

## 2016 Pancreatic Cancer: Global view

**Endoscopic approach to the diagnosis of pancreatic cystic tumor**

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**Abstract**

Because of the aging of the population, prevalence of

medical checkups, and advances in imaging studies, the number of pancreatic cystic lesions detected has increased. Once these lesions are detected, neoplastic cysts should be differentiated from non-neoplastic cysts. Furthermore, because of the malignant potential of some neoplastic pancreatic cysts, further differentiation between benign and malignant cysts should be made regardless of their size. Although endoscopic ultrasound (EUS) has a very high diagnostic performance for pancreatic cystic lesions among the various imaging modalities, EUS findings alone are insufficient for the differentiation of pancreatic cysts and diagnosis of malignancy. In addition, cytology by EUS-guided fine-needle aspiration (FNA) has a high specificity but a low sensitivity for diagnosing malignancy in pancreatic cystic tumors. The levels of amylase, lipase, and tumor markers in pancreatic cystic fluid are considered auxiliary parameters for diagnosis of benign and malignant cysts, and a definitive diagnosis of malignancy using these parameters is difficult. Thus, in addition to EUS, cytology by EUS-FNA, and cystic fluid analysis, new techniques based on EUS-guided through-the-needle imaging, such as confocal laser endomicroscopy and cystoscopy, have been explored in recent years.

**Key words:** Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasound-needle aspiration; Pancreatic cystic tumor; Cytology

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**Core tip:** The number of pancreatic cystic lesions detected has increased. Neoplastic cysts should be differentiated from non-neoplastic cysts. Further differentiation between benign and malignant cysts should be made regardless of their size. In addition to endoscopic ultrasound (EUS), cytology by EUS-fine-needle aspiration, and cystic fluid analysis, new techniques based on EUS-guided through-the-needle imaging, such as confocal laser endomicroscopy and

cystoscopy, have been explored in recent years. We reviewed an endoscopic approach to the diagnosis of pancreatic cystic tumor.

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## INTRODUCTION

Because of the aging of the population, prevalence of medical checkups, and advances in imaging studies, the number of incidentally detected pancreatic cystic lesions has increased. Pancreatic cystic lesions include a variety of entities, including non-neoplastic pancreatic pseudocysts, such as those resulting from pancreatitis, and retention cysts, as well as neoplastic pancreatic cysts and solid tumors with cystic degeneration. As differential diagnosis of these lesions is important in the consideration of therapeutic strategies<sup>[1]</sup>, it is essential to differentiate between neoplastic pancreatic cysts, including intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), and serous cystic neoplasm (SCN), and to further determine whether they are benign or malignant<sup>[1]</sup>.

Diagnostic imaging modalities used in the evaluation of pancreatic cystic lesions include abdominal ultrasound (US), contrast-enhanced computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and endoscopic retrograde pancreatography (ERP). US is a non-invasive method but is affected by the presence of gastrointestinal gas, making the evaluation of the entire pancreas difficult. Although CT is superior in depicting solid lesions, radiation exposure and allergic reactions to contrast media, limit its application. MRCP is superior in depicting pancreatic cystic lesions, while EUS is highly valued, as it provides high image resolution despite the presence of gastrointestinal gas, allowing close observation of the entire pancreas. Although ERP is superior in depicting details of the pancreatic duct and allows a pathologic diagnosis by cytology of the pancreatic juice at same time, attention should be paid to pancreatitis as a potential complication of endoscopic retrograde cholangiopancreatography (ERCP). At present, the lesions are comprehensively diagnosed by a combination of these methods. In recent years, EUS, EUS-guided fine-needle aspiration (FNA), contrast-enhanced EUS, and other modalities of interventional EUS, have been especially useful in the accurate differentiation of pancreatic cystic tumors<sup>[1,2]</sup>.

## TRANSPAPILLARY DIAGNOSIS

A transpapillary approach is significant for the diagnosis

of either, main-duct or branch-duct type of IPMNs formed in the pancreatic duct<sup>[3]</sup>. This approach allows to demonstrate the presence of mucus, and is also effective in the diagnosis of concurrent pancreatic ductal carcinoma. However, for the diagnosis of SCNs and MCNs, which generally do not communicate with the pancreatic duct, the transpapillary diagnostic approach not only lacks significance but may also cause pancreatitis after ERCP. IPMN are pancreatic cystic tumors in which transpapillary diagnosis is significant.

