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Diagnosis of pancreatic tumors by endoscopic ultrasonography

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Abstract

Pancreatic tumors are highly diverse, as they can be solid or cystic, and benign or malignant. Since their imaging features overlap considerably, it is often difficult to characterize these tumors. In addition, small pancreatic tumors, especially those less than 2 cm in diameter, are difficult to detect and diagnose. For characterizing pancreatic tumors and detecting small pancreatic tumors, endoscopic ultrasonography (EUS) is the most sensitive of the imaging procedures currently available. This technique also provides good results in terms of the preoperative staging of pancreatic tumors. EUS-guided fine needle aspiration (EUS-FNA) has also proved to be a safe and useful method for tissue sampling of pancreatic tumors. Despite these advantages, however, it is still difficult to differentiate between benign and malignant, solid or cystic pancreatic tumors, malignant neoplasms, and chronic pancreatitis using EUS, even when EUS-FNA is performed. Recently, contrast-enhanced EUS with Doppler mode (CE-EUS) employing ultrasound contrast agents, which indicate vascularization in pancreatic lesions, has been found to be useful in the differential diagnosis of pancreatic tumors, especially small pancreatic tumors. However, Doppler ultrasonography with contrast-enhancement has several limitations, including blooming artifacts, poor spatial resolution, and low sensitivity to slow flow. Consequently, an echoendoscope was developed recently that has a broad-band transducer and an imaging mode that was designed specifically for contrast-enhanced harmonic EUS (CEH-EUS) with a second-generation ultrasound contrast agent. The CEH-EUS technique is expected to improve the differential diagnosis of pancreatic disease in the future. This review describes the EUS appearances of common solid and cystic pancreatic masses, the diagnostic accuracy of EUS-FNA, and the relative efficacies and advantages of CE-EUS and CEH-EUS along with their relative advantages and their complementary roles in clinical practice.

Key words: Contrast-enhanced endoscopic ultrasonography; Endoscopic ultrasonography; EUS-guided fine needle aspiration; Pancreas; Sonazoid

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INTRODUCTION

Although the morphology of pancreatic tumors is highly diverse, these tumors can be classified broadly into solid and cystic tumors. Solid pancreatic masses may be due to the inflammation associated with chronic pancreatitis or they may be caused by a malignancy[1,2]. Ductal pancreatic adenocarcinoma is the most common malignant pancreatic neoplasm as it accounts for more than 95% of all malignant solid pancreatic tumors[3]. Only a minority of pancreatic tumors are neuroendocrine tumors. Other pancreatic tumors such as squamous cell carcinomas and primary pancreatic lymphomas are even rarer. Cystic tumors comprise 10%-15% of all cystic masses and 1%-5% of all pancreatic malignancies[4]. The imaging features of benign and malignant cystic lesions overlap considerably. Moreover, solid pancreatic tumors with cystic degeneration can mimic primary cystic tumors. Thus, it is often difficult to differentiate benign lesions from malignant lesions, and solid tumors from cystic pancreatic tumors. Compared to other imaging techniques, endoscopic ultrasonography (EUS) has been shown to be more accurate in terms of local staging and predicting vascular invasion and tumor resectability, particularly with tumors less than 2 cm in diameter[5-7]. Furthermore, EUS permits a pancreatic mass to be aspirated and/or biopsied during an examination, which allows a histological diagnosis to be made and benign masses to be differentiated from malignant masses.

EUS has also been adapted to employ an ultrasound (US) contrast agent. This technique is termed contrast-enhanced EUS (CE-EUS), and it has been used to assess the microvascular structures of pancreatic tumors. However, because this technique is associated with several imaging limitations, contrast-enhanced harmonic EUS (CEH-EUS) was developed recently. This technique employs an echoendoscope with a broad-band transducer and an imaging mode that was designed specifically for CEH-EUS with a second generation US contrast agent. All of these non-invasive methods have improved the discrimination between malignant and benign masses and the differential diagnosis of the pancreatic masses. In this article, the EUS imaging findings of the common pancreatic solid and cystic masses are reviewed. In addition, the diagnostic accuracy of EUS-guided fine needle aspiration (EUS-FNA) is examined. Finally, the efficacies and relative advantages of CE-EUS, CEH-EUS, and other diagnostic EUS adapted procedures and their complementary role in clinical practice are discussed.

ENDOSCOPIC ULTRASONOGRAPHY

EUS was developed in the 1980s to overcome problems associated with the transabdominal US imaging of the pancreas caused by intervening gas, bone, and fat. Since the EUS high-frequency transducers can be positioned *via* the stomach and duodenum in direct proximity to the pancreas, this technique yields detailed high-resolution images of the pancreas that far surpass those achieved by computed tomography (CT) or magnetic resonance imaging (MRI). The high resolution of these images permits the detection of lesions as small as 2-3 mm in diameter and their relationship with adjacent blood vessels such as the portal vein and mesenteric vasculature to be characterized. As a result, EUS is more accurate than other imaging techniques in terms of local staging and predicting vascular invasion and tumor resectability, particularly with tumors less than 2 cm in diameter[5-7]. EUS is also useful for locating occult pancreatic tumors in patients who have liver metastases and an unknown primary tumor. For example, when EUS was applied to 33 patients whose CT images only revealed metastatic tumors derived from an unknown primary tumor, primary pancreatic tumors were detected in 17 patients[8]. The identification of these primary pancreatic tumors meant that these patients could be treated with pancreas-specific chemotherapy, which improved their outcome.

SOLID PANCREATIC LESIONS

Solid pancreatic masses include benign masses, namely focal chronic pancreatitis, and malignancies, namely ductal adenocarcinomas, neuroendocrine tumors, lymphomas, and metastases.

Focal chronic pancreatitis

Regardless of whether CT, MRI, or even EUS is used, it is very difficult to reliably distinguish between chronic pancreatitis masses, namely masses that are due to advanced inflammation or fibrosis, and malignant tumors. To diagnose chronic pancreatitis, nine EUS criteria are currently accepted. Four are parenchymal criteria: hyperechogenic foci, hyperechogenic strands, pseudocysts, and lobularity. Five are ductal criteria: dilated main pancreatic ducts (MPDs), visible side branches, and hyperechogenic walls of the MPD[9-11]. When these 4-5 diagnostic criteria are used, the diagnostic sensitivity of EUS ranges between 84% and 100%, while its specificity ranges between 60% and 95%[12-16]. In addition, Rösch *et al*[17] and Glasbrenner *et al*[18] independently proposed EUS criteria that are suggestive of an inflammatory mass, namely inhomogeneous echo pattern, calcification, peripancreatic echo-rich stranding, and cysts. Their EUS criteria of malignant masses included: signs of invasion of adjacent organs, enlargement of adjacent lymph nodes, and masses with irregular outer margins (Figure 1). While these criteria markedly improved the diagnostic specificity of EUS, the sensitivity of the technique remained rather low, which means that the B-mode images of EUS are still insufficient for discriminating between chronic pancreatitis and malignant tumors.

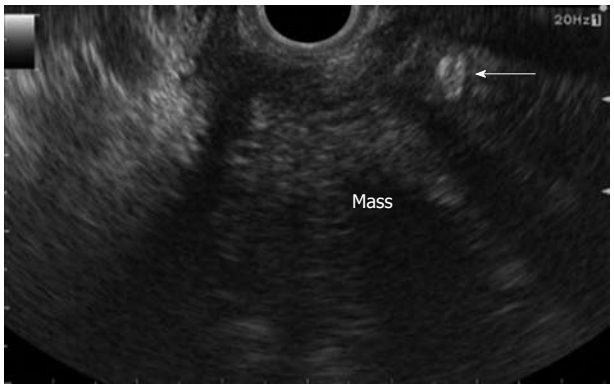

Figure 1 Focal chronic pancreatitis. Endoscopic ultrasonography (EUS) shows a mass with an irregular, inhomogeneous echo pattern, and calcification (arrow) at the head of the pancreas.

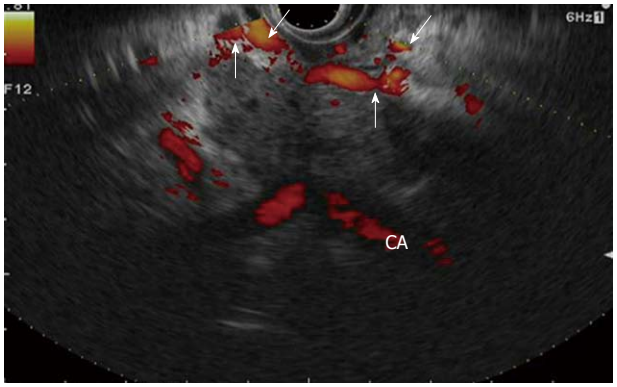

Figure 2 Pancreatic adenocarcinoma. EUS shows a heterogeneous hypoechoic mass with irregular margins at the body of the pancreas, infiltrating the celiac artery, and development of collateral vessels around the tumor (arrows). CA: Celiac artery.

Pancreatic adenocarcinoma

Pancreatic adenocarcinomas typically have the EUS appearance of a heterogeneous hypoechoic mass with irregular margins (Figure 2). However, relying on these morphological features alone only yields a diagnostic specificity of 53% since these features can also be seen in focal pancreatitis, neuroendocrine tumors, and metastases[19]. However, with a sensitivity of 89%-100%, EUS has been remarkably successful in the early detection of small adenocarcinomas[20-22]. In our institute, helical CT and EUS can detect pancreatic carcinomas 2 cm or less in diameter with a sensitivity of 50% and 94.4%, respectively. Thus EUS is significantly more sensitive than helical CT for detecting small pancreatic tumors[23].

Compared to other imaging techniques, EUS also facilitates more accurate staging, which improves the management of pancreatic cancer. Indeed, it has been suggested that EUS is most useful for assessing peripancreatic vascular and lymph node involvement. Many large series have found that when EUS is used for staging, the T stage accuracy ranges between 78%-91% and the nodal (N) stage accuracy ranges between 41%-86%[24-28]. In general, the T stage accuracy based on EUS findings

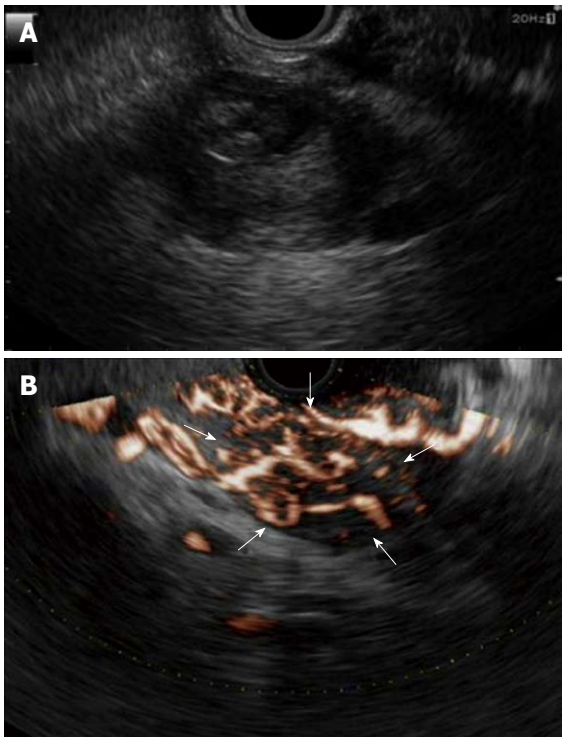

Figure 3 Neuroendocrine tumor. A: EUS shows a heterogeneous appearance; cystic, with a solid component or pure fluid 31 mm in diameter; B: EUS using Doppler mode shows a hypervascular mass at the tail of the pancreas (arrows).

is highest for patients with smaller tumors, whereas helical CT is more accurate in staging larger tumors[26-29]. When all four features that are suggestive of malignant lymph nodes, namely round shape, well-delimitated, size > 1 cm, and hypoechogenity, are present the chance of malignancy is 80%-100%[30].

Another benefit of EUS with regard to pancreatic tumors is that it can show the invasion of the great peripancreatic vessels with an accuracy of 67%-93%[17,31,32]. The splenic vein, portal vein and proximal superior mesenteric artery are easier to visualize on EUS than the other major peripancreatic vessels[33,34]. The vascular invasion criteria are as follows: irregularity of the interface with the vessels, intravascular tumor growth, and nonvisualization of the vessel, with collateral circulation growth. EUS can detect vascular invasion with a sensitivity and specificity of 42%-91% and 89%-100%, respectively[17,31,32]. While the accuracy can be rather low, this is because the staging accuracy of EUS can be influenced by several factors, including the experience of the endosonographer, the presence of imaging artifacts, and the endosonographer's knowledge of the results of previous imaging tests.

Neuroendocrine tumors

On EUS, neuroendocrine tumors usually appear as a hypoechogenic well-delimited lesion with intense vascularization; moreover, 60%-75% of all neuroendocrine tumors are less than 1.5 cm in diameter[35,36]. Lesions greater than 3 cm are likely to have an increased potential for malignancy and a heterogeneous appearance, namely cys-

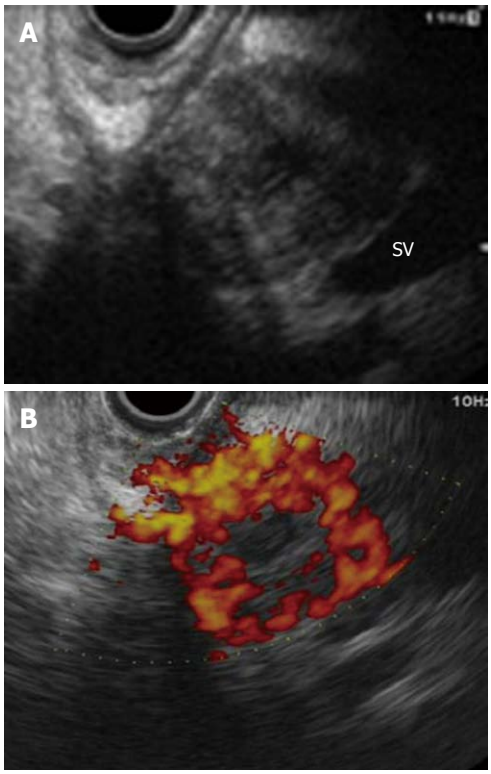

Figure 4 Metastatic pancreatic cancer from renal cell carcinoma. A: EUS shows a heterogeneous hypoechoic mass with a central necrotic area at the head of the pancreas; B: Contrast-enhanced Doppler EUS shows a hypervascular mass. SV: Splenic vein.

tic, with a solid component or pure fluid[37] (Figure 3A). The accuracy and specificity with which EUS can localize neuroendocrine tumors are 93% and 95%, respectively[38]. Since typical neuroendocrine tumors are known to be hypervascular tumors, EUS employing a Doppler mode is useful for observing the vascularity of identified neuroendocrine tumors (Figure 3B).

Primary pancreatic lymphoma

Primary pancreatic lymphoma is rare, comprising 1.3%-1.5% of all malignant pancreatic tumors. It is characterized by non-specific symptoms, laboratory tests and imaging results. Consequently, it can be very difficult to differentiate pancreatic lymphoma from pancreatic cancer on the basis of clinical and imaging data alone[39,40]. One report has described the EUS appearance of a pancreatic lymphoma as a bulky localized tumor in the pancreas without significant dilation of the MPD. Furthermore, if enlarged lymph nodes are encountered below the level of the renal veins, pancreatic lymphoma may be suspected. These EUS appearances may be useful for distinguishing between pancreatic lymphoma and other malignant pancreatic masses[41].

Metastatic pancreatic cancer

While primary pancreatic adenocarcinoma is the most common malignant tumor of the pancreas, a recent study showed that 3% of all pancreatic resections performed for malignant disease are due to pancreatic metastases of renal cell carcinomas[42]. Most pancreatic metastases develop from primary kidney, lung, breast, colon, or skin tumors[43] (Figure 4A and B). Confirming the metastatic nature of a pancreatic tumor is not an easy task, even for pathologists. However, metastatic tumors are more likely to have well-defined borders than primary pancreatic cancers[44].

CYSTIC PANCREATIC LESIONS

Cystic neoplasms of the pancreas often pose a diagnostic dilemma. They can be essentially classified according to malignant potential into mucinous and non-mucinous lesions with significant differences in the natural history and survival between the two groups. Mucinous tumors have recently been classified into mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). Non-mucinous cysts include neoplastic cysts [serous cyst adenomas (SCAs) and solid pseudopapillary tumors], inflammatory cysts (pseudocysts), and epithelial cysts (adult polycystic disease and cystic fibrosis). Mucinous lesions are premalignant or malignant tumors, and surgical resection is generally recommended on operative candidates. Of the non-mucinous lesions, SCAs, whose potential for malignancy is low, and pseudocysts, which are always benign, are generally only resected if they are causing symptoms or complications[45-47].

The morphological features of cystic pancreatic lesions that can be determined by EUS include the presence of a wall, septa, solid component, the number and size of cysts, and the dilatation and thickening of the MPD. The presence of intracystic mucin or floating debris, pancreatic duct dilation, echogenic ductal wall thickening, and focal cyst wall nodularity or thickening are distinctly usual and suggestive of a mucinous tumor. These EUS features are thus useful for the differential diagnosis of cystic pancreatic lesions[48-53], although the accuracy with which they can be used to diagnose malignant cystic pancreatic tumors is rather low (51%-82%). Their usefulness is particularly limited in the case of large lesions (> 5-6 cm) that escape the focal field of the transducer[18,54-56].

Pseudocysts

The diagnosis of pseudocysts is generally not a clinical dilemma if there is a history of pancreatitis. However, cysts occurring in the setting of pancreatitis are not always pseudocysts; IPMN, for example may present with pancreatitis. Mature pseudocysts often have a thick wall surrounding a round collection of fluid, whereas early pseudocysts have a thin wall containing a collection of complex fluids[48] (Figure 5). To differentiate pseudocysts from cystic malignancies, it is useful to know that internal cyst debris and pancreatic parenchymal changes are observed more frequently in pseudocysts, and that mural nodules and septa are present more frequently in cystic

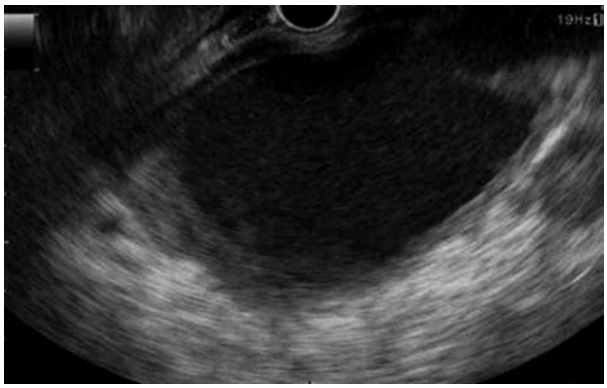

Figure 5 Pseudocyst. EUS shows a cystic lesion with a thick wall surrounding a round fluid collection at the body of the pancreas.

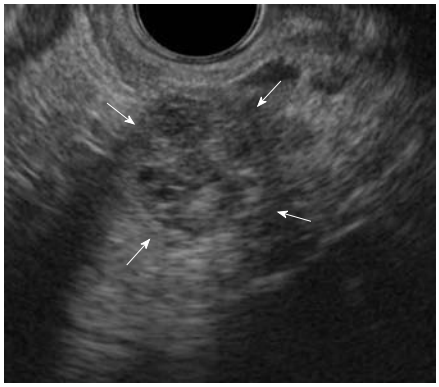

Figure 6 Serous cyst adenoma. EUS shows a mass with a "honeycomb appearance" at the body of the pancreas 13 mm in diameter (arrows).

malignancies[57]. However, several studies have concluded that when used in isolation, morphological features cannot reliably differentiate between malignancies and cystic lesions including pseudocysts[58,59].

SCAs

SCAs occur predominantly in young females. Although several reports have found that 50% to 70% are located in the pancreatic body or tail, other studies have found them more commonly in the head or neck region (63%). Although there are case reports of the malignant transformation of SCAs, they are largely benign cystic lesions and as such are often managed non-surgically[59,60]. SCAs usually appear as focal, well-demarcated lesions that contain multiple, and small (less than 1-2 cm in diameter) fluid-filled microcysts. The microcysts are separated by dense fibrous septa, producing a honeycomb appearance (Figure 6). Central fibrosis or calcification may be seen, particularly in large lesions, and can result in sunburst calcification. While this is a pathognomonic feature, it is present in only about 10% of patients with SCAs. A less common macrocystic variant contains larger (greater than 2 cm) cysts. They are typically microcystic. A solid variant contains numerous tiny cysts, each 1-2 mm in diameter, and appears as a homogeneous hypoechoic mass that can be mistaken for a ductal carcinoma.

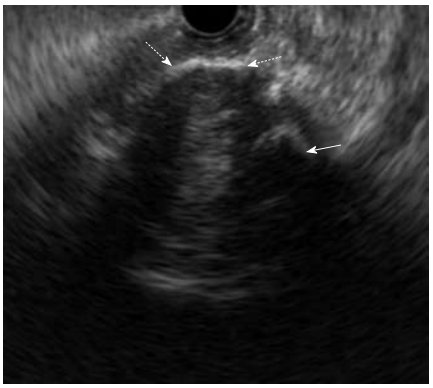

Figure 7 Solid pseudopapillary tumor. EUS shows a tumor in part of the calcified wall (dashed arrows) with acoustic shadow and inner calcifications (arrow) at the body of the pancreas 12 mm in diameter.

Solid pseudopapillary tumors

These tumors have a fairly well-defined behavior and malignant risk and are often managed surgically. In these cases, EUS plays a limited role because of the large size of the lesions and the resulting limitation of the examination field. However, typical EUS images of these tumors reveal well-delimited tumors with inner cystic formations and calcification (Figure 7). The atypical pure fluid forms are difficult to differentiate from the MCNs.

IPMN

IPMNs are more common in the elderly and are located more frequently in the head of the pancreas. IPMNs are characterized by the papillary proliferation of the ductal epithelium that is responsible for mucus production, which leads to the dilatation of the excretory pancreatic ducts. In a minority of cases, an endoscopic diagnosis of an IPMN can be established if a papulous papilla with mucin extrusion, also sometimes referred to as a "fish-eye" ampulla, is seen[61] (Figure 8A). These lesions can progress from hyperplasia to dysplasia, then to carcinoma *in situ*, and finally to invasive carcinoma. Macroscopically, IPMN is characterized by the mucinous dilatation of the pancreatic ducts, with involvement of either the MPD alone (main duct type), the side branch ducts alone (side branch type), or both (combined type)[62-64] (Figure 8B-D). Although communication with the MPD is a feature of side branch type IPMN and helps to exclude MCN, the absence of communication does not exclude IPMN because the mucus can block the flow of contrast into the abnormal side branch. EUS can: (1) visualize the communication between the MPD and a dilated side pancreatic duct; (2) help to make a differential diagnosis between an intraductal mucus deposit (as filaments or hyperechogenic round structures surrounded by a hyperechogenic ring) and a hypoechogenic intraductal polypoid lesion; and (3) visualize the thickening of the pancreatic duct wall or mural nodes. The diagnostic accuracy of EUS for IPMN is 92%, which is higher than that provided by US (82%) or endoscopic retrograde cholangiopancreatography (89%). Although not specific, an underlying malignancy

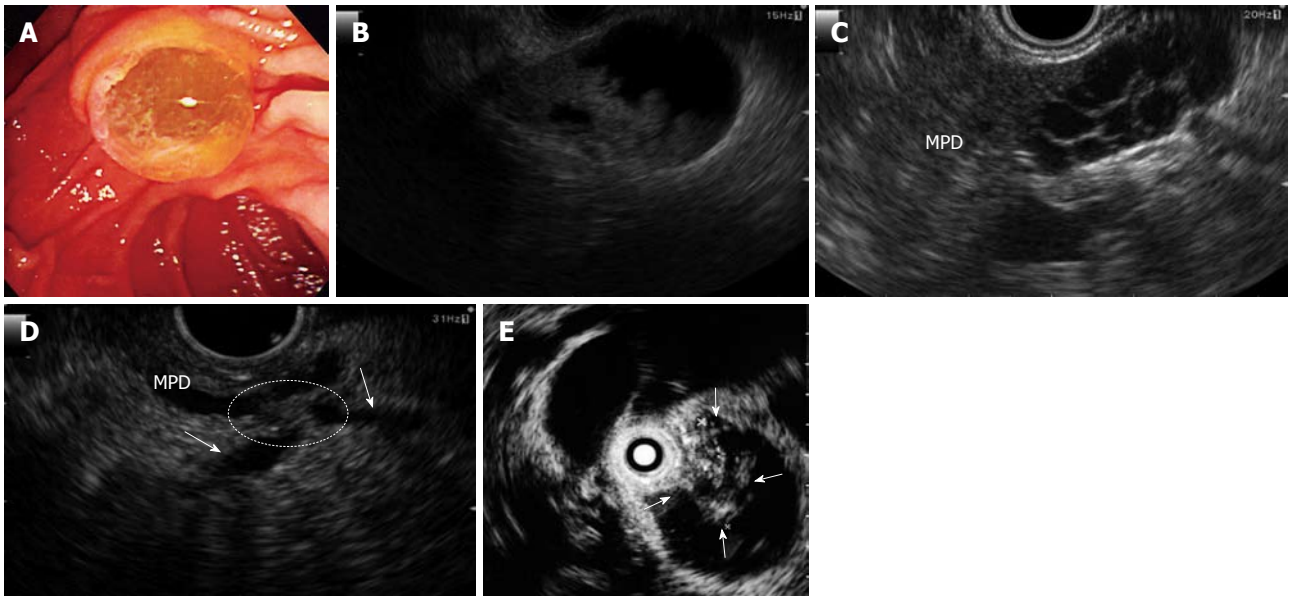

Figure 8 Intraductal papillary mucinous neoplasms (IPMN). A: An endoscopic diagnosis of an IPMN can be established if the "fish-eye" ampulla is visualized in minority cases; B: IPMN of main duct type. EUS shows a mural nodule within by the mucinous dilatation of the pancreatic ducts, with involvement of the main duct at the tail of the pancreas; C: IPMN of side branch type. EUS shows a multiple dilatation of the side branch at the neck of the pancreas; D: IPMN of the combined type. EUS show a mural nodule stretching (circle) over the main pancreatic duct and side branches (arrows) at the body of the pancreas. E: IPMN of main duct type. Intraductal ultrasonography (IDUS) can identify tumor nodule development into the main pancreatic duct (arrows). MPD: Main pancreatic duct.

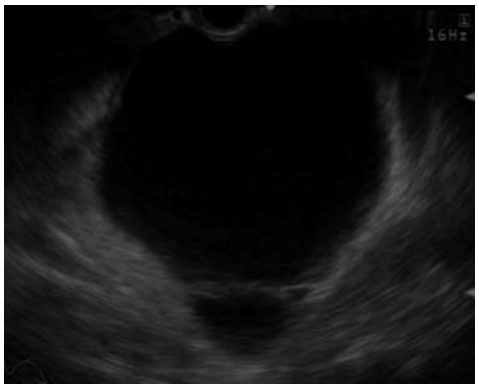

Figure 9 Mucinous cystic neoplasms (MCN). EUS shows a separated macrocyst 40 mm in diameter.

is suggested by an MPD diameter greater than 10 mm, branch-duct type IPMNs that have a cystic lesion diameter greater than 40 mm and a thick, irregular septum, and the presence of mural nodules that exceed 10 mm in diameter[49].

In cases where the pancreatic duct is sufficiently dilated, intraductal ultrasonography (IDUS) that utilizes a thin caliber (approximately 2 mm in diameter) ultrasonic probe with high-frequency ultrasound (12-30 MHz) can be useful. This technique results in images that have a high spatial resolution and can be used to determine the extent of a tumor along the MPD or the progression of a tumor from a branch duct into the MPD. Thus, it provides critical information for surgical candidates with IPMN. It can also detect flat lesions that are less than 500 μm in height[65], but the depth of image penetration is limited (Figure 8E).

MCN

MCNs are more common in middle-aged women and are located more frequently in the body and tail of the pancreas. Although MCNs are typically macrocystic tumors that are > 2 cm in diameter, there are also small MCNS that are only a few, millimeters in diameter (Figure 9). Peripheral calcifications are found in 15% of patients but can also occur in other cystic lesions, as well as in mural nodes or vegetations[66]. Pancreatic duct communication is seldom seen because MCNs originate within the peripheral ductal system. Angiography, although rarely performed on these lesions, shows that most MCNs are hypervascular. Evidence of malignancy includes the presence of cyst wall irregularity and thickening, intracystic solid regions, or an adjacent solid mass. The presence of "ovarian type stroma" is strongly suggestive of an MCN lesion, although MCNs with "non-ovarian type stroma" have also been reported[67,68].

EUS-FNA

EUS-FNA has proved to be a safe and useful method for tissue sampling of pancreatic masses. The safety of EUS-FNA for evaluating pancreatic lesions is now well established[69-71]. Several studies have reported that the rate of complications, which include pancreatitis, infection, and bleeding, is 0%-2%[69,72,73]. In addition, a multicenter study evaluating the safety of EUS-FNA of solid pancreatic masses found that, 14 of 4958 patients developed pancreatitis[69]. The accuracy of EUS-FNA for the diagnosis of pancreatic carcinoma and neuroendocrine tumors is reported to be 80%-95%[72-75] and 46%-83%[75,76], respectively. The low accuracy for endo-

crine tumors may be because inadequate hemorrhagic samples are often obtained: this reflects the vascular nature of these tumors. In terms of the diagnostic sensitivity of EUS-FNA, a study of 282 patients with pancreatic solid tumors with and without chronic pancreatitis found that the diagnostic sensitivity of EUS-FNA was significantly lower for chronic pancreatitis cases (73.9% *vs* 91.3%, $P = 0.02$)[36]. Another study of 69 patients with chronic pancreatitis showed that compared to EUS alone, EUS-FNA of the patients' masses improved the sensitivity, specificity and overall accuracy with which inflammatory conditions could be differentiated from pancreatic adenocarcinomas (63.6% *vs* 72.7%, 75.9% *vs* 100%, 73.9% *vs* 95.7%, respectively)[77]. However, the relatively poor sensitivity of EUS-FNA means that even this technique is insufficient for distinguishing between inflammatory and malignant masses. If the EUS-FNA data are suggestive of pancreatitis but other diagnostic modalities, including EUS, point to pancreatic cancer, close follow-up tests must be performed.

EUS-FNA of a cystic lesion may improve the accuracy of EUS since it permits the cystic fluid to be analyzed and a cytological diagnosis to be made. The cytological analyses include specific testing for the presence of columnar epithelial cells that stain for mucin (which is suggestive of MCNs or IPMNs), or cuboidal epithelial cells that stain for glycogen (which is suggestive of SCAs). In relation to this, a recent cooperative, multicenter trial in the United States studied 112 patients with cystic lesions of the pancreas who first underwent EUS-FNA and then surgical resection of their masses (which provided a histological diagnosis)[54]. The accuracy with which EUS, cystic fluid cytology, and staining of the cyst fluid for tumor markers such as carcinoembryonic antigen (CEA) provided the correct diagnosis was assessed. Of the 112 patients, 68, 7, 25, 5 and 5 were found to have mucinous, serous, inflammatory, endocrine, and other cystic lesions, respectively. Immunostaining for CEA differentiated between mucinous and non-mucinous cystic lesions with significantly greater accuracy (79%) than EUS morphology (51%) or cytology (59%). The investigators concluded that cystic lesions should be aspirated and that the fluid should be analyzed for CEA to differentiate between mucinous and non-mucinous lesions. In contrast, another study found that cystic fluid aspiration and CEA analysis did not improve diagnoses made on the basis of EUS[78]. In this study, 34 patients with a cystic lesion underwent EUS-FNA followed by resection of the lesion. The abilities of EUS, cytology, and cystic fluid analysis to provide a diagnosis were compared. Histological analysis revealed that the lesions were benign (simple cysts, pseudocysts, or SCAs) or malignant/potentially malignant (MCAs, IPMNs, cystic islet cell tumors, or cystic adenocarcinomas). The diagnostic sensitivities of EUS, cytology and CEA were 91%, 27%, and 28%, respectively ($P = 0.01$), their specificities were 60%, 100%, and 25%, respectively, and their accuracies were 82%, 55%, and 27%, respectively. If EUS was combined with cytopathology and CEA, its diagnostic accuracy did not improve further. It was concluded that cystic fluid cytology and CEA analysis does not improve the diagnostic ability of EUS.

Table 1 Pancreatