

Cystic pancreatic lesions, the endless dilemma

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Abstract

Cystic pancreatic lesions involve a wide variety of pathological entities that include neoplastic and non-neoplastic lesions. The proper diagnosis, differentiation, and staging of these cystic lesions are considered a crucial issue in planning further management. There are great challenges for their diagnostic models. In our time, new emerging methods for this diagnosis have been discovered. Endoscopic ultrasonography-guided fine-needle aspiration cytology with chemical and molecular analysis of cyst fluid and EUS-guided fine needle-based confocal laser endomicroscopy, through the needle microforceps biopsy, and single-operator cho-langioscopy/pancreatography are promising methods that have been used in the diagnosis of cystic pancreatic lesions. Hereby we discuss the diagnosis of cystic pancreatic lesions and the benefits of various diagnostic models.

Key Words: Pancreatic cystic lesion; Endoscopic diagnosis; Endoscopic ultrasonography; Cyst fluid markers; Endoscopic ultrasonography-guided fine needle-based confocal laser endomicroscopy; Through the needle microforceps biopsy; Single operator cholangioscopy/pancreatography

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Core Tip: Pancreatic cystic lesions are commonly recognized with increasing frequency and have become a more common finding in clinical practice. Today, there has been an increased incidence in cystic pancreatic lesions that have in turn caused a lot of diagnostic modalities to emerge. We discuss the various methods of the diagnosis of cystic pancreatic lesions and compare these modalities.

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INTRODUCTION

Currently, pancreatic cystic lesions (PCLs) are commonly recognized with increasing frequency and have become a more common finding in clinical practice; their detection rate is rising with the advances in imaging technology, and there is an increased incidence of detection of unsuspected small PCLs[1]. The frequency of detection of pancreatic cysts reported in the literature ranges from 0.7% to 36.7%[2,3].

They comprise a broad spectrum of entities ranging from benign cysts to potentially malignant or malignant cystic lesions[4,5]; they differ greatly in the clinical behavior and malignant potential that give these lesions a diagnostic challenge[1].

The proper diagnosis, differentiation between neoplastic and non-neoplastic PCLs, and staging of these cystic lesions are considered a crucial issue for planning further management[6]. Endoscopic ultrasonography (EUS) and transpapillary diagnosis are the two major endoscopic approaches used. EUS-guided fine-needle aspiration (FNA) cytology, EUS-guided fine needle-based confocal laser endomicroscopy (nCLE), and needle microforceps biopsy are promising methods that have been used in the differential diagnosis of mucinous and non-mucinous pancreatic cysts[7].

The great benefits of EUS in detecting small lesions, making a differential diagnosis, and tumor staging provide a great challenge as many benign and malignant cystic lesions and also inflammatory cysts have a similar endosonographic appearance. Moreover, the permission of the evaluation of cyst fluid obtained by EUS-FNA for the early diagnosis or prediction of prognosis is a major concern to increase the diagnostic accuracy for more proper management[7].

EUS-FNA enables the use of aspirated samples for cytopathology examination and biochemical analyses, which provide an opportunity to further enhance diagnosis and medical decision-making[8] (Figure 1); therefore, the addition of FNA to various imaging modalities has been associated with increasing the diagnostic accuracy of PCLs[9].

The combination of both EUS-FNA findings with cystic fluid tumor markers analysis, along with clinical, radiologic, histologic, genetic, and molecular characteristics, enhances the diagnostic accuracy of PCLs and helps to construct a novel model in the era of cystic pancreatic lesion diagnosis[10].

EUS-guided radiofrequency ablation (EUS-RFA) is now considered an interesting alternative to doing major surgery with high morbidity and mortality for small, mostly benign, pancreatic lesions[11,12].

Owing to the close proximity of the transducer of EUS to the liver, from the transgastric and transduodenal routes, EUS allows good visualization of the liver anatomy and its vasculature by providing detailed images, and this plays a significant role in detecting small-sized liver metastasis from malignant pancreatic lesions, as well as potentially obtaining EUS-FNA with higher diagnostic accuracy[13]. This can be achieved in most liver segments except segment VII and VI which are very difficult to be visualized during EUS examination.

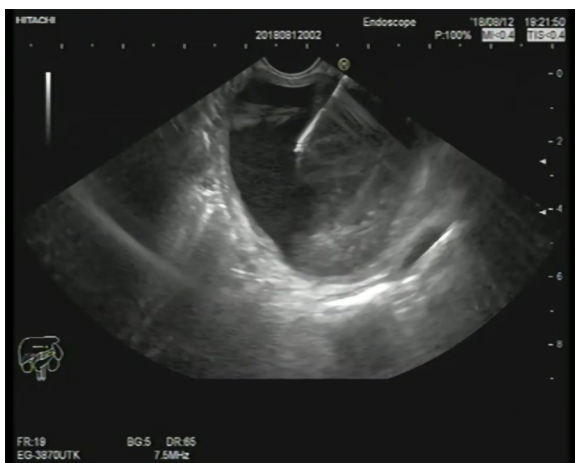


Figure 1 Endoscopic ultrasonography-guided fine-needle aspiration of a pancreatic mucinous cystic neoplasm.