## Pancreatic juice cytology

As the pancreatic juice in IPMNs is viscous and often difficult to aspirate, pancreatic juice cytology is used to improve the diagnostic performance of ERCP by allowing the collection of pancreatic juice *via* an implanted endoscopic naso-pancreatic drainage tube. Branch-duct type IPMN, which communicates with the main pancreatic duct, is well indicated for this technique because mucus-containing abundant tumor cells are found in the main pancreatic duct.

IPMNs are high mucous-producing and often well-differentiated adenocarcinomas, even when they are cancerous. Therefore, the diagnosis of this type of tumors using pancreatic juice cytology is difficult. To overcome these limitations, the genetic analysis of pancreatic juice is being studied to aid the objective evaluation of malignancy. Such studies show that tumor markers, including carcinoembryonic antigen (CEA), telomerase activity, matrix metalloproteinase activity, human telomerase reverse transcriptase, mRNA, sonic hedgehog, K-ras, and p-53, present in pancreatic juice may be useful in the assessment of cancer risk in patients undergoing ERP, while complementing pancreatic juice cytology findings<sup>[4-10]</sup>.

## EUS DIAGNOSIS

The differential diagnosis of pancreatic cystic lesions can be made by focusing on EUS findings, *i.e.*, size, number, overall cyst shape, state of cyst walls, and features of cystic contents, as well as the presence of underlying lesions<sup>[11]</sup>. Sedlack *et al*<sup>[12]</sup> classified 34 resected pancreatic cystic lesions into two groups: A group of benign pancreatic cysts, including simple cysts, pseudocysts, and SCNs, and a group of malignant or malignant potential lesions including MCNs, IPMNs, neuroendocrine tumors with necrotic lesions, and cystic adenocarcinomas. Comparison of the diagnostic performance between the 2 groups showed that EUS had a sensitivity, specificity, and diagnostic accuracy of 91%, 60% and 72%, respectively. Song *et al*<sup>[13]</sup> evaluated 75 pancreatic cysts (58 neoplastic pancreatic cysts and 17 pancreatic pseudocysts) using EUS, and showed that, while intracystic debris and pancreatic parenchymal changes were characteristic EUS findings of pancreatic pseudocysts, the presence of septa and nodes were typical of neoplastic pancreatic cysts. Song *et al*<sup>[13]</sup> reported that although EUS is useful in the diffe-

rential diagnosis of pancreatic cystic lesions, it might be insufficient on its own, to completely differentiate pancreatic cysts. In addition, in a multicenter study conducted by Brugge<sup>[14]</sup> to evaluate the performance of EUS in the diagnosis of pancreatic cyst malignancy, low sensitivity, specificity, and diagnostic accuracy values of 56%, 45% and 51%, respectively, were observed. Moreover, Ahamad *et al.*<sup>[15]</sup> demonstrated that the diagnostic accuracy of EUS for pancreatic cysts and non-cystic lesions varied from 40% to 93% among 8 endoscopists, indicating that experience and skills influence the diagnostic performance of this method.

## DIFFERENTIATION OF PANCREATIC CYSTIC LESIONS USING CONTRAST-HARMONIC EUS

Differentiation between neoplastic (IPMNs, MCNs, and SCNs) and non-neoplastic pancreatic cystic lesions is important. Although there are sporadic reports on the use of B-mode imaging for pancreatic cystic lesions diagnosis<sup>[16,17]</sup>, reports on similar studies using contrast-harmonic (CH)-EUS are limited. However, because CH-EUS clearly depicts the internal structure and shape of lesions, it appears to be useful for picking up the characteristic imaging findings of each lesion. Compared to conventional B-mode imaging, CH-EUS facilitates pancreatic duct observation by depicting it as a structure without blood flow. In consequence, communication between a lesion and the pancreatic duct, an important aspect for differentiation of pancreatic cystic lesions, can be easily confirmed. In cases of IPMN in which a structure is observed in the dilated pancreatic duct, differentiation between a mucinous mass or tumor resulting from papillary growth by B-mode imaging, is often difficult. However, the CH mode allows their differentiation according to the presence or absence of blood flow.

## EUS-FNA DIAGNOSIS

In Japan, because of a reported incident of peritoneal metastasis caused by EUS-FNA for IPMN<sup>[18]</sup>, doctors have become reluctant to perform the procedure. However, EUS-FNA is commonly used for the diagnosis of pancreatic cystic tumors worldwide, as well as for the evaluation of pancreatic cystic fluid, in terms of its nature (mucinous or serous), cytology, and measurement of CEA/amylose levels<sup>[19]</sup>.

