

Pancreatic cystic lesions: How endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle

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Abstract

Cystic lesions of the pancreas are being diagnosed with increasing frequency, covering a vast spectrum from benign to malignant and invasive lesions. Numerous investigations can be done to discriminate between benign and non-evolutive lesions from those that require surgery. At the moment, there is no single test that will allow a correct diagnosis in all cases. Endoscopic ultrasound (EUS) morphology, cyst fluid analysis and cytohistology with EUS-guided fine needle aspiration can aid in this difficult diagnosis.

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Key words: Pancreatic cystic lesions; Endoscopic ultrasound; Endoscopic ultrasound fine needle aspiration

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INTRODUCTION

A search on Medline with the key-words “pancreatic cyst” would find 7074 results, at the time of writing. Why so much interest? There are three answers to this question.

Firstly, there has been an increase in the diagnosis of these lesions, itself a result of improvements in imaging techniques, such as multidetector computerized tomography (MDCT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). From an autoptic point of view, these lesions are very common. About a quarter of examined pancreases show cystic lesions, 16% of which contain atypical epithelium and 3% high grade dysplasia^[1]. Currently, about 1% of patients in hospitals receive, often accidentally, a diagnosis of a pancreatic cystic lesion^[2,3]. During imaging tests (MDCT, MRI, EUS) for other reasons, between 13% and 20% of exams will show a pancreatic cystic lesion (PCL)^[4] and, more importantly, most of these lesions (90%) are neoplasms with premalignant or malignant features and not pancreatic pseudocysts^[5].

Secondly, pancreatic cystic lesions are a large group of varying entities, with a wide variability of biological behavior, from benign to borderline to malignant (Table 1).

Thirdly, and most importantly, until now there has not been a unique test accurate enough to make a differential diagnosis in all of these lesions.

This last point is the focus of this review. We cannot, in fact, make the right decision for our patients if

we are not able to determine exactly what kind of lesion we are studying and so predict the likelihood of developing a malignancy. In the last 10 years we have seen enormous improvements in our diagnostic arsenal. Radiological diagnostic modalities have seen the advent of new CT scans, the emergence of MRI with the help of cholangio-pancreato-RM and, last but not least, the diffusion of EUS, with the possibility of fine needle aspiration (FNA) and analysis of the intracystic fluid. In this review, we will analyze these diagnostic modalities, with particular attention on the EUS aspect of pancreatic cystic lesions, in order to draw some possible and plausible conclusions on the state of the art.

DIAGNOSIS OF PANCREATIC CYSTIC LESIONS

Epidemiological and clinical aspects

Firstly we focus on the prevalence of the different PCLs. Serous cystadenoma neoplasm (SCN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) represent about 90% of all pancreatic cystic neoplasms. These lesions, together with pancreatic pseudocysts (PP), are responsible for 90% of all pancreatic cystic lesions^[5-8]. Knowing this, we focus more on these lesions in our diagnostic reasoning.

As in every diagnostic work up in medicine, we start with epidemiological and clinical aspects that in the case of PCLs offer several important indications (Table 2).

SCN represents 32%-39% of all cystic neoplasms^[2,9], with a peak of incidence at 62 years of age (although the range is quite wide), a slight prevalence in females (3-4:1)^[10] and a slight preference for the pancreatic head (50%)^[11]. It is usually asymptomatic unless it is larger than 4 cm, in which case the symptoms are caused by the mass effect. Of the thousands of reported cases in the literature, there are only 26 reported cases of malignancy^[12], so it can often be considered a benign lesion.

IPMN represents 21%-33%^[2] of all pancreatic cystic neoplasms, although it is likely that its prevalence is greater because of an increase in the diagnosis of small branch duct lesions, particularly in elderly patients. IPMN can involve the main pancreatic duct (MD-IPMN), the branch pancreatic duct (BD-IPMN) or both (MIX-IPMN), although in about 20% of cases such a distinction is not possible^[13-15]. In the differential diagnosis of other pancreatic cystic lesions, however, we have to take BD-IPMN into consideration because the classic aspects of MD-IPMN do not require a differential diagnosis with other pancreatic cysts but rather with chronic pancreatitis. There is a slight prevalence in males (60%), with a mean age 65 years, although it can also affect young patients. The most common localizations are the head of pancreas, most often in the uncinate process^[15]. Most patients are asymptomatic^[16]. When associated with symptoms, IPMN can present with pain similar to chronic pancreatitis, weight loss, jaundice, steatorrhea, diabetes or intermittent acute pancreatitis, which is the sentinel symptom

Table 1 Cystic lesions of the pancreas^[19] (reprinted with permission of Dr. Parra-Herran CE)

Cystic lesions of the pancreas
Non-neoplastic cysts (30%-40%)
No lining
Inflammatory pseudocyst
Paraduodenal wall cyst
Infection-related cyst
True lining
Mucinous non-neoplastic cysts (mucocèles, retention cysts)
Cystic hamartoma
Enterogenous (congenital, duplication) cyst
Endometriotic cyst
Lymphoepithelial cyst
Squamous cyst of pancreatic ducts
Others (unclassified)
Neoplastic cysts (60%-70%)
True lining
Mucinous lining (30%)
Intraductal papillary mucinous neoplasm (20%)
Mucinous cystic neoplasm (10%)
Serous lining (20%)
Serous cystadenoma (microcystic, oligocystic)
Von Hippel-Lindau-associated pancreatic cyst
Serous cystadenocarcinoma
Squamous lining (< 1%)
Epidermoid cyst within intrapancreatic accessory spleen
Dermoid cyst
Acinar cell lining (< 1%)
Acinar cell cystadenoma
Acinar cell cystadenocarcinoma
Endothelial lining (< 1%)
Lymphangioma
Solid tumors with cystic change (5%)
Solid pseudopapillary tumor
Ductal adenocarcinoma with cystic change
Neuroendocrine tumor with cystic change
Other invasive carcinomas with cystic change
No lining (< 1%)
Mesenchymal neoplasms with cystic change
Others (unclassified)

in 15% of cases, both in MD and BD-IPMN^[17], due to obstruction of the pancreatic duct with mucin.