CYSTIC LESIONS OF THE PANCREAS: TYPES, DIAGNOSIS

Pancreatic cysts are classified into inflammatory fluid collections and neoplastic and non-neoplastic pancreatic cysts. They may also be related to other diseases such as polycystic kidney disease or Von Hippel Lindau disease[14].

According to the revised Atlanta classification, inflammatory fluid collections are further categorized into acute peripancreatic fluid collections, pseudocysts, acute necrotic collections, and walled-off pancreatic necrosis[15].

Pancreatic cysts can range from simple cysts to neoplastic ones, so proper diagnosis and management are important. Mucinous cysts (Figure 2), for example, carry unpredictable potential malignant transformation[16]. Various methods are used to diagnose the type of the cystic lesion such as sonographic appearance, cytopathological examination of the cystic fluid, and tumor markers analysis from the cystic fluid.

Some sonographic findings are indicative of malignancy, including a thick wall, septations, and the presence of mural nodules[17]. Still, sonographic appearance or cytopathological examination has a low predictive value for diagnosis[18,19]. Mucin staining, carcinoembryonic antigen (CEA), CA19-9, and amylase levels in the cystic fluid improve the diagnosis of pancreatic cysts[20-22]. A study carried out by Okasha *et al*[10] shows that the highest AUC was that of cystic CEA, with a cutoff value of 160 ng/mL, and that it had a sensitivity of 60.4% and a specificity of 85%. It also mentioned that the best cutoff value for cystic CA19-9 was 1318 U/mL with a sensitivity of 64.1% and a specificity of 68.1%. The cutoff value of the cyst amylase level was 5500 U/L, with 84.2% sensitivity and 37.1% specificity. The sensitivity of mucin staining in detecting mucinous cystic neoplasm (MCN) was 85.45%, and specificity was 86.05% with an accuracy of 85.87%.

Low CEA with cuboidal epithelial cells, clear cytoplasm, and excess glycogen can diagnose serous cystic lesions (Figure 3)[23]. The presence of mucin, ovarian-like stroma with a degree of cell atypia is mainly found with mucinous pancreatic cysts[24]. Intraductal papillary mucinous neoplasm (IPMN) also produces mucin but is connected to the pancreatic duct with various degrees of dysplasia[23]. Malignant transformation in IPMN can be diagnosed by measuring cyst fluid CA19-9[25,26]. CEA > 192 ng/mL can differentiate between mucinous and non-mucinous cysts[27]. Cystic fluid amylase is helpful in diagnosing pseudocysts, especially if above > 250 IU/L[28], but cannot distinguish mucinous from non-mucinous cysts[29]. Table 1 shows different types of pancreatic cysts.

IMAGING DIAGNOSIS OF CYSTIC LESIONS OF THE PANCREAS

Ultrasound, computed tomography (CT) scan, and EUS are the most commonly used imaging modalities in diagnosing cystic pancreatic lesions. Still, magnetic resonance imaging (MRI), particularly T2-weighted images[30], and magnetic resonance cholangiopancreatography have better results in detecting the communication between pancreatic cysts and the pancreatic duct system, in addition to better detection for the

Table 1 Different parameters in different types of pancreatic cysts

Type of cyst	CEA	CA-19-9	Amylase	Mucin stain
Inflammatory pseudocyst	Normal	↑	↑	Negative
Lymphoepithelial cysts	Normal	Normal	Normal	Negative
Serous cystic neoplasms	Normal	Normal	Normal	Negative
Mucinous cystic neoplasm	↑	↑	Normal	Positive
Intraductal papillary mucinous neoplasm	↑/Normal	↑/Normal	↑/Normal	Positive
Solid papillary neoplasm	-	-	-	Negative

CEA: Carcinoembryonic antigen.