The nature of the cystic fluid collected by EUS-FNA is important for differentiation of pancreatic cystic tumors. IPMNs and MCNs, or SCNs should be suspected if the fluid is mucinous, or serous, respectively.

The cytology of pancreatic cystic tumors by EUS-FNA, has a high specificity for diagnosis of malignancy similar to that of ERP, albeit with a low sensitivity. Moreover, in cases of multilocular cysts, sufficient specimens may not be collected due to the small diameter of each cyst or

high viscosity of the cystic fluid, which limits its aspiration with a puncture needle. The inability to collect sufficient amounts of cells seems to be the cause of the low sensitivity. The rate of successful collection of specimens required for cytology is reported to be approximately 80%, and the differential diagnostic accuracy for pancreatic cysts ranges from 13%-96%<sup>[12,15,20-26]</sup>. In addition, the diagnosis of malignancy has a specificity of 86%-100% and a sensitivity of 25%-88%. The international guidelines for the differential diagnosis between benign and malignant lesions, therapeutic strategies, and follow-up procedures of main-duct and branch-duct type IPMNs were revised in 2012. According to the revised guidelines, the cytological assessment of especially worrisome features (main pancreatic duct diameter of 5-9 mm and absence of either nodes or growth in main-duct and branch-duct type, respectively) is important. The results of a meta-analysis showed that, despite the high specificity and diagnostic accuracy of cytology, its sensitivity is low, with a possibility of misdiagnosing malignant lesions as benign, concluding that cytology needs to be complemented by the additional measurement of CEA, carbohydrate antigen (CA) 19-9, micro-RNA, *etc.*<sup>[27]</sup>.

Amylase, CEA, and CA19-9 levels in cystic fluid are highly useful for IPMNs, MCN, and SCN differentiation. Amylase levels in cystic fluid are high in IPMNs because they communicate with the pancreatic duct. By contrast, as MCNs and SCNs do not communicate with the pancreatic duct, their amylase levels are typically low. In addition, a cut-off amylase value in cystic fluid set at 250 U/L, has a sensitivity and specificity of 44% and 98%, respectively, for excluding pancreatic pseudocysts from the diagnosis of pancreatic cystic lesions<sup>[28]</sup>.

CEA levels in cystic fluid are useful for differentiation between MCN (including IPMN) and SCN. A CEA cut-off value in cystic fluid of 192 ng/mL, had a 79% diagnostic accuracy for MCN, which was higher than that of 59% using diagnostic imaging by EUS<sup>[22]</sup>. In a cyst containing  $\geq 800$  ng/mL of CEA in cystic fluid, or diagnosed as malignant by cytology, the specificity for diagnosing the cyst as MCN was 98%-100%. Moreover, a CEA level in cystic fluid  $\leq 5$  ng/mL had a 95% specificity for the diagnosis of a pancreatic cyst as benign, of which, 6% were, however, MCNs<sup>[28]</sup>.

A CA19-9 level in cystic fluid  $\leq 37$  U/mL has an accuracy and specificity for diagnosing a pancreatic cystic tumor as benign of 46% and 94%, respectively. CA19-9 is useful for complementing diagnosis of benign and malignant pancreatic cystic tumors<sup>[28]</sup>.

Thus, analysis of amylase, CEA, and CA19-9 levels in cystic fluid improves the ability to differentiate mucinous from serous pancreatic cystic tumors. Because malignant SCN is rare, its reliably diagnosis is important. However, levels of amylase, CEA, and CA19-9 in cystic fluid are reportedly not helpful for differentiation of cancer among MCN<sup>[29]</sup>.

Various attempts have been made to improve the diagnosis of malignancy in pancreatic cystic tumors. As

a reason for the low sensitivity of cystic fluid cytology is the scarcity of cell components in cystic fluid, attempts to collect more cells have been reported. These include, abrasion of cystic wall by brushing<sup>[30]</sup>. Abrasion/puncture of cystic wall with the tip of a puncture needle while cystic fluid is aspirated<sup>[31]</sup>, and direct biopsy of cystic wall with miniature biopsy forceps that can be passed through a puncture needle<sup>[32]</sup>. Although of cystic fluid specimens collected by all of these techniques contain more cell components than those collected by conventional aspiration, they have failed to improve the diagnostic performance for malignancy. This is attributed to the fact that the grade of atypism is not always consistent in the cystic wall itself. If target biopsy of nodular lesions can be performed, diagnostic performance may be improved.