The risk of malignancy is very high (mean 70%) in MD-IPMN but low in BD-IPMN (mean 25%) and virtually nonexistent in the absence of risk factors, which are clinical symptoms, mural nodes, cyst size > 3 cm, main pancreatic duct dilation over 6 mm and malignant cytology^[18].

With these first two kinds of pancreatic cystic lesions, there are essentially no clinical and demographic aspects that are of real use for diagnosis.

The frequency of MCNs is reported to range from 10% to 45%^[2], although the real incidence is likely less than that of serous cystadenoma and IPMN^[8,19]. MCNs are present almost exclusively in females (95%), with a mean age of 53 years (range 19-82 years) and located in 95% of cases in the body-tail of the pancreas^[17,18,20,21]. Gender and localization are very important characteristics in the differential diagnosis of pancreatic cystic lesions because they have a high negative predictive value for MCNs.

Table 2 Major features of four most common cystic lesions

Feature	SCN	MCN	IPMN	Pseudocyst
Prevalent age	Middle aged	Middle aged	Elderly	Variable
Sex	F > M	F ¹	M > F	M > F
Alcohol abuse	No	No	No	Yes
History of pancreatitis	No	No	Frequent	Yes ¹
Location	Evenly	Body-tail ¹	Head	Evenly
Malignant potential	Very rare	Moderate to high	Low to high	None

¹Mark the most useful epidemiological and clinical information (printed with permission of Dr. M Raimondi). SCN: Serous cystadenoma neoplasm; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm.

Regarding potential malignancy, these lesions certainly have to be considered potentially evolutive. The Sendai International Guidelines^[18] recommend resection of all these lesions, although a recent report^[21] on 163 resected MCNs showed only 5.5% *in situ* carcinoma and 12% truly invasive carcinoma, less than previously reported, and all malignant lesions were at least 40 mm in size or with nodules.

Pancreatic pseudocysts are quite common, with some reports^[22] indicating that they comprise up to 70% of all cystic lesions. However, there are now a number of non-inflammatory small cystic lesions diagnosed with the widespread use of imaging. PPs are slightly more prevalent in males and age is variable. They are evenly distributed in the gland, although the important point is that they are rarely asymptomatic. To formulate a suspicion of pseudocyst, there will almost always be a history of acute or chronic pancreatitis, or at least there will be imaging from CT, MRI or EUS compatible with chronic pancreatitis and a history of alcohol abuse, trauma, recent surgery or family history of pancreatitis. It is now accepted that in patients with no history of acute or chronic pancreatitis, a strong work-up should be done to exclude possible neoplastic cystic lesions before suspecting PPs^[22,23].

Finally, although some demographic and clinical characteristics are suggestive of specific lesions and have to be taken into account in the diagnostic evaluation, these characteristics are not sufficient by themselves for a definitive diagnosis in all such lesions.

Imaging characteristics

CT and MRI are the two radiological techniques used for the diagnosis of pancreatic cystic lesions. CT is often the first modality in the diagnosis of these lesions, which are usually detected during exams done for other reasons. The multidetector row CT gives a very good image of the lesions, clearly showing the lesions and the rest of pancreatic parenchyma^[24-26]. Some characteristics, such as calcification, can be seen only with this modality. However, a recent review of diagnostic accuracy of CT showed a range of between 20% and 90%^[27].

MRI with cholangiopancreatography (MRCP) allows

optimal depiction of the internal features of pancreatic cysts, such as septa, cyst contents such as debris, as well as the pancreatic ductal system and its connection to the cyst^[26,28-31].

A classification system of cyst morphology^[32] has been proposed for narrowing the differential diagnosis and improving the diagnostic yield. Pancreatic cysts can be classified into four subtypes: (1) unilocular cysts; (2) microcystic lesions; (3) macrocystic lesions; and (4) cysts with a solid component. Although this classification is useful, it cannot by itself be used as a final solution for differential diagnoses because of the overlap of morphological aspects of different lesions, especially in small cysts (< 3 cm).

Accuracy of CT and MRI in characterizing cystic pancreatic masses for malignancy has been proven but they have only limited accuracy for the diagnosis of specific lesions (less than 50%)^[33,34].

A study of 136 resected patients with incidental pancreatic cysts showed that, on cross sectional imaging (CT, MRI or both), diagnosis was correct in only 63% of cases^[14].

Regarding the indications of 18-fluorodeoxyglucose positron emission tomography (PET) in PCLs, a study showed that it is more accurate than the International Consensus Guidelines in distinguishing benign from malignant (invasive and non-invasive) IPMNs^[35] but it has no role in determining specific diagnosis of PCLs and there are no studies comparing PET with other diagnostic tools (such as EUS-FNA).

In conclusion, both CT and MRCP are helpful in characterizing cystic pancreatic lesions, with an acceptable accuracy in determining malignancy but low accuracy in determining a specific diagnosis.

More studies are needed in order to determine the role of PET in the management of PCLs.

EUS in cystic lesions

EUS has many features that make it, hypothetically, the ideal tool for evaluating pancreatic cystic lesions. The strict proximity between the transducer and the lesions allows for a very precise definition of the structural component of the cysts and some components of pancreatic cysts, such as the honeycomb pattern or small mural nodules, are better visualized with EUS than with other modalities.

With EUS, it is possible to define cystic localization, size, locularity, internal structural features, mural nodules, contours, cystic wall, pancreatic duct and calcification. One of the problems with this technique related to the morphological aspects of pancreatic cystic lesions is the plurality of terms used by different authors to define them.