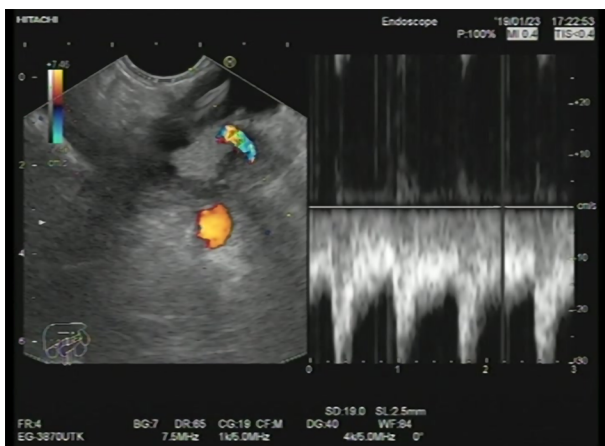


Figure 2 Mucinous cystic neoplasm of pancreatic tail with a mural nodule showing a vessel inside.

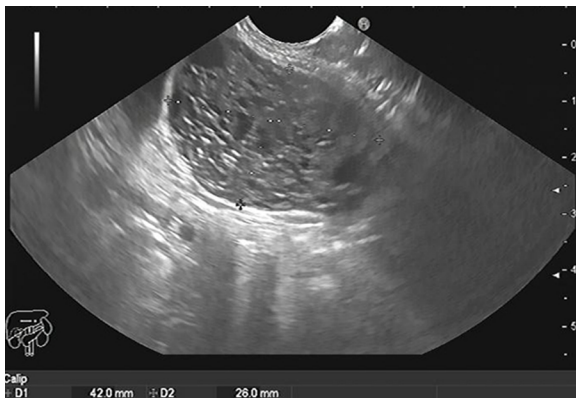


Figure 3 Microcystic serous cystadenoma of the body of the pancreas.

mural nodules[31-35]. Variable data are available for comparing the accuracy of CT and MRI in diagnosing pancreatic cysts. (Figure 4). A study carried out by Visser *et al*[36] concluded similar accuracy for both modalities. Procacci *et al*[37] described successful CT diagnosis for pancreatic cysts in 60% of examined cases. Another study done by Abraham *et al*[38] showed that both modalities carried equal performance accuracy.

Contrast-enhanced ultrasound is one of the most used imaging techniques. According to it, pancreatic lesions are divided into type I, with unilocular cysts; type II, presented as microcystic lesions; type III, with macrocystic lesions; and, lastly, type IV, containing cystic lesions with solid components or an irregularly thickened cystic wall[39]. According to this classification, type I is mostly a pancreatic pseudocyst. Type II represents serous cystadenoma mostly. Type III includes mainly mucinous



Figure 4 Computed tomography shows inflammatory pancreatic pseudocyst.

cystadenoma. Lastly, type IV is for solid pseudopapillary tumors and pancreatic masses with cystic degeneration[40].

Serous cystadenoma usually shows a honeycomb appearance in CT scan and EUS. The presence of central calcification is pathognomonic[41]. It is presented either as oligocystic or microcystic lesion[42] with low malignant potential transformation[43] and can be in any part of the pancreas.

Mucinous pancreatic cysts usually appear as unilocular lesions in a CT scan or EUS with no communication with the main pancreatic duct (MPD)[24]. They mainly appear in the body and tail of the pancreas. They have a high risk of malignant transformation[24] and generally appear in females in the fourth decade with mucin and ovarian-like stroma inside the cystic fluid. The presence of mural nodules during EUS examination favors malignant diagnosis. According to a study by Okasha *et al*[9], during the examination of 77 patients with PCLs, 11 out of 28 had mural nodules during EUS examination, 9 of which were proved to be mucinous cystadenocarcinoma.

IPMNs are divided into main duct, branched duct, or mixed according to the communication with the main or side branch pancreatic ducts[44]. The lesions are mostly solitary and located in the pancreatic head, but multifocal lesions can be detected[45].

ENDOSCOPIC DIAGNOSIS OF CYSTIC LESIONS OF THE PANCREAS

Some pancreatic tumors may exhibit cystic degeneration such as solid pseudopapillary neoplasms, cystic neuroendocrine tumor, and ductal adenocarcinoma[46]. However; the most common are MCNs, IPMNs, serous neoplasms (SCNs), and pseudocysts. In most cases, IPMN is multilocular connected to the pancreatic duct and usually located at the pancreatic head, whereas MCNs are rounded with a thick wall and located at the pancreatic tail. Mural nodules can sometimes be detected in both types of cysts, such as localized epithelial protrusions, and represent high-risk stigmata for both MCNs and IPMNs, but they are not typically found in SCNs. Hence, both IPMNs and MCNs have malignant potential. By contrast, SCNs do not have a predilection toward malignant transformation. Therefore, it is important to determine cyst type and its malignant potential so as to assign a treatment strategy and follow-up plan.

For the diagnosis of cystic lesions of the pancreas, 3 approaches have been described: (1) Diagnosis by EUS that involves morphology of the cyst during EUS, EUS-FNA, EUS-guided fine nCLE, through the needle biopsy (TTNB), and contrast-enhanced harmonic EUS; (2) Endoscopic retrograde cholangiopancreatography (ERCP); and (3) Single-operator cholangioscopy/pancreatocopy.