### **Procedural accidents**

While serious complications or procedural accidents associated with EUS-FNA for pancreatic cystic lesions have not been reported, pancreatitis (0.5%-4%)<sup>[33]</sup>, cyst infection (< 1%)<sup>[20,33,34]</sup>, and intracystic hemorrhage (< 1%)<sup>[15,20,35]</sup>, rarely occur. Cyst infections can be prevented by infusion of antibiotics before EUS-FNA or oral administration of antibiotics for 2 to 5 d after puncture, while EUS-FNA can be safely performed using a 22-gauge puncture needle<sup>[15,33]</sup>.

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## **EUS-GUIDED THROUGH-THE-NEEDLE IMAGING OF PANCREATIC CYSTIC TUMORS**

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### **Confocal laser endomicroscopy**

In many reports, confocal laser endomicroscopy (CLE) has been described as useful for virtual biopsy and provides images similar to pathological images during endoscopic observation<sup>[36]</sup>. There are a CLE device that incorporates an endoscope and probe-based CLE (pCLE) in which a probe is inserted through the forceps channel of the endoscope for observation. These devices are reported to be useful for detailed examination of the gastrointestinal tract before therapeutic endoscopy.

### **Needle-based CLE**

A prototype device (Cellvizio AQ-Flex-19<sup>®</sup>, Mauna Kea Technologies, Paris, France) with a diameter smaller than that of pCLE has been developed. This device can be inserted in an EUS-FNA 19-gauge needle and used to perform EUS-guided needle-based CLE (nCLE) for the diagnosis of pancreatic cysts.

The *in vivo* CLE Study in the Pancreas With Endosonography of Cystic Tumors trial<sup>[37]</sup>, compared the findings of EUS-guided nCLE with those of pathological analysis. When the findings of nCLE were classified into 3 categories, *i.e.*, epithelial structure, non-epithelial structure, and intracystic floating components, an abnormal epithelial structure, mainly including papillary projections, was a characteristic finding of mucinous

tumors. In addition, nCLE of IPMNs revealed dark aggregates with high cell density in areas suspected of dysplasia, while blood vessels, which are non-epithelial structures, were seen as white bands in other areas. SCNs, only showed non-epithelial structures, whereas no epithelial structure was observed. Although the specificity of the findings of EUS-guided nCLE was 100%, the sensitivity was low, with a value of 57.9%. According to a report indicating that findings reflecting hypervascular patterns of cystic walls and septa of SCNs are useful, there was no technical problem, whereas it was difficult to puncture lesions of the pancreatic head with a 19-gauge needle<sup>[38]</sup>.

### **Cystoscopy**

Cystoscopy is a diagnostic procedure in which a pancreatic cystic tumor is punctured with a 19-gauge FNA needle, and a SpyGlass probe made of optic fiber directly is inserted into the pancreatic cyst to observe cystic contents and the nature of the cystic wall. According to cystoscopy, the cystic fluid in IPMNs and MCNs is mucus. Regarding the cystic wall, IPMNs have papillary projections or communicate with the pancreatic duct, while MCNs have a smooth cystic wall. However, the cystic fluid of SCNs is clear, while the cystic wall is smooth and has abundant blood vessels.

### **Combination of cystoscopy and nCLE**

In the Diagnosis of Pancreatic Cysts: EUS-guided Through-the-needle Confocal Laser-induced Endomicroscopy and Cystoscopy Trial (DETECT study)<sup>[39]</sup>, the contribution of the cystoscopy and nCLE combination to further improve diagnostic performance, was evaluated. For the diagnosis of mucinous cysts, the specificity of both cystoscopy and nCLE was 100%, whereas their sensitivity was also relatively favorable with values of 71% and 77%, respectively. Furthermore, when these 2 modalities were combined, the specificity remained at 100%, and the sensitivity was elevated to 88%, indicating an improved diagnostic performance. However, in terms of diagnosis of malignancy, the image quality of cystoscopy and nCLE decreased as the diameter of a probe reduced. Therefore, the image quality of this technique is insufficient at present.

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## **CONCLUSION**

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We have described the endoscopic diagnosis of pancreatic cystic tumors. While the diagnosis of benign and malignant cysts is especially important, the diagnostic performance of endoscopy is still insufficient. Further advances, mainly in EUS technology are thus awaited in the future.

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