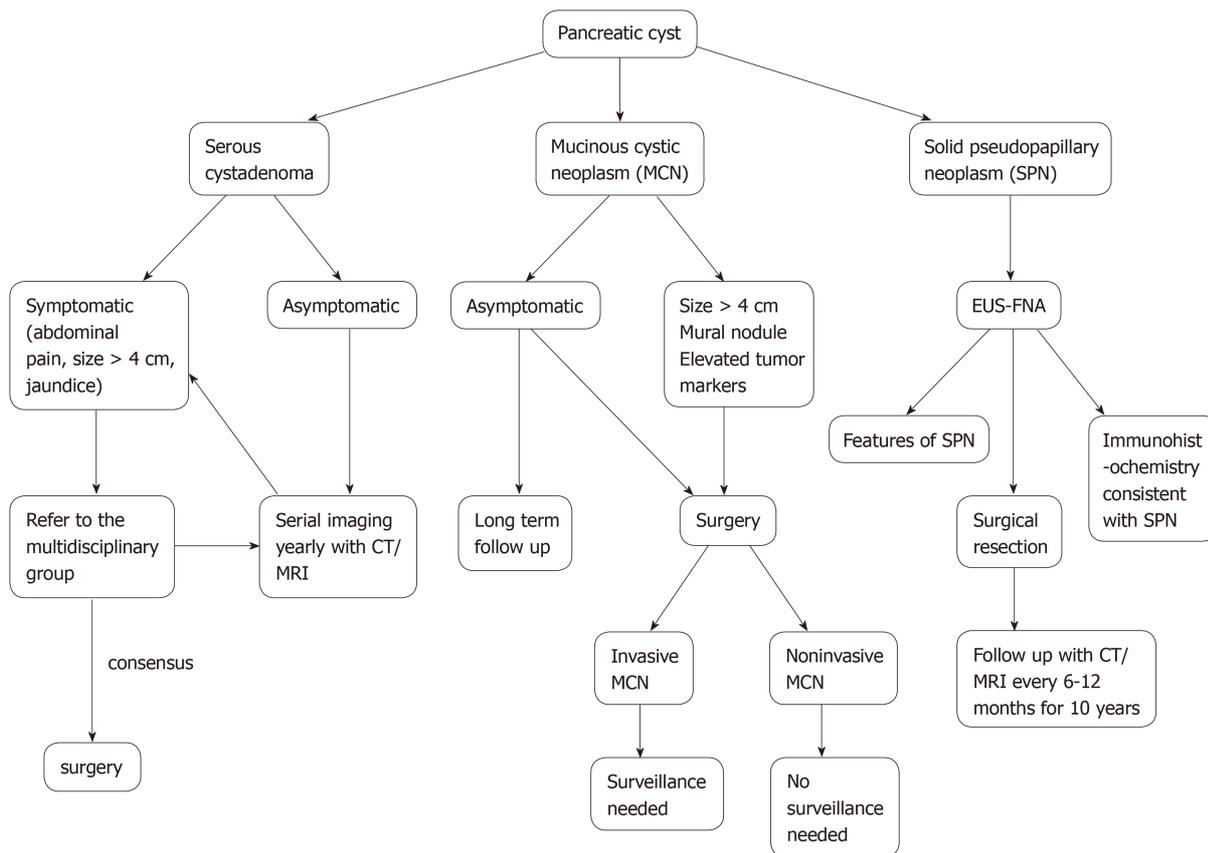
### **American College of Radiology guidelines<sup>[33]</sup>**

ACR guidelines are for the management of PC found incidentally on CT/MRI. These guidelines are based on the age of the patient and the size of the cyst. Cyst size < 1.5 cm and age < 65 years, CT/MRI every year for 5 years, followed by every 2 years for 4 years. Stop surveillance if stable over 9 years. Cyst size < 1.5 cm and age 65-79 years, CT/MRI every 2 years for a total of 10 years. Stop surveillance if the cyst is stable for 10 years. If there is interval change and cyst size < 1.5 cm, consider CT/MRI every year or EUS-FNA. If EUS-FNA shows a mucinous cyst or indeterminate cyst, CT/MRI every 6 mo for 2 years, followed by every year for 2 years and every 2 years for 6 years. Stop surveillance if the cyst is stable after 10 years.

Cyst size 1.5-1.9 cm with MPD communication, CT/MRI every year for 5 years, followed by every 2 years for 4 years. Stop surveillance if cyst size stable for over 9 years. Cyst size 2-2.5 cm with MPD communication, CT/MRI every 6 mo for 2 years, followed by every year for 2 years and subsequently every 2 years for 6 years. Stop surveillance if cyst size is stable for 10 years. If there is interval change and cyst size ≤ 2.5 cm, CT/MRI every 6 mo for 2 years, followed by every year for 2 years and subsequently every 2 years. If cyst size > 2.5 cm, consider EUS-FNA. If EUS-FNA shows a mucinous cyst or indeterminate cyst, CT/MRI every 6 mo for 2 years, followed by every year for 2 years and every 2 years for 6 years.