Locularity is determined by the presence of septa and can be classified as unilocular (or monolocular) or multilocular (or multicystic). The cystic component can be classified "with microcystic area" or "without microcystic area". The microcystic area is defined as an area where small (less than 2-3 mm each) cysts aggregate

Table 3 Endoscopic ultrasound morphology and cystic fluid analysis in pancreatic cystic lesions

	Serous cystadenoma	Mucinous cystic neoplasm	BD- IPMN	Pseudocyst
Localization				
Head	+++	+/-	+++	++
Body-tail	++	+++	++	++
Locularity				
Unilocular	+	+	+	+++
Multilocular	+++	+++	+++	+
Internal structural features				
Microcystic aspect	+++	-	+	-
Bunch of grape aspect	+	-	+++	-
Countours				
Round	+	+++	+	+++
Lobulated	+++	+/-	+	+/-
Irregular	+/-	-	+++	-
Central scar	+	-	-	-
Visible cystic wall	-	++	+	+/-
Multifocality	-	-	++	+/-
Debris	-	-	-	++
Visible communication with pancreatic duct	-	-	++	+
Calcification				
Central	+	-	-	-
Periphery	-	+	-	+/-
Solid lesion	-	+	+	-
CEA				
≥ 192 mg/mL	+/-	++	++	+/-
≥ 5 mg/mL	+	+++	+++	++
≤ 5 mg/mL	+++	+/-	+/-	+
Amylase				
> 250 U/L	+	+/++	++/+++	+++
K-RAS mutation	-	++	++	-
Mucin	-	+	+	-
Cytology	Glycogen	Mucinous	M u c i - n o u s	I n f l a m m a - t o r y

+++; Very frequent; ++; Moderately frequent; +; Infrequent; +/-; Possible but very infrequent. BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; CEA: Carcinoembryonic antigen.

(usually more than 6 cysts) separated by thin-walled septa, producing a honeycomb-like appearance^[36].

The contour can be round (or ovoid), lobulated or irregular. Lobulated is defined as the presence of rounded contours that cannot be described as the borders of the same circle^[37]. Irregular is defined as the presence of high irregularity in the contours.

The wall cyst is considered thin if it is 2 mm or less and thick if more than 2 mm for at least 25% of the lesion circumference^[37].

Specific EUS aspects of a single cystic lesion can be observed (Table 3).

In SCNs, there is controversy over the site of the pancreas most frequently affected^[38] but probably these cysts are evenly distributed.

Visualization of the microcystic area within the cyst, located either at the centre of the cyst (Figure 1A) or next to a macrocystic area^[36] (Figure 1B) or in the internal septa of the lesions^[39] (Figure 1C), is very typical of these lesions. The thin internal septa are hypervascular on Doppler^[40]. The best modality for depicting this as-

pect is EUS. The microcystic area is present in about 85% of SCNs and is highly accurate in the specific diagnosis of these lesions^[36]. A central stellate scar (sunburst)^[38], sometimes calcified, is pathognomonic but is seen in 20%-30% of cases on MDCT but only in 11% of cases with EUS^[39].

The capsule is usually poor developed and there is often a poor distinction between the tumor and the surrounding pancreatic parenchyma^[37,39,41].

These lesions usually have lobulated contours^[36] (Figure 1C).

In lesions in which the cysts are a few millimeters in size, the tumor can have a solid appearance due to innumerable interfaces^[40], the so called "pseudosolid form" (Figure 1D). A third morphological pattern is also known as the "oligocystic variant" with few cystic spaces^[40].

Unilocular SCNs with no microcystic component account for about 10% of all these lesions. The only characteristics that can help in identifying these is the absence of a discernible cystic wall^[39] and lobulated contour^[36,37], although in this case a more reliable diagnostic tool is analysis of cystic fluid.

In SCN, communication with the pancreatic duct is never seen^[41].

EUS aspects of MCNs are variable^[38]. They are a well defined, single, round^[18] (orange like)^[18] cyst that can be unilocular^[36,37] but more typically present with multiple macrocystic locules (usually less than 6^[36], which are usually > 1-2 cm in diameter^[39,42,43]) divided by septa^[20,36,40,44] (Figure 2A and B) and with no macroscopic communication with the pancreatic duct^[18,44]. The aspect is of a "cysts in cyst"^[18]. MCNs commonly have a visible cystic wall (> 2 mm)^[17,37-39]. Thick mucoid cyst content can appear granulated on EUS^[38].

Focally thickened cystic wall or internal septa, clear intramural nodules or solid component, and dilation of the pancreatic duct are associated with invasive malignancy^[20,21,45-48]. Goh *et al.*^[45] reported that none of the 40 malignant (carcinoma *in situ* or invasive) MCNs in his study were < 3 cm; only one was < 4.5 cm (3 cm). In a study by Crippa *et al.*^[21], all MCNs with cancer were either 40 mm in size or had nodules.

Peripheral wall curvilinear calcifications (egg shell calcification) are characteristic of these lesions, although present in less than 10%-25% of cases^[49], and are considered predictive of malignancy^[47].

BD-IPMNs (and sometimes MIX-IPMNs) need a differential diagnosis with the other pancreatic cystic lesions. MD-IPMNs most need a differential diagnosis with chronic pancreatitis. The typical aspect of BD-IPMNs is multiloculated lesion^[28,50], with a "bunch of grapes"^[18,50] aspect (Figure 3A), produced by multiple secondary pancreatic ducts dilated by mucin. So these aspects produce two important image characteristics of these lesions: firstly, the lesions have "cysts by cyst" aspect^[18] different from MCNs, which have a "cyst in cyst" aspect^[18]. In addition, these lesions do not have a round shape but do have an irregular contour. A study by Kubo *et al.*^[36] showed that all MCNs had a round ap-

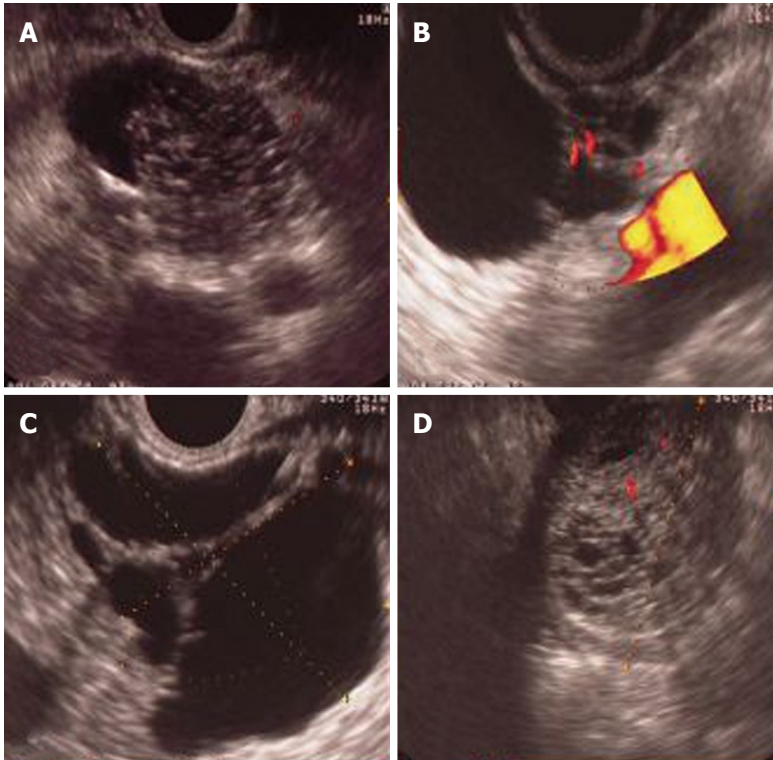


Figure 1 Serous cystoadenoma. A: Microcystic area, centrally located; B: Beside microcystic area; C: Peripheral and internal septa microcystic area, lobulate contour; D: Pseudo-solid form.

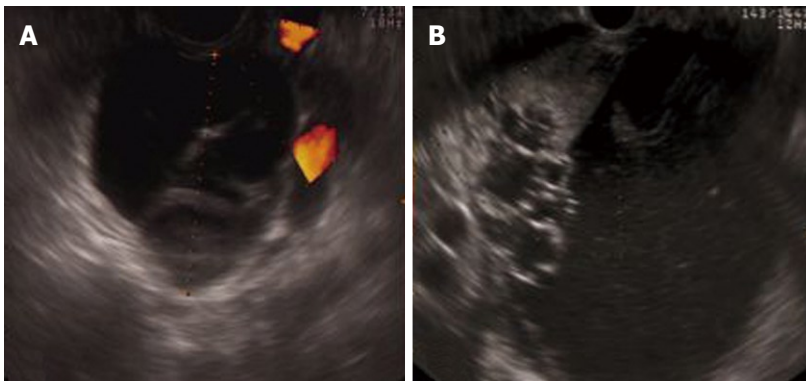


Figure 2 Mucinous cystic neoplasm. A-B: Round lesions with septa (aspects of cysts in cyst with round contour).



Figure 3 Branch duct intraductal papillary mucinous neoplasm. A: "Bunch of grapes" lesion (cysts by cyst aspects with irregular contour); B: Finger-like aspect; C: Clubbed-like aspect.

pearance and only 7% of BD-IPMNs appeared round. Another typical aspect of a BD-IPMN is a cystic lesion composed of finger (Figure 3B), tubular or clubbed-like

dilation (Figure 3C) of secondary pancreatic ducts.

All the aspects of BD-IPMNs described above can be seen in the same lesions, so radiologists have called



Figure 4 Pancreatic pseudocyst. Round lesion without septa and with visible hyperechoic debris inside.

the aspect of BD-IPMNs a “pleomorphic cystic shape”, which is defined as one containing three or more cysts, including oval, tubular or clubbed-finger-like cysts^[28,51].

However, these lesions are sometimes formed by only one large ectatic pancreatic secondary duct and in this case the lesions will be unilocular^[50,52], round and impossible to distinguish from other unilocular pancreatic cystic lesions by EUS aspect only. One of the most important diagnostic tools for BD-IPMNs is identifying whether there is communication between the lesion and the pancreatic duct. MRI was significantly more accurate than MDCT in identifying this characteristic in one study^[13]. However, EUS, although operator dependent, can be very useful, particularly when CT or RMN are equivocal. Kim *et al*^[53] demonstrated that there is no difference between MRI and EUS in showing communication between pancreatic cystic lesions and the pancreatic duct.

Another specific sign for diagnosis of IPMNs is the presence of cystic dilation of the small branches of the pancreatic ductal system in two or more areas within the pancreatic parenchyma. Multifocality has been reported in about 30% of IPMN^[18] and is quite specific to these lesions because only rarely do other lesions have this characteristic (simple cyst or serous cystoadenoma in Von Hippel-Lindau syndrome, multiple neuroendocrine tumor with cystic aspects, metastasis with cystic pattern). During EUS exams, an endoscopic view of the papilla should be always done to exclude mucin extruding from the patulous papilla (fish mouth papilla), which is diagnostic of IPMN^[38], although this phenomenon is present in only 30% of cases, almost all of which with MD or MIX IPMN^[15].

Pais *et al*^[54] showed that in 74 operated patients, EUS features of a solid lesion, a dilated main pancreatic duct, ductal filling defects and thickened septa were predictive of malignancy in IPMNs.

The most frequent aspect of PPs is a round, unilocular cyst without internal septation or mural nodules, with less than 10%-20% appearing multilocular^[23,36]. The appearance of the cystic wall can vary, from imperceptible or minimally visible to that of a uniform thickness^[37,47]. Internal debris visible at EUS as hyperechoic mate-

rial inside the cyst (Figure 4) can be seen floating with change of the decubitus of the patient or during aspiration of intracystic fluid. It is important to look for this characteristic because it is highly specific to pseudocysts. Macari *et al*^[55] reported that on MRI, 13 of 14 (93%) pseudocysts had debris but only 1 (4%) of 22 cystic neoplasms had debris. Debris is very easily seen with EUS. Sometimes, MCNs with very viscous mucin can have an intracystic fluid with a granular aspect that looks like debris^[38]. Gonzalez Obeso *et al*^[23] reported a 22% rate of pseudocysts with internal debris seen on EUS and in this study, a diagnosis of pseudocyst either was suggested or made definitively by the endosonographer for the majority of patients (69%).

Despite the fact that pseudocysts typically communicate with the pancreatic duct, this is often not identifiable on cross-sectional or EUS imaging^[52].

A characteristic to be taken into account is that pseudocysts, different from cystic neoplasms, can show rapid changes in the arc in just a few weeks, either rapidly increasing or decreasing, until spontaneous resolution^[47,52].

The EUS aspect of chronic pancreatitis (CP) should always be taken in to serious account and, despite some limits, EUS is the most useful single test for evaluating CP^[56]. A pancreatic cystic lesion without a history of acute or chronic pancreatitis, or without the presence of a risk factor and imaging clearly diagnostic of chronic pancreatitis, regardless of the EUS aspects, should be considered a pancreatic cystic neoplasm until other tests can definitively exclude it.

A review by Oh *et al*^[27] of seven studies^[42,57-62] of the diagnostic accuracy of EUS morphology in differentiating cystic lesions of the pancreas, reported results of between 51% and 90%. Furthermore, in one study of videotapes of EUS procedures from 31 consecutive cases^[63], there was little more than chance inter-observer agreement among experienced endosonographers on a diagnosis of neoplastic *vs* non-neoplastic lesions, specific type and the EUS features of pancreatic cystic lesions.

The differences in the results are due to the intrinsic differences among these studies. Some studies were done to identify whether EUS was able to detect the occurrence of overtly malignant change^[42,58], others to differentiate benign from premalignant lesions^[60-62], and another to differentiate all subtypes of lesions^[59]. All but one^[61] were retrospective. Some studies were done of EUS imaging^[60] or videotape^[63] that may not have completely reproduced the findings as compared with an actual real-time examination and endosonographers were not aware of the history or prior imaging studies. The combination of clinical history and cross-sectional imaging, along with real-time EUS, may increase the contribution of EUS to the characterization of cystic lesions of the pancreas. Definitions of EUS criteria for specific lesions and malignancy were sometimes different among these studies and reflect the lack of a uniform nomenclature for describing the EUS features of cystic lesions.

On the other hand, O'Tool *et al*^[39] found EUS to be

better in delineating the internal structures of cysts, such as septa, thick content and mural nodule. The combination of a cystic wall that is thickened and the absence of microcysts had a sensitivity of 100% and specificity of 78% for a diagnosis of MCN compared with macrocystic SCN. Song *et al.*^[44] showed that absence of septa and mural nodules and the presence of parenchymal change are indicators of a pseudocyst rather than a cystic neoplasm, with 88% accuracy.

More recently, Kubo *et al.*^[36] observed that 8 of 11 monolocular cystic lesions in his study were non-neoplastic and that 11 of 12 SCNs included microcystic areas. All MCNs were round, while 93% of IPMNs were not. In a multivariate analysis, he concluded that locularity (presence of septa) and a cystic component (presence of microcystic area) were important for a differential diagnosis of potentially malignant cystic pancreatic tumors and that the characteristics of cystic tumors revealed by EUS are useful for differential diagnoses.

There are few studies comparing radiological and EUS accuracy in pancreatic cystic lesions^[53,62,64]. Gerke *et al.*^[62] found an accuracy in classification into benign and malignant or potentially malignant cystic lesions of 66% for EUS and 71% for CT scan, with very poor agreement between them. More recently, Kim *et al.*^[53] found that there was no difference between the ability of MRI and EUS to correctly classify lesions as cystic or solid (accuracy, 90%-98% *vs* 88%; $P > 0.05$) for the characterization of septa, mural nodule, main pancreatic duct dilatation, communication with the main pancreatic duct and a prediction of malignancy.

EUS-FNA

Linear array echoendoscopy allows for EUS-FNA of solid and cystic lesions. In PCLs, EUS-FNA allows evaluation of extracellular mucin, cytological and sometimes histological analysis, biochemical, tumor markers and molecular analysis^[65] and the complication rate for EUS-FNA of cystic pancreatic lesions from a systematic review^[66] was slightly more than that for solid ones (2.75% *vs* 0.82%), with pancreatitis being the most frequent. The others were pain and bleeding that were self-limiting, and infection, which has become very rare since the introduction of antibiotic prophylaxis.

The risk of seeding is very low, with only one published case of peritoneal seeding after EUS-FNA of a PCLs^[67]. The EUS-FNA techniques for pancreatic cystic lesions are quite simple. The needles normally used are the same as those for solid lesions, 19, 22 and 25 G. Doppler is recommended to avoid puncture of intervening vessels, as is crossing the normal pancreatic parenchyma as little as possible to help avoid pancreatitis. Other recommendations include complete drainage of the cyst in a single needle passage, antibiotic prophylaxis with intravenous antibiotics just before the procedure, followed by the oral route for 3-5 d to reduce the risk of infection.

Only one study with ten patients was done on the use of Trucut biopsy in pancreatic cystic lesions^[68], so there

is little data on this technique. A recently published prospective study by Hong *et al.*^[69] described techniques for obtaining more cellularity for cytological diagnosis. This technique consists of attempting to obtain a cystic wall biopsy (CWB) by puncturing the far wall of the cyst and moving the needle back and forth through the wall, after aspiration of fluid from the cyst. The author reports that 81% of the specimens had cellular material adequate for cytological assessment, which was higher than has previously been reported for standard FNA.

A new device, the Echobrush (Cook Medical), was tested in several studies^[70-72]. Although better results than those for standard needles have been^[70] reported, some limitations have to be considered. The brush takes only a 19 G needle, so stiffness limits its use, especially for lesions in the pancreatic head and uncinate process. In addition, it can only be used for lesions that are at least 2 cm in diameter and a high rate of complications (8%-10%) and one death have been reported^[71]. More studies are needed.

A meta-analysis^[73] comparing EUS-FNA-based cytology with surgical biopsy or histology and including 376 patients from eleven^[42,58,59,61,74-80] studies showed a low sensitivity (63%), but good specificity (88%) in differentiating mucinous cystic lesions from non-mucinous lesions, with a diagnostic accuracy of 89%. However, the authors concluded that review literature on diagnostic accuracy of EUS-FNA-based cytology for pancreatic cystic lesions is limited and heterogeneous, and that well-designed randomized trials are needed in this field.

The largest study of FNA cytology is a prospective cooperative pancreatic cyst study^[61] of 112 surgically proven lesions that showed a sensitivity, specificity and accuracy of 34.5%, 83% and 51%, respectively. A prospective two center study to investigate the technical success of EUS-FNA in pancreatic cysts in 143 patients was recently published^[81]. de Jong *et al.*^[81] reported that EUS-FNA was possible in 90% of patients but that cytological diagnosis was obtained in only 31%, due to insufficient cellularity of aspirate liquid, and that biochemical analysis was possible in only 49%, due to insufficient amount of fluid or high viscosity. These numbers are much lower than those reported in another prospective study by Frossard *et al.*^[59]. In that study, cytological analysis was done in 127 patients with pancreatic cysts and a classifying diagnosis was provided in 98 cases (77%). The authors used the FNA needle to obtain fluid and a mini biopsy, while the cytologist used a liquid-based cytology, the ThinPrep 2000 (Cytoc Corp., Marlborough, MA), a cell preparation processor that provided a monolayered cell population. Both mini biopsy and cyst fluid process may have made the difference in this study, although not all authors agree with the use of liquid-based cytology to process cyst fluid^[48].

Greater agreement among cytopathologists and in general among physicians involved in PCL treatment is needed on processing of cyst fluid for cytology.

Looking for the presence of extracellular mucin in

aspirate from PCLs may aid in making a diagnosis, at least in distinguishing mucinous from non mucinous lesions, although it is not present in approximately 50% of mucinous cysts. Although mucin may be visible at aspiration, thick sheets of colloidal-like mucin that cover much of the slides need to be watched for. This type of mucin is sufficient for a diagnosis of mucinous cyst, even if acellular^[48]. Mucin stain (alcian blue, mucicarmine) may lead to an erroneous interpretation of wisp mucin from gastrointestinal contaminants as indicative of mucinous cyst. Liquid-based cytology attenuates the appearance of mucin and Pitman *et al*^[48] do not recommended it for processing cyst fluid.

Correct execution of sampling^[69], an experienced cytopathologist and correct treatment of smears and aspirated fluid^[59,73,81] can improve the sensitivity of these tests, although new methods for improving the yield of FNA are needed. The Echobrush or CWB could conceivably improve results, although larger randomized trials are needed to confirm results and safety.

To enhance the diagnostic capability of cytology, cyst fluid can be analyzed for tumor markers and amylase. The overall cystic fluid amount for dosage of tumor markers and amylase is about 0.5 mL for each, so with just 1 mL it is possible to do both tests. Several tumor markers in aspirate from PCLs have been considered: Carcinoembryonic antigen (CEA), CA 19-9, CA 72-4 and CA-125. CEA is considered the most accurate marker in differentiating mucinous from non-mucinous cysts. There is continual debate in the literature over the best cut-off of CEA levels for discriminating mucinous from non-mucinous cysts. The value of cut-off ranges from 20 ng/mL to 800 ng/mL in different studies, obviously with greater sensitivity for a low cut-off value and greater specificity for higher ones^[27,49]. However, the most frequently utilized cut-off derives from a large prospective study by Brugge *et al*^[61] on 112 patients who underwent surgery. It established that a level of 192 ng/mL has a diagnostic sensitivity of 75%, a specificity of 84% and an accuracy of 79% in differential diagnosis of mucinous and non-mucinous cysts. In another pooled analysis from 12 studies, a value of > 800 ng/mL arrived at a specificity of 98%, but a sensitivity of only 48%^[82].

Very low values of CEA are extremely useful. CEA levels of less than 5 ng/mL have been found in the pooled analysis of published studies^[82] to be highly diagnostic for serous cystadenomas or pseudocysts (sensitivity 50%, specificity 95%). A retrospective analysis^[83] of patients with histologically confirmed cysts showed that cyst fluid CEA of less than 5 ng/mL for a diagnosis of non-mucinous lesions had a sensitivity of 44%, specificity of 96% and diagnostic accuracy of 78%. Very few mucinous cysts have values below 5 ng/mL^[83,84].

For pseudocysts there are more widespread values. Rarely do they have a value above 192 ng/mL (5%-14%)^[23,83] and only 25% have a value of less than 5 ng/mL^[23,83]. In a paper on 21 pseudocysts, the median of intracystic fluid CEA was 41 ng/mL (mean 129 ng/mL) so, compared

with serous cystadenomas, they do have significantly higher levels of cyst fluid CEA^[23].

For practical purposes, we can summarize the information on CEA dosage in cystic fluid from different studies: values above 192 ng/mL support the interpretation of mucinous cyst, with increasing specificity mirroring an increase in CEA concentrations. Values lower than 5 ng/mL strongly support a diagnosis of non-mucinous cyst, particularly of serous cystadenoma. Pseudocysts rarely have values above 192 ng/mL and the median value to be expected is about 40 ng/mL (Table 3). A few reports have suggested that CEA can predict malignancy if it is found to exceed some value (ranging between 200 ng/mL and 5000 ng/mL), with varied specificity and sensitivity, although many large studies^[61,82,83,85] have shown that CEA is not useful in differentiating benign from malignant cyst.

Although CEA is not the solution to all diagnostic problems in pancreatic cystic lesions, the 2007 American College of Gastroenterologists Guidelines recommend it as the first test to do if minimal fluid is acquired during aspiration^[86].

Amylase levels in pancreatic cystic fluid are used to investigate the possibility that the cyst is communicating with the pancreatic duct. There is no definitive value to demonstrate communication with the pancreatic duct. Values between 250 U/L and 5000 U/L can be found in different studies^[82,84].

Amylase values in pseudocysts are usually in the thousands and almost never under 250 U/L^[82,83,87]. Amylase values are over 5000 U/L in 3/4 of IPMN^[83,84]. In serous cystadenoma, the amylase value is usually less than 250 U/L^[16,82,83], although there are a number of exceptions. MCN very rarely have macroscopic communication with the pancreatic duct, so the expected level of amylase is low in pancreatic cystic fluid^[20]. There are several studies^[16,83,87] that have shown that amylase intracystic fluid levels in MCN can be elevated, with no differences between IPMN and pseudocysts, perhaps because of diminutive connections between the cyst and the ductal system.

There are some reports that speculate on the presence of malignancy in IPMN and MCN with low levels of amylase in intracystic fluid, assuming that rapid uncontrolled cellular growth could occlude any macroscopic or microscopic ductal connections^[83-87]. At present, there are insufficient data for investigating this suspicion.

In summary, we can say that pseudocysts rarely have intracystic fluid values of less than 250 U/L, IPMN have elevated values in 75% of cases, and serous cystadenomas usually, but not always, have values below 250 U/L. MCN can have widely variable values (Table 3).

Molecular analyses have been done on intracystic fluid. The largest study in this field is the PANDA study^[88], which was a prospective, multicenter study to evaluate the role of cystic fluid DNA analysis in differentiating mucinous from nonmucinous cysts. It showed that, in 113 patients with pancreatic cysts, elevated amounts of

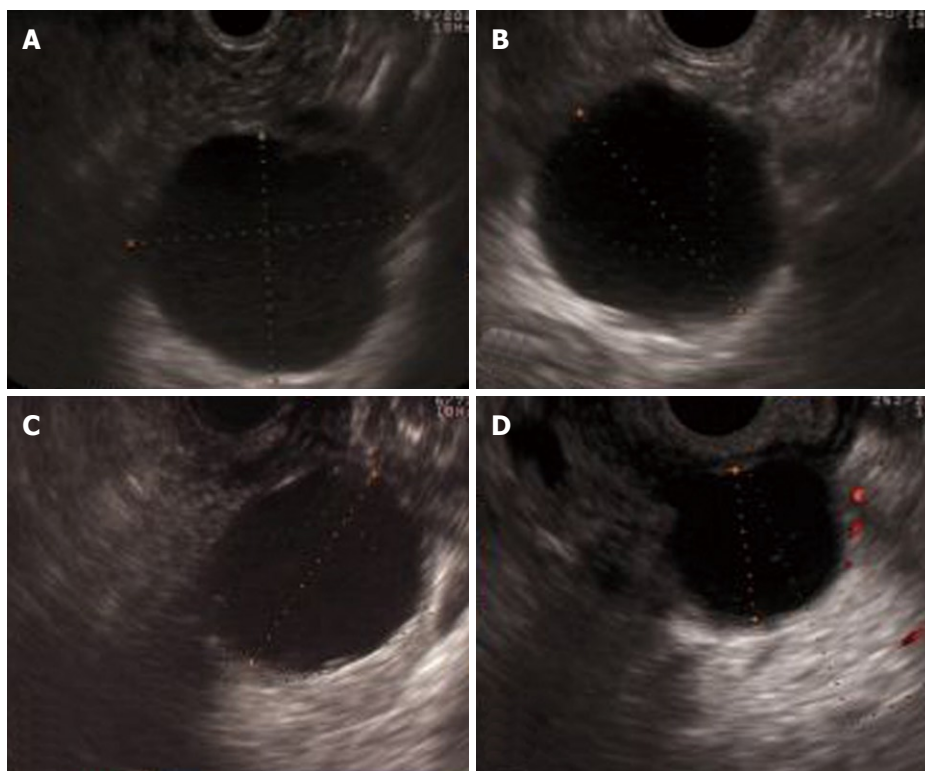


Figure 5 Unilocular aspects in cystic pancreatic lesions. A: Sixty year old female, no symptoms. Lesion in pancreatic head, no visible communication with pancreatic duct. Carcinoembryonic antigen (CEA) 1.5 ng/mL, Amylase 125 U/L, K-RAS mutations negative. Cytology: Cuboidal cell periodic acid-Schiff positive, no mucus. Diagnosis: Unilocular serous cystoadenoma; B: Seventy-nine year old female, no symptoms. Multiple cystic lesion in pancreatic head and tail. Lesion in pancreatic tail with visible communication with pancreatic duct. CEA 12 000 ng/mL, amylase 12 870 U/L, K-RAS mutation positive. Cytology: Mucin and cuboidal cell with mild atypia and papillary arrangement. Diagnosis: Multifocal branch ducts-intraductal papillary mucinous neoplasm; C: Fifty year old female. Lesion in pancreatic body, no visible communication with pancreatic duct. CEA 280 ng/mL, amylase > 15 000 U/L, K-RAS mutation positive. Cytology: Acellular without mucin. Surgical histology: Mucinous cystoadenoma; D: Forty-five year old male, history of alcoholism and recurrent acute pancreatitis. Lesion in pancreatic body. CEA 61 ng/mL, amylase > 15 000 U/L, K-RAS mutations negative. Cytology: Inflammatory cells and pigmented histocytes. Diagnosis: Pancreatic pseudocyst.

pancreatic cyst fluid DNA, high-amplitude mutations and specific mutation acquisition sequences were indicators of malignancy and the presence of a k-ras mutation was indicative of a mucinous cyst.

Another study^[89], however, showed a poor correlation between CEA levels and molecular analysis, although the combination of CEA and molecular analysis achieved 100% sensitivity for the diagnosis of mucinous cyst. Molecular analysis needs very small quantities of intracystic fluid (0.4 mL) and is surely a promising test. However, high cost and availability pose some limits. Accuracy of molecular analysis needs to be tested before drawing any definitive conclusions. In addition, reproducibility has to be tested in other laboratories and a cost-benefit analysis for comparison with current tests has to be done.

Glycosylation variants of mucins^[90], proteomic analysis^[91] and microRNA expression profile^[92,93] are among the emerging tests under investigation that could potentially become biomarkers in cyst fluid samples.

CONCLUSION

There is no single test accurate enough to make a sure diagnosis in every pancreatic cystic lesion and so the diagnosis of such lesions is a puzzle, with bits of infor-

mation deriving from demographic, clinical, radiological, EUS morphological and intracystic fluid analyses.

EUS morphology alone cannot provide for a sure diagnosis in all cases and a recently published paper on inter observer agreement confirms that such agreement is generally low^[94]. This same paper also showed that the more expert the endosonographers, the higher the rate of agreement, probably because they “speak the same language”. So it is likely that having greater agreement on what to look for and the meaning assigned to specific morphological aspects of pancreatic cystic lesions would improve the weight of EUS morphology. Palazzo *et al*^[95] underlines this concept, proposing the creation of an international expert educational image bank for CPLs that could help to standardize image analysis. However, there are some studies that have clearly shown that EUS shows clearer images of some cystic aspects, such as diffuse or localized microcystic aspects, lobulated contours for serous cystoadenomas, debris for pseudocysts, connections with the pancreatic duct, grape-like, finger- or clubber-like aspects for IPMNs, and rounded contour and internal septa for MCN. Moreover, some EUS aspects, such as intracystic nodules, pericystic solid mass, localized thickening of the parietal wall or of the intracystic septa, and dilation of the pancreatic duct, are

Table 4 Accuracy of endoscopic ultrasound morphology in differentiating pancreatic cystic lesions (printed with permission of Dr M. Raimondi)

Author	No. of patients	Study design	Accuracy (%)
Koito <i>et al</i> ^[57]	52	Retrospective	94
Cellier <i>et al</i> ^[64]	21	Retrospective	76
Pais <i>et al</i> ^[54]	51	Retrospective	86
Ahmad <i>et al</i> ^[60]	38	Retrospective	66
Sedlack <i>et al</i> ^[42]	34	Retrospective	82
Hernandez <i>et al</i> ^[58]	9	Retrospective	89
Frossard <i>et al</i> ^[59]	67	Retrospective	73
Brugge <i>et al</i> ^[61]	112	Prospective	51
Gerke <i>et al</i> ^[62]	66	Retrospective	67
Total	450		Median 72.5 (mean 77)

predictive of malignancy and some of these aspects are frequently better seen with EUS.

Analyses of data from nine studies^[42,54,57-62,64] (Table 4), with a total of 450 patients, of accuracy of EUS morphology in differentiating CPLs showed a median of 72.5% (mean 77%). This is better than the 50%-60% accuracy of radiology^[33-35] and slight different from the accuracy of CEA (79%)^[61]. Compared with cytology, the accuracy of EUS morphology varies a great deal because of the significant heterogeneity in the results of the cytology studies, with an accuracy ranging between 51% and 93%^[73] but with a median of 73%, which is quite close to the accuracy of EUS morphology. Moreover, EUS allows for the execution of FNA for cytological examination and intracystic fluid analysis, especially in such doubtful lesions as unilocular cystic pancreatic lesions, which do not have specific EUS aspects (Figure 5).

In general, cytology in every study showed low sensitivity and high specificity, allowing, when positive, to predict the type of lesion. CEA showed good accuracy for mucinous lesions when the cut-off was 192 ng/mL and a high specificity for serous cystadenomas when using the low cut-off of 5 ng/mL. Amylase levels are undoubtedly useful for excluding pseudocyst. There are other diagnostic tests beyond intracystic fluid that are very promising, such as molecular analysis, variants of mucins, proteomic analysis and mRNA analysis, although larger studies than those done to date are needed for validation.

Several case reports and case series have shown the utility of EUS-FNA in diagnosing much rarer PCLs, such as cystic change of pancreatic neuroendocrine tumors^[96], solid papillary neoplasm^[97], lymphoepithelial cyst^[98], pancreatic schwannoma^[99] and pancreatic cystic lymphangioma^[100].

We can conclude by saying that diagnosis of pancreatic cystic lesions is composed of different bits of information, derived from a number of different sources. EUS morphology and EUS-FNA are important diagnostic tools and can be useful in solving this difficult diagnostic puzzle.

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