DIAGNOSIS BY EUS

EUS became an indispensable tool for the diagnosis of cystic pancreatic lesions and the treatment of various nonmalignant pancreatic cysts. Nevertheless, EUS has significant importance in the early detection of small lesions, and the diagnostic accuracy of EUS imaging ranges from 40% to 96% when compared to histopathological examination of the surgical specimen[16].

In a single prospective study, the sensitivity and specificity were 56% and 45%, respectively. For EUS morphological diagnosis, by differentiating mucinous from non-mucinous cysts, the overall accuracy therefore lowered to 51%[22]. In contrast, EUS was superior to CT for detecting lesions, especially those less than 2 cm in size (83% *vs* 33%)[47].

In addition, EUS was equivalent to MRI in detecting communications of the PCLs to the MPD, thus differentiating IPMNs from MCNs and SCNs[48]. Furthermore, Binmoeller *et al*[47], in their consensus guidelines, recommended initial evaluation of IPMNs by EUS regardless of the presence or absence of high-risk stigmata or worrisome features in CT or MRI. In that study, the diagnostic accuracy was 100% when compared to ultrasound, CT, or MRI, which showed a rate of detection of malignant IPMNs at 47%, 53%, and 53%, respectively. Additional reports depicted that EUS is the modality of highest sensitivity for detecting mural nodules in malignant IPMNs[49-51].

EUS-FNA and cyst fluid analysis

Typically, the morphological features of cystic pancreatic lesions are not an independent factor in differentiating malignant from nonmalignant lesions. In addition, recent reports concluded that the appearance of PCLs during EUS evaluation was not sufficient in predicting their malignant potential[52,53].

In their study that included 77 patients with PCLs, Okasha *et al*[9] conducted FNA guided by either EUS or abdominal ultrasound for over 2 years. As a result, 28 (39.3%) had MCN, and 11 had mural nodules on EUS examination. Nine were proved to be mucinous cystadenocarcinoma, and 2 were diagnosed as IPMN, representing 81.8% of all cases of mucinous adenocarcinoma and 28.6% of all cases of IPMN, respectively. CEA was analyzed in 62 patients (80.5%). The cutoff value of 105 ng/dL showed a statistical difference between mucinous and non-mucinous lesions with a sensitivity and specificity of 80% and 77%, respectively. The reported accuracy was 78% for mucinous lesions. In addition, CA19-9 did not add much in differentiating neoplastic from non-neoplastic lesions. By contrast, the accuracy of positive mucin staining in differentiating between mucinous and non-mucinous, as well as neoplastic and non-neoplastic lesions was 91% and 80%, respectively. On the whole, the afore mentioned study concluded that cyst fluid analysis increases the yield of diagnostic accuracy of the PCL when there is insufficient clinical and poor morphological data using different imaging modalities[9].

In their study, Hawes *et al*[54] had depicted the essential role of EUS-FNA of the cyst fluid and its analysis regarding CEA, amylase, and cytology for the diagnosis of indeterminate cysts whose potential nature could not be predicted by imaging alone. On the other hand, cyst wall sampling using EUS-FNA may increase the diagnostic yield by 37%[55].

In the meantime, EUS-FNA shows the highest utility for high-risk stigmata for the malignant potential of PCLs, namely mural nodule or mass lesion, cyst size > 3 cm, or MPD dilation during EUS evaluation[52,56-62].

Molecular analysis of cyst fluid has been proposed to increase the diagnostic yield of PCLs. Typically, KRAS mutation analysis has increased the diagnostic accuracy of IPMNs to 81%[63]; when combined with CEA, it increased its sensitivity to 84% for mucinous cysts[64].

An international, multi-institution survey of the use of EUS in the diagnosis of PCLs

A committee member of the International Society of EUS Task Force conducted and drafted a multicenter survey-based study. This survey was distributed among 60 EUS experts in their centers around the world, this survey discussed the role of FNA in cystic pancreatic lesions, the analysis of cyst fluid and its role in differentiating specific types of various PCLs, and the bleeding risk that may complicate this procedure. It has been concluded that the utility of EUS diagnosis of PCLs based on the morphology is limited, but when combined with other imaging modalities such as CT or MRI, as well as FNA, it will lead to augmentation of the diagnostic yield and increased sensitivity and specificity of EUS as a diagnostic tool[7].

EUS-guided fine nCLE

Confocal laser endomicroscopy (nCLE) technology has recently been added as a diagnostic tool for PCLs evaluation. It permits visualization of the epithelial lining inside the cyst. In addition, IV fluorescein can be used during EUS-nCLE to further display the blood vessels supplying the cyst as well as other structures such as mural nodules[65].