Cyst size 1.5-2.5 cm without MPD communication or cannot be determined, CT or MRI every 6 mo for 2 years, followed by every year for 2 years and subsequently every 2 years for 6 years. Stop surveillance if cyst size is stable after 10 years. If there is interval change and cyst size ≤ 2.5 cm, consider CT/MRI every 6 mo for 1 year, followed by every year for 5 years and subsequently every 2 years. If cyst size is > 2.5 cm, consider EUS-FNA.

Cyst size > 2.5 cm and low risk by imaging, consider CT/MRI every 6 mo for 2 years. If stable after 2 years, CT/MRI every year for 2 years and subsequently every 2 years for 6 years. Stop surveillance if stable in cyst size. Any interval changes in cyst size, consider EUS-FNA. Age ≥ 80 years with cyst size ≤ 2.5 cm, CT/MRI every 2 years for 4 years. Stop surveillance if the cyst is stable in size. If there is interval change and cyst size ≤ 2.5 cm, consider CT/MRI every year. Stop surveillance if cyst size stable or



**Figure 2** Algorithm for the management of pancreatic cysts. MCN: Mucinous cystic neoplasm; SPN: Solid pseudopapillary neoplasm; EUS-FNA: Endoscopic Ultrasound-Fine Needle aspiration; CT: Computed tomography; MRI: Magnetic resonance imaging.

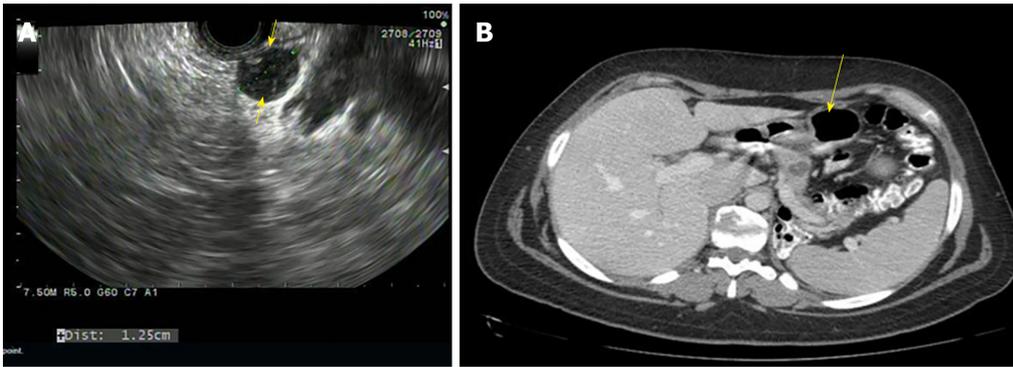
not a surgical candidate. If there is interval change and cyst size > 2.5 cm, consider EUS-FNA. Age ≥ 80 years with cyst size > 2.5 cm and low risk by imaging, consider CT/MRI every 2 years for 4 years. Stop surveillance if cyst size is stable. If there is interval change in cyst size, consider EUS-FNA.

Surveillance of PC using different guidelines is illustrated in **Table 2**. Overall, there is no consensus on the surveillance of PC without high-risk stigmata or worrisome features. European guidelines recommend surveillance of MCN/IPMN cysts < 4 cm with EUS/MRI. American College of Gastroenterology (ACG) guidelines recommend surveillance of IPMN/MCN based on cyst size (< 1 cm, 1-2 cm, 2-3 cm, > 3 cm) with MRI and after surgical resection, follow up is recommended based on the degree of dysplasia. AGA recommends follow up with MRI if cyst size < 3 cm without solid component or MPD dilation. Lifelong surveillance is recommended if they are fit for surgery. Revised IAP or Fukuoka guidelines are based on cyst size (< 1 cm, 1-2 cm, 2-3 cm, and > 3 cm) but with increased surveillance using CT/MRI and EUS as needed. ACR guidelines are proposed for the management of asymptomatic incidental PC found on imaging and they are based on cyst size, age, low risk on imaging, and MPD communication. They are classified into age < 65 years with cyst size < 1.5 cm, age 65-79 years with cyst size < 1.5 cm, cyst size 1.5-1.9 cm with MPD communication, cyst size 1.5-2.5 cm without MPD communication, low risk by imaging with cyst size > 2.5 cm, age ≥ 80 years with cyst size ≤ 2.5 cm and age ≥ 80 years with low risk by imaging and cyst size > 2.5 cm. Surveillance is recommended using CT/MRI and EUS-FNA as needed.

## ROLE OF BLOOD AND CYSTIC MARKERS IN THE DIAGNOSIS OF PC

### European guidelines<sup>[28]</sup>

Serum cancer antigen (CA 19-9) can be considered when there is a concern for the malignant transformation of IPMN<sup>[34,35]</sup>. Guanine nucleotide-binding protein (GNAS) and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations using next-



**Figure 3** Endoscopic ultrasound - mucinous cystadenoma and computed tomography - mucinous cystadenoma. A: Endoscopic ultrasound-mucinous cystadenoma; B: Computed tomography-mucinous cystadenoma.

generation sequencing techniques can be used in identifying mucin-producing cysts when the diagnosis is not clear<sup>[36,37]</sup>. Cyst fluid carcinoembryonic antigen (CEA) > 192 ng/mL can help distinguish mucinous from non-mucinous cysts<sup>[38]</sup>. Cyst fluid amylase level can help identify pseudocysts but may not differentiate mucinous from non-mucinous cysts<sup>[11,39]</sup>. A combination of cytology, cyst fluid amylase, CEA and molecular markers can help differentiate mucinous from non-mucinous cysts.

#### **ACG guidelines<sup>[30]</sup>**

Cyst fluid cytology can assess for HGD-IPMN or cancer when imaging features are insufficient to warrant surgery. Cyst fluid CEA (> 192 ng/mL) can help differentiate IPMNs and MCNs from other cyst types<sup>[40]</sup>. Molecular markers like KRAS and GNAS mutations can help identify IPMNs or MCNs when the diagnosis is not clear<sup>[41,42]</sup>. Cyst fluid amylase level < 250 IU/L can help exclude the diagnosis of pseudocyst<sup>[11]</sup>.

#### **AGA guidelines<sup>[31]</sup>**

Cyst fluid cytology is recommended for the evaluation of high-risk features on imaging and positive cytology increases the specificity for diagnosing malignancy. The role of cyst fluid molecular markers is not clear and further research is needed.

#### **Revised IAP 2017 guidelines<sup>[27]</sup>**

Cyst fluid CEA (> 192 ng/mL) can distinguish mucinous from non-mucinous but not benign from malignant cyst<sup>[38]</sup>. Cyst fluid cytology can be diagnostic but sometimes limited by scant cellularity<sup>[43,44]</sup>. Cyst fluid amylase can differentiate benign from malignant MCN and amylase levels are higher in pseudocysts than non-pseudocysts<sup>[45]</sup>. The role of molecular markers like KRAS and GNAS mutations is still evolving.

#### **ACR guidelines<sup>[33]</sup>**

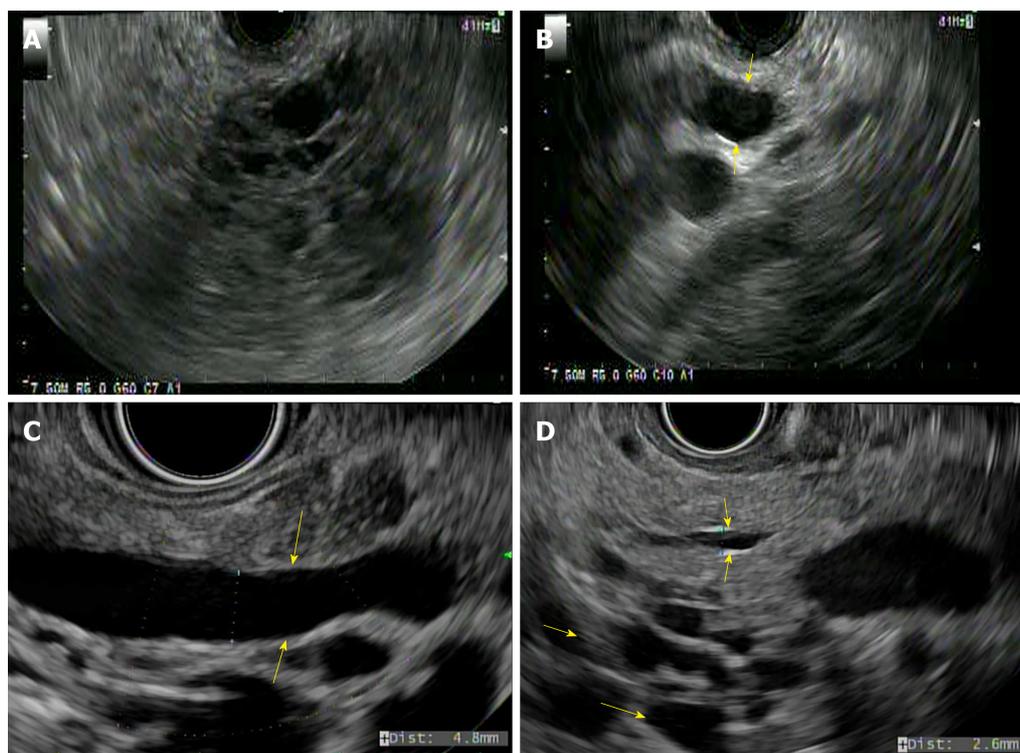
Cyst fluid CEA > 192 ng/mL can help identify a mucinous cyst<sup>[46]</sup>. Cyst fluid amylase >250 IU/L suggests pseudocyst<sup>[11]</sup>. KRAS and GNAS molecular markers can help differentiate mucinous from non-mucinous cysts<sup>[47]</sup>. Cyst cytology can identify dysplastic cells. The role of cystic fluid analysis in the diagnosis of PC using different guidelines is illustrated in **Table 3**. Overall, cyst fluid analysis complements imaging and can help differentiate mucinous from non-mucinous cysts. Cytology can aid in distinguishing HGD-IPMN and cancer. Cyst fluid CEA > 192 ng/mL can differentiate mucinous from non-mucinous cysts. Cyst fluid amylase > 250 IU/L can accurately diagnose pseudocysts. The use of molecular markers is still evolving, and it is promising for the future.

## **EUS-FNA INDICATIONS**

#### **European guidelines<sup>[28]</sup>**

EUS-FNA can improve diagnostic accuracy with cyst fluid CEA, amylase, and cytology in differentiating mucinous *vs* non-mucinous cysts. Also, it distinguishes malignant *vs* benign cysts when CT or MRI is unclear. EUS-FNA should be performed only when results are expected to change clinical management.

#### **ACG guidelines<sup>[30]</sup>**



**Figure 4 Endoscopic ultrasound.** A: Solid pseudopapillary neoplasm, hypoechoic foci (solid areas) with anechoic cystic spaces; B: Main duct-intraductal papillary mucinous neoplasm; C: Mixed duct-intraductal papillary mucinous neoplasm; D: Branch duct-intraductal papillary mucinous neoplasm.

EUS-FNA is indicated in IPMNs/MCNs with jaundice or acute pancreatitis secondary to the cyst, new-onset or worsening diabetes and increase in cyst size  $> 3$  mm/year during surveillance, significantly elevated serum CA 19-9, mural nodule, solid component within cyst or pancreatic parenchyma, dilation of MPD  $> 5$  mm, focal dilation of PD concerning for MD-IPMN or obstructing lesion, and mucin-producing cyst size  $\geq 3$  cm; it is also indicated when the diagnosis of cysts is unclear; results will likely alter management; and when cyst fluid CEA can differentiate IPMNs and MCNs from other cyst types.

#### **AGA guidelines<sup>[31]</sup>**

EUS-FNA is indicated when a pancreatic cyst has at least 2 high-risk features such as cyst size  $\geq 3$  cm, dilated MPD, and solid component.

#### **Revised IAP 2017 or Fukuoka guidelines<sup>[32]</sup>**

EUS-FNA is recommended with pancreatitis, cyst size  $\geq 3$  cm, thickened/enhancing cyst wall, the main duct size 5-9 mm, non-enhancing mural nodule, an abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum level of CA19-9, and cyst growth rate  $\geq 5$  mm/2 years.

#### **ACR guidelines<sup>[33]</sup>**

EUS-FNA is indicated for a mural nodule, wall thickening, dilation of MPD  $\geq 7$  mm, or extrahepatic biliary obstruction/jaundice. The indications of EUS-FNA for the diagnosis of PC using different guidelines are illustrated in Table 4. Overall, EUS-FNA is indicated when the results are likely to change the management. EUS-FNA is recommended for cyst  $\geq 3$  cm, mural nodule, thickened cyst wall, solid component in cyst, MPD  $> 5$  mm, abrupt change in caliber of PD with distal pancreatic atrophy, lymphadenopathy, cyst growth  $\geq 3$ -5 mm/year, acute pancreatitis, new-onset or worsening diabetes, jaundice and increased serum CA 19-9 level.

## **INDICATIONS FOR SURGERY**

#### **European guidelines<sup>[28]</sup>**

Absolute indications for surgery include positive cytology for malignant/ HGD-IPMN, solid mass, jaundice (tumor-related), enhancing mural nodule  $\geq 5$  mm, and MPD  $\geq 10$  mm. Relative indications for surgery include cyst growth rate  $\geq 5$ mm/year,

Table 2 Surveillance of pancreatic cysts

Surveillance of pancreatic cysts	
European guidelines <sup>[28]</sup>	<p>Mucinous cystic neoplasm: Cyst size &lt; 4 cm without symptoms or mural nodules should undergo surveillance every 6 mo for the 1<sup>st</sup> year using EUS/MRI or both<sup>[29]</sup>. Followed by annually, if no changes. Lifelong surveillance if they are fit for surgery</p> <p>Intraductal papillary mucinous neoplasm (IPMN): Every 6 mo for cysts less than 4cm or low-grade dysplasia for the 1<sup>st</sup> year with CA 19-9, EUS/MRI or both. Followed by yearly, until no longer fit for surgery</p> <p>After surgical resection, HGD or MD-IPMN should have imaging every 6 mo for the 1<sup>st</sup> 2 yr. Followed by yearly surveillance. Lifelong surveillance if they are fit for surgery</p>
American College of Gastroenterology (ACG) guidelines <sup>[30]</sup>	<p>Intraductal papillary mucinous neoplasm/Mucinous cystic neoplasm (IPMN/MCN): Cyst size &lt; 1 cm: MRI every 2 yr × 4 yr. If stable in size, consider prolonging the time interval. Any increase in size, consider EUS-FNA in 6 mo and reevaluate</p> <p>Cyst size 1-2 cm: MRI every 1 yr × 3 yr. If stable, consider MRI every 2 yr × 4 yr. Once stable, consider prolonging the interval</p> <p>Cyst size 2-3 cm: MRI/EUS every 6-12 mo for 3 yr. If stable, MRI every 1-year × 4 yr. Once stable, consider prolonging the interval. Any increase in cyst size should be referred to the multidisciplinary group and consider EUS-FNA</p> <p>Cyst size &gt; 3 cm: Referral to the multidisciplinary team. MRI alternating with EUS every 6 mo for 3 yr. Once stable in size, MRI alternating with EUS every year for 4 yr. Once stable in size, consider prolonging the interval</p> <p>Stop surveillance when a patient is no longer a surgical candidate or after surgical resection of MCN if no invasive cancer</p> <p>The risk of recurrence of IPMN after surgery varies based on the degree of dysplasia</p> <p>EUS/MRI every 6 mo after surgical resection of IPMN with HGD</p> <p>MRI every 2 yr after surgical resection of IPMN with low to intermediate grade dysplasia in the absence of pancreatic cysts in the remnant pancreas. However, if IPMN or pancreatic cysts are present in the remnant pancreas, then surveillance should be based on cyst size</p>
American Gastroenterology Association (AGA) guidelines <sup>[31]</sup>	<p>Cyst size &lt; 3 cm without a solid component or PD dilation recommend MRI in 1 yr, followed by every 2 yr for 5 yr.</p> <p>Recommend stopping surveillance if no change in cyst characteristics after 5 yr or not a surgical candidate</p>
Revised IAP 2017 or revised Fukuoka guidelines <sup>[32]</sup>	<p>Branch duct-Intraductal papillary mucinous neoplasm (BD-IPMN): Cysts without high-risk stigmata should undergo CT/MRI every 3-6 mo to establish stability if prior imaging is not available. Subsequently, surveillance should be based on size stratification</p> <p>For cyst size &lt; 1 cm, CT/MRI every 2 yr</p> <p>For cyst size 1-2 cm, CT/MRI every 6 mo for a year, followed by every year for 2 yr and prolong the interval if stable</p> <p>For cyst size 2-3 cm, EUS in 3-6 mo for 1 year. Increase the interval to 1 yr with EUS/MRI as appropriate. Consider surgery in young patients with a need for prolonged surveillance</p> <p>For cyst size &gt; 3 cm, close surveillance alternating MRI with EUS every 3-6 mo. Strongly recommend surgery in young patients</p> <p>In surgically resected IPMN, surveillance is recommended with cross-sectional imaging twice a year for patients with a family history of pancreatic ductal adenocarcinoma, surgical margin positive for HGD and non-intestinal sub-type of IPMN. For all others, every 6-12 mo of cross-sectional imaging is recommended</p>
American College of Radiology (ACR) guidelines <sup>[33]</sup>	<p>Cyst size &lt; 1.5 cm and age &lt; 65 yr: CT/MRI every year for 5 yr, followed by every 2 yr for 4 yr. Stop surveillance if stable over 9 yr</p> <p>Cyst size &lt; 1.5 cm and age 65-79 yr: CT/MRI every 2 yr for a total of 10 yr. Stop surveillance if the cyst is stable for 10 yr</p> <p>If there is interval change and cyst size &lt; 1.5 cm, consider CT/MRI every year or EUS-FNA. EUS-FNA shows a mucinous cyst or indeterminate cyst, CT/MRI every 6 mo for 2 yr, followed by every year for 2 yr and every 2 yr for 6 yr. Stop surveillance if the cyst is stable after 10 yr</p> <p>Any further interval growth of cyst should be referred to surgery for further evaluation</p>

	<p>Cyst size 1.5-1.9 cm with MPD communication: CT/MRI every year for 5 yr, followed by every 2 yr for 4 yr. Stop surveillance if cyst size stable for over 9 yr</p> <p>Cyst size 2-2.5 cm with MPD communication: CT/MRI every 6 mo for 2 yr, followed by every year for 2 yr and subsequently every 2 yr for 6 yr. Stop surveillance if cyst size is stable for 10 yr</p> <p>If there is interval change and cyst size <math>\leq 2.5</math> cm, CT/MRI every 6 mo for 2 yr, followed by every year for 2 yr and subsequently every 2 yr. If cyst size <math>&gt; 2.5</math> cm, consider EUS-FNA</p> <p>If EUS-FNA shows a mucinous cyst or indeterminate cyst, CT/MRI every 6 mo for 2 yr, followed by every year for 2 yr and every 2 yr for 6 yr</p> <p>EUS-FNA is recommended for any mural nodule, wall thickening, dilation of MPD <math>\geq 7</math> mm or extrahepatic biliary obstruction/Jaundice irrespective of cyst size</p> <p>Cyst size 1.5-2.5 cm without MPD communication or cannot be determined: CT or MRI every 6 mo for 2 yr, followed by every year for 2 yr and subsequently every 2 yr for 6 yr. Stop surveillance if cyst size is stable after 10 yr</p> <p>If there is interval change and cyst size <math>&lt; 2.5</math> cm, consider CT/MRI every 6 mo for 1 year, followed by every year for 5 yr and subsequently every 2 yr. If cyst size is <math>&gt; 2.5</math> cm, consider EUS-FNA</p> <p>Cyst size <math>&gt; 2.5</math> cm: If a cyst is a low risk by imaging, consider CT/MRI every 6 mo for 2 yr. If stable after 2 yr, CT/MRI every yr for 2 yr and subsequently every 2 yr for 6 yr. Stop surveillance if stable in cyst size</p> <p>Any interval changes in cyst size, consider EUS-FNA. Any high-risk stigmata like jaundice, enhancing mural nodule, wall thickening and MPD <math>\geq 10</math> mm refer to surgery for evaluation</p> <p>Age <math>\geq 80</math> yr with cyst size <math>\leq 2.5</math> cm: CT/MRI every 2 yr for 4 yr. Stop surveillance if cyst size is stable in size: If there is interval change and cyst size <math>\leq 2.5</math> cm, consider CT/MRI every year. Stop surveillance if the cyst stabilizes or not a surgical candidate; If there is interval change and cyst size <math>&gt; 2.5</math> cm, consider EUS-FNA</p> <p>Age <math>\geq 80</math> yr with cyst size <math>\geq 2.5</math> cm: If low risk by imaging, consider CT/MRI every 2 yr for 4 yr. Stop surveillance if cyst size is stable; If there is interval change in cyst size, consider EUS-FNA</p> <p>High risk (mural nodule, wall thickening, dilation of MPD <math>\geq 7</math> mm or extrahepatic biliary obstruction/Jaundice) features by imaging should be referred to EUS-FNA</p> <p>High-risk stigmata (jaundice, enhancing mural nodule, wall thickening, and MPD <math>\geq 10</math> mm) by EUS or imaging refer to surgery for evaluation</p>
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MCN: Mucinous cystic neoplasm; EUS-FNA: Endoscopic ultrasound-Fine needle aspiration; MRI: Magnetic resonance imaging; IPMN: Intraductal papillary mucinous neoplasm; HGD: High-grade dysplasia; MD-IPMN: Main duct-Intraductal papillary mucinous neoplasm; PD: Pancreatic duct; MPD: Main pancreatic duct.

increased levels of serum CA 19-9 ( $\geq 37$  U/mL), MPD dilation 5-9.9 mm, cyst diameter  $\geq 40$  mm, new-onset diabetes mellitus, acute pancreatitis caused by the cyst, or enhancing mural nodule  $< 5$  mm.

### **ACG guidelines<sup>[30]</sup>**

Referral to multidisciplinary team is recommended for evaluation of surgery with jaundice or acute pancreatitis secondary to the cyst, significantly elevated serum CA 19-9 level, presence of a mural nodule or solid component within the cyst, MPD dilation  $> 5$  mm, focal dilation of PD for MD-IPMN or an obstructing lesion, IPMNs or MCNs  $\geq 3$  cm and the presence of HGD-IPMN or pancreatic cancer on cytology.

### **AGA guidelines<sup>[31]</sup>**

Surgery is recommended for cysts with both a solid component and a dilated PD and/ or concerning features on EUS-FNA positive for HGD/cancer.

### **Revised IAP 2017 guidelines<sup>[32]</sup>**

Absolute indications for surgery include obstructive jaundice in a patient with a cystic lesion of the head of the pancreas, enhancing mural nodule  $> 5$  mm and MPD  $\geq 10$  mm. Relative indications for surgery include cyst  $\geq 3$  cm, enhancing mural nodule  $< 5$  mm, thickened cyst wall, MPD 5-9 mm, an abrupt change in caliber of PD with distal pancreatic atrophy, lymphadenopathy, increased serum level of CA 19-9 and cyst growth rate  $\geq 5$  mm/2 years.

### **ACR guidelines<sup>[33]</sup>**

**Table 3 Cyst fluid analysis**

	<b>Cyst fluid analysis</b>
European guidelines <sup>[28]</sup>	Cyst fluid CEA with cytology, or KRAS/GNAS mutation analysis for differentiating IPMN or MCN from other pancreatic cysts
American College of Gastroenterology (ACG) guidelines <sup>[30]</sup>	Cyst fluid CEA to differentiate IPMNs and MCNs from other cyst types Cyst fluid cytology to assess for HGD or pancreatic cancer when imaging features are alone insufficient for surgery Molecular markers like KRAS or GNAS mutations can help identify IPMNs or MCNs when the diagnosis is not clear
American Gastroenterology Association (AGA) guidelines <sup>[31]</sup>	Cyst fluid cytology is recommended for the evaluation of high-risk features on imaging. The role of molecular markers is not clear and further research is needed
Revised IAP 2017 guidelines <sup>[32]</sup>	Cyst fluid CEA can distinguish mucinous from non-mucinous cysts. CEA level $\geq 192$ -200 ng/mL is 80% accurate for the diagnosis of mucinous cyst <sup>[38,45]</sup> Cyst fluid cytology can be diagnostic but sometimes limited by scant cellularity <sup>[43,44]</sup> Cyst fluid amylase can differentiate benign from malignant MCN and amylase levels are higher in pseudocysts than non-pseudocysts <sup>[45]</sup> . The role of molecular markers like KRAS and GNAS mutations is still evolving
American College of Radiology guidelines <sup>[33]</sup>	Cyst fluid CEA $\geq 192$ ng/mL can help identify a mucinous cyst <sup>[46]</sup> Cyst fluid amylase $> 250$ IU/L suggests pseudocyst <sup>[11]</sup> KRAS and GNAS molecular markers can help differentiate mucinous from non-mucinous cysts <sup>[47]</sup> Cyst cytology can identify dysplastic cells

CEA: Carcinoembryonic antigen; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; GNAS: Guanine nucleotide-binding protein; KRAS: Kirsten rat sarcoma viral oncogene homolog; HGD: High-grade dysplasia.

Absolute indications for surgery include obstructive jaundice with a cyst in the head of the pancreas, enhancing solid component within the cyst and MPD  $\geq 10$  mm in the absence of obstruction. Relative indications include cyst size  $\geq 3$  cm, thickened cyst wall, non-enhancing mural nodule, and MPD  $\geq 7$  mm. The indications of surgery for various PCNs using different guidelines are illustrated in [Table 5](#). Overall, the absolute indications for surgery are consistent among all the guidelines and the cysts with relative indications for surgery can be closely followed with imaging and/EUS-FNA.

## WHERE YOU GO “FIRST” MATTERS?

At MD Anderson cancer center, we get referrals from all over the country and abroad for evaluation of PC. By the time, patients come to us, they have already been seen two or three physicians with the recommendation for surgical resection. The majority of these patients do not need require resection but can be clinically followed with repeat imaging studies. Accurate characterization of the pancreatic cyst is the key in the management of PC. All patients with pancreatic cyst who are referred to MD Anderson cancer center get automatically enrolled in the pancreatic cyst database. There is a team of pancreatic surgeons, advanced endoscopists with expertise in EUS-FNA, oncologists, radiologists, and gastrointestinal pathologists who work closely with a concerted effort in accurately diagnosing and managing PC. Any high-risk features on imaging will be referred for EUS-FNA. If EUS-FNA shows HGD/cancer, the patients will be referred for surgical evaluation. Cyst fluid analysis can help distinguish mucinous from non-mucinous cysts. Surveillance is based on the type, size of the cyst, MPD dilation, and any high-risk features. We use both ACG and revised Fukuoka guidelines in the surveillance of PC.

## CONCLUSION

With the increased incidence of asymptomatic PC on imaging, accurate diagnosis is the key in the management. A multidisciplinary team approach involving advanced endoscopist, pathologist, radiologist, and surgeon is paramount in the comprehensive

Table 4 Endoscopic ultrasound-fine needle aspiration indications

	Endoscopic ultrasound-Fine needle aspiration indications
European guidelines <sup>[28]</sup>	Differentiating mucinous <i>vs</i> non-mucinous Malignant <i>vs</i> benign CT or MRI unclear Only when results are expected to change clinical management
American College of Gastroenterology guidelines <sup>[30]</sup>	Jaundice Acute pancreatitis Significantly elevated serum CA 19-9 Mural nodule A solid component within cyst or pancreatic parenchyma Dilation of MPD $\geq$ 5 mm Focal dilation of PD Cyst size > 3 cm When the diagnosis of cysts is unclear or results will likely alter management Cyst fluid CEA to differentiate IPMNs and MCNs from other cyst types New onset or worsening diabetes Increase in cyst size > 3 mm/yr
American Gastroenterology Association guidelines <sup>[31]</sup>	At least 2 high-risk features Cyst size $\geq$ 3 cm Dilated MPD Solid component
Revised IAP 2017 or revised Fukuoka guidelines <sup>[32]</sup>	Pancreatitis Cyst $\geq$ 3 cm Enhancing mural nodule < 5 mm Thickened/enhancing cyst wall Main duct size 5-9 mm An abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy Lymphadenopathy Increased serum level of CA19-9 Cyst growth rate $\geq$ 5 mm/2 yr
American College of Radiology guidelines <sup>[33]</sup>	Mural nodule Wall thickening Dilation of MPD $\geq$ 7 mm Extrahepatic biliary obstruction/Jaundice

EUS-FNA: Endoscopic ultrasound-Fine needle aspiration; MPD: Main pancreatic duct; PD: Pancreatic duct; MCN: Mucinous cystic neoplasm; CEA: Carcinoembryonic antigen; CT: Computed tomography; MRI: Magnetic resonance imaging; IAP: International association of pancreatology; IPMN: Intraductal papillary mucinous neoplasm.

management of PC. Surgical resection should be selectively offered considering absolute indications, high-risk features on imaging/EUS, and clinical setting of each patient. Surveillance using a cross-sectional imaging or EUS should be individualized based on the cyst type, size, involvement of the main duct, and/or presence of a mural nodule. Lastly, surgical resection should be performed at high volume centers to optimize the outcomes in morbidity and mortality.

Table 5 Indications of surgery for pancreatic cysts

	Absolute indications of surgery	Relative indications of surgery
European guidelines <sup>[28]</sup>	Intraductal papillary mucinous neoplasm: Cytology positive for malignancy/High-grade dysplasia; Solid mass; Jaundice; Mural nodule $\geq 5$ mm; Main pancreatic duct dilation $> 10$ mm  Mucinous cystic neoplasm: Size $\geq 4$ cm  Symptomatic Mural nodule	Cyst growth rate $> 5$ mm/yr  Serum CA 19-9 $> 37$ U/mL  MPD dilation 5-9 mm  Cyst diameter $\geq 40$ mm  New-onset diabetes mellitus  Acute pancreatitis related to IPMN  Mural nodule $< 5$ mm
American College of Gastroenterology guidelines <sup>[30]</sup>	Intraductal papillary mucinous neoplasm or Mucinous cystic neoplasm:  Referral to EUS-FNA/Multidisciplinary; team:  Jaundice  Acute pancreatitis  Significantly elevated CA 19-9  Mural nodule  A solid component in cyst/pancreatic parenchyma  MPD $> 5$ mm  Focal dilation of PD or MD-IPMN  HGD/Pancreatic cancer on cytology	N/A
American Gastroenterology Association guidelines <sup>[31]</sup>	Pancreatic cysts:  EUS-FNA cytology positive for -  HGD/cancer  Both solid component and dilated PD on MRI and EUS	N/A
Revised IAP 2017 or revised Fukuoka guidelines <sup>[32]</sup>	Obstructive jaundice with pancreatic head cyst  Enhancing mural nodule $\geq 5$ mm  MPD $\geq 10$ mm	Pancreatitis  Enhancing mural nodule $< 5$ mm  Thickened/enhancing cyst wall  Main duct size 5-9 mm  An abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy  Lymphadenopathy  Increase in serum level of CA 19-9  Cyst growth rate $\geq 5$ mm/2 yr
American College of Radiology guideline <sup>[33]</sup>	Obstructive jaundice with a cyst in the head of the pancreas  Enhancing solid component within a cyst  MPD $> 10$ mm in the absence of obstruction	Cyst $\geq 3$ cm  Thickened/enhancing cyst wall  Non-enhancing mural nodule  MPD $\geq 7$ mm

IPMN: Intraductal papillary mucinous neoplasm; HGD: High-grade dysplasia; MPD Main pancreatic duct; PD: Pancreatic duct; EUS-FNA: Endoscopic ultrasound-Fine needle aspiration.

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