Furthermore, each cyst type has a characteristic pattern when being visualized during EUS-nCLE. For instance, IPMN has finger-like projections and branched vascularity, whereas MCNs are lined by multiple epithelial layers. Typically, SCNs appear as a densely arranged superficial network of capillary vessels, whereas pseudocysts and SPENs appear as lightly colored inflammatory cells against a dark background and nets of dark cells separated by blood vessels[66].

INSPECT, DETECT, CONTACT-1 and -2, and INDEX trials are recent studies that validated the safety and feasibility of EUS-nCLE and its ability to augment the yield diagnosis of PCLs. In the most recent CONTACT-2 study, which included 78 patients, the sensitivity for EUS-nCLE to diagnose premalignant PCLs from benign lesions was 96%, and specificity was 95%, whereas for positive predictive value, the negative predictive values were 98% and 91%, respectively[67].

By contrast, in their study that evaluated the inter-observer agreement of EUS-nCLE, Karia *et al*[68] concluded that the inter-observer agreement and accuracy were low and that further studies are needed to validate EUS-nCLE as an accurate diagnostic tool.

Contrast-enhanced EUS

Contrast-enhanced EUS (CE EUS) can be a useful and substantial tool in differentiating between different types of pancreatic cystic neoplasms (PCNs). Recently, it has been widely applied. The CE EUS agent is a type of contrast that does not interfere with the interstitial space. As a result, it has the ability to reflect the microcirculation of tissues required for clinical correlation and diagnosis of various PCNs. Recent studies proved that CE EUS can differentiate solid pancreatic lesions of different origins. In their study, Zhong *et al*[69] revealed that CE EUS had an added accuracy in comparison to CT/MRI and fundamental B-mode EUS (CEEUS *vs* CT: 92.3% *vs* 76.9%; CE EUS *vs* MRI: 93.0% *vs* 78.9%; CE EUS *vs* fundamental B-mode EUS: 92.7% *vs* 84.1%) and that was consistent with previous reports.

TTNB

TTNB is a method used for better tissue acquisition in pancreatic cysts, which increases the diagnostic yield. Taking a biopsy from the wall of the cystic lesion ensures a better cytological gain. TTNB was first used in 2010 by Aparicio *et al*[70], associated with a spyglass fiber optic probe. Then, Moray microforceps were introduced in the field and proved better histological diagnosis[71,72].

The cyst is firstly punctured by a 19-gauge EUS-FNA needle. The forceps are then introduced through the fine needle, trans-gastric or trans-abdominal, to reach the wall of the cyst. The jaws of the forceps are pushed openly against the cystic wall and then closed to be pulled back, causing tenting. Crinò *et al*[73] recommended 3 passes per patient for adequate tissue acquisition and one bite with a “tent sign” for effective grip by the forceps. Yang *et al*[74] suggested 3 bites per pass, with a total of 3 passes for each case.

Technical failure is attributed to loss of echoendoscope flexibility when both the needle and forceps are introduced or when the site of puncture is difficult. Basar *et al*[75] recorded failed biopsy in 9.6% of the cases. Aparicio *et al*[70] attributed inadequate material to clots in 10 cases and amorphous materials in another 5 investigated cases. Kovacevic *et al*[76] linked failure to difficult transgastric puncture and difficult manipulation with a maximally flexed echoendoscope.

DIAGNOSIS BY ERCP

ERCP is not routinely required for the evaluation of PCLs. Nevertheless, duodenoscopy may reveal some specific findings in the main-duct IPMN, such as mucinous material flowing out of the patulous pancreatic duct (Fish Mouth appearance), which is seen in 20% to 55% of patients with main-duct IPMNs and is considered a pathognomonic finding for this type of IPMN[77-80].

Pancreatoscopy is an emerging alternative for direct visualization of stones, tumors, and mucus, and when combined with an intraductal ultrasound, its accuracy in differentiating between benign and malignant IPMN reached 88% in one study[77].

ERCP-guided tissue acquisition, whether by brush cytology, biopsy specimens of fixed filling defects or strictures, or random biopsy specimens of dilated duct walls, is used for the evaluation of PCLs. Although ERCP tissue sampling has a relatively low diagnostic yield, transpapillary biopsy with standard or pediatric-sized forceps resulted in a diagnosis of 11 out of 13 patients with IPMN in one study[78].

Pancreatoscopy using a video scope with narrow-band imaging or *via* a fiberoptic probe has been described in several reports to acquire tissue or cytology[81-84].

SINGLE-OPERATOR CHOLANGIOSCOPY/PANCREATOSCOPY

A mother-baby endoscope was used for a while during pancreatobiliary examination but had many problems. Single-operator cholangioscopy/pancreatoscopy has succeeded in overcoming the problems faced by the mother-baby endoscope: high cost, fragile baby scope, and absence of an irrigation channel. In addition to that, single-operator cholangioscopy/pancreatoscopy has a disposable access catheter for reusable optic probe[85]. A microforcep can be introduced to gain a specimen for histopathological examination[86,87]. A study was done to evaluate the benefit of using single-operator cholangioscopy/pancreatoscopy in diagnosing IPMN with 100% sensitivity and specificity for detecting the malignancy, as well as determining the operative excision line in 3 patients[84]. Another case report for a 74-year-old man with chronic pancreatitis and marked weight loss was diagnosed by a single-operator cholangioscopy/pancreatoscopy with IPMN[88].

We demonstrated a simplified flow chart for the diagnosing of PCLs as shown in Figure 5.

EUS-RFA

RFA through a 19G needle using a monopolar probe has been recently described for the management of PCLs. It has been considered a safe and effective procedure that depends on thermal ablation and induces coagulative necrosis of thermosensitive pancreatic tissue[89-91].

In their study, Pai *et al*[91] conducted RFA ablation on 8 patients, where 6 had a PCN and 2 had a cystic neuroendocrine tumor in the head region. It was concluded that EUS-RFA is a safe procedure and that the response rate demonstrated a 100% resolution of PCNs in most cases[92].

By contrast, potential adverse events may arise as a result of the effect of thermal injury, which can lead to biliary leakage and pancreatic and vascular injury[78]. Nevertheless, the data of PCNs' EUS-RFA are limited to a few human case series and animal data, and an ongoing Phase II multicenter trial of EUS-RFA has been conducted to evaluate the outcomes of the pancreatic cyst at 12 mo following cyst RFA[93].

THE FUTURE RESEARCH DIRECTIONS IN THE DIAGNOSIS OF CYSTIC PANCREATIC LESIONS AND THE ROLE OF MOLECULAR ANALYSIS OF PANCREATIC CYSTIC FLUID

Testing for mutations related to pancreatic malignancies increases the diagnostic accuracy of cystic pancreatic lesions[62,94-100]. The routine molecular analysis of *KRAS*/*GNAS* mutations gives high sensitivity and specificity, reaching 90% in detecting mucinous lesions[101-104]. *KRAS* mutations still do not grade the level of malignancy. Springer *et al*[105] concluded in their study that mutations in the von Hippel-Lindau (*VHL*) gene (3p35), with a loss of heterozygosity at gene locus on chromosome 3 and chromosome 3p aneuploidy, were detected in approximately 67% of serous cystic adenomas.

A study carried out by Arner *et al*[106] mentioned that "The addition of DNA molecular analysis alters the clinical management of PCLs most often when CEA levels are intermediate (45-800 ng/mL) or when no CEA concentration is available".

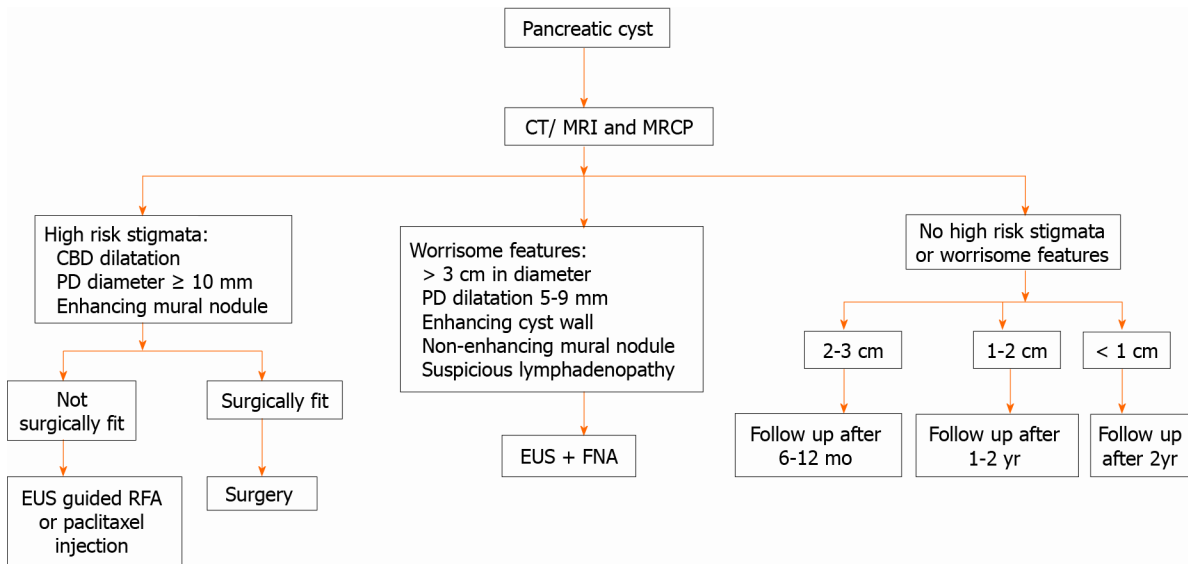


Figure 5 Approach to a patient with a pancreatic cyst. CT: Computed tomography; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; CBD: Common bile duct; PD: Pancreatic duct; EUS: Endoscopic ultrasonography; RFA: Radiofrequency ablation; FNA: Fine-needle aspiration.

GNAS mutations alone can be detected in up to 66% of mucinous neoplastic lesions, and their detection may reach 96% of cases when combined with KRAS mutations [107]. They were also found in 100% of IPMN cases with sensitivity and specificity of 89% and 100%, respectively, for the detection of a mucinous cyst[108].

Other investigated mutations include TP53 mutations, deletions in p16/CDKN2A, SMAD4, mutations in TP53, PIK3CA, and/or PTEN. They are highly sensitive for IPMN[108]. According to a systematic review by Zhang and Pitman[109], although molecular testing is not an alternative to cytological and chemical testing, it can still add value to the diagnostic yielding.

Studies using DNA analysis of cyst fluid seem to be promising but require further attention.

The last randomized clinical studies discussing the radiological and imaging modalities of PCLs are shown in Table 2[108,110-120]; however further studies are warranted not only to improve diagnostic ability but also determine a clear strategy for the use of novel endoscopic techniques for the diagnosis of PCLs.

CONCLUSION

The real clinical challenge in the management of cystic pancreatic lesions is to identify those patients who should undergo pancreatic resection for early non-metastatic cancer and high-risk precancerous cystic lesions while appropriately observing those patients with limited or no potential for malignant transformation. In the context of many aspects of the EUS management of PCLs, available data are currently insufficient to make evidenced-based decisions.

In conclusion, by combining the use of EUS modalities with cystic fluid tumor markers, analysis constructs a novel diagnostic model for PCLs. Also, it indeed highlights that the accurate diagnosis of PCLs requires a well-experienced multidisciplinary and multimodal team approach, side by side with the integration of clinical findings, imaging, cytology, cyst fluid analysis, and molecular testing.

Table 2 The last randomized clinical studies in the radiological and imaging modalities of pancreatic cystic lesions

Ref.	Country	Sample size	Study period/design	Aim of study	Conclusion
Singhi <i>et al</i> [108], 2018	Pittsburgh	595	2014-2017/prospective	Evaluation of preoperative pancreatic cyst fluid (PCF) DNA testing	Preoperative next-generation sequencing of PCF for <i>KRAS</i> / <i>GNAS</i> mutations is highly sensitive for IPMNs and specific for mucinous PCLs. In addition, the combination of <i>TP53</i> / <i>PIK3CA</i> / <i>PTEN</i> alterations is a useful preoperative marker for advanced neoplasia
Basar <i>et al</i> [75], 2018	United States	42	2015-2016/retrospective	Comparison between the tissue acquisition and diagnostic tissue yield of microforceps biopsy (MFB) with cyst fluid cytology	The cyst tissue acquisition yield for MFBs was 90%. Although cytology of cyst fluid and MFB were comparable in distinguishing mucinous and nonmucinous cysts and detecting cysts at high risk for malignancy, MFB was far superior to cytology for providing a specific cyst diagnosis
Kovacevic <i>et al</i> [76], 2018	Multicenter	28	NR/retrospective	Evaluation of the use of EUS-guided MFB in diagnosing pancreatic cystic lesions in a multicenter clinical setting	The use of the microforceps is feasible with acceptable rates of technical and clinical success
Mittal <i>et al</i> [110], 2018	United States	27	2016-2017/retrospective	Assessment of the technical feasibility, diagnostic yield, and safety of EUS-guided MFB for PCLs	MFBs were associated with high technical success, and an excellent safety profile and may be a useful adjunctive tool, complementing existing EUS-FNA sampling protocols for PCLs
Zhang <i>et al</i> [111], 2018	United States	48	2016-2017/retrospective	Comparing the diagnostic performance of the MFB with the current conventional analysis of PCF	PCF analysis and MFB have comparable performance in distinguishing between mucinous and non-mucinous cysts and for detecting high-risk cysts. However, MFB was found to be superior for diagnosing specific cyst subtypes, thus adding a significant value to preoperative patient management
Cheesman <i>et al</i> [112], 2019	United States	41	NR/retrospective	Comparing the diagnostic outcomes and changes in clinical management resulting from MFB and nCLE use in PCL	The combination of cyst fluid cytology/chemistry along with MFB and/or nCLE results in a significantly higher rate of a specific PCL diagnosis and has a major impact on changing clinical management decisions including need for continued surveillance or surgery. MFB and/or nCLE should thus be utilized with standard cyst fluid cytology/chemistry when performing EUS-FNA of PCL
Crinò <i>et al</i> [73], 2019	Italy	61	2016-2018/prospective	Evaluation of the diagnostic yield of EUS-guided through-the-needle MFB sampling of pancreatic cystic lesions according to the number of macroscopically visible samples retrieved	Two TTNB macroscopically visible specimens reached 100% histologic adequacy and a specific diagnosis in 74% of patients. The collection of a third specimen did not add any additional information and should be avoided to possibly decrease the risk of adverse events
Robles-Medrandá and Olmos[113], 2019	Ecuador	36	2013-2018/retrospective	Defining the role of through-the-needle technologies such as nCLE and EUS- through-the-needle MFB in the diagnosis of pancreatic cyst malignancy	EUS-through-the-needle direct intracystic MFB and nCLE improves malignancy detection in pancreatic cysts
Samarasena <i>et al</i> [114], 2019	United States	15	NR/retrospective	Reporting the technical success and safety of EUS-guided through the needle biopsy (TTNB) for pancreatic cystic lesions	This technique has the potential to improve the diagnostic yield of EUS-FNA for pancreatic cystic neoplasms
Vestrup Rift <i>et al</i> [115], 2019	Denmark	27	2016-2017/retrospective	Analysis of the results of next-generation sequencing of microbiopsies from pancreatic cysts	Next-generation sequencing of microbiopsies may have the potential to improve diagnostic decision-making
Yang <i>et al</i> [116], 2019	United States	114	2016-2018/prospective	Comparing the yield of tissue acquired with EUS-guided TTNB with that of samples collected by EUS-guided FNA, and the accuracy of analysis of each sample type in the diagnosis of mucinous PCLs	TTNB collection of tissues for histologic analysis is safe and feasible, with an acquisition yield of 83.3%. Histologic analysis of samples collected by TTNB identified a larger proportion of mucinous PCLs compared with cytologic analysis of samples collected by FNA-even among samples categorized as equivocal, based on the level of carcinoembryonic antigen (CEA)
Wilen <i>et al</i> [117], 2019	United States	30	2016-2018/retrospective	Evaluation of the feasibility and added value of cyst wall biopsy using micro forceps in the diagnosis of pancreatic cysts	Cyst wall biopsy was able to make the diagnosis in 44% of cases where cytology was non-diagnostic and in 64% of cases when composite fluid markers and cytology was non-diagnostic. The high rate of histologic and IHC evaluation suggests that it offers

Krishna <i>et al</i> [118], 2020	United States	144	2015-2018/ Prospective	Comparing the accuracy of EUS with nCLE in differentiating mucinous from non-mucinous PCLs with that of measurement of CEA and cytology analysis	the potential to incorporate tissue-based biomarkers in the diagnosis and management of pancreatic cysts Analysis of cysts by nCLE identified mucinous cysts with greater accuracy than measurement of CEA and cytology analysis. EUS with nCLE can be used to differentiate mucinous from non-mucinous PCLs
Keane <i>et al</i> [119], 2019	United Kingdom	56	2014-2016/ prospective	Defining the safety and efficacy of nCLE in diagnosis of indeterminate PCL	EUS-nCLE under conscious sedation in the day case setting is safe and provides additional information to standard EUS-FNA for diagnosing indeterminate PCL
Napoleon <i>et al</i> [67], 2019	France	78	2013-2016/ prospective	Evaluation of the diagnostic performance of nCLE for large single non-communicating PCLs using surgical histopathology or EUS-FNA cytohistopathology as a reference diagnosis	nCLE had excellent diagnostic performance that surpassed that of CEA and EUS for the diagnosis of large single non-communicating PCLs. The nCLE procedure should be considered in patients with indeterminate PCLs to ensure a more specific diagnosis
Cheesman <i>et al</i> [120], 2020	United States	44	2016-2018/ retrospective study	Comparing the diagnostic outcomes and changes in clinical management resulting from MFB and nCLE use in PCLs	MFB and nCLE led to significant improvements in specific PCL diagnosis, which in turn has major impacts in clinical management

IPMN: Intraductal papillary mucinous neoplasm; PCL: Pancreatic cystic lesion; EUS: Endoscopic ultrasonography; FNA: Fine-needle aspiration; NR: Not reported; nCLE: Needle-based confocal laser endomicroscopy; IHC: Immunohistochemistry.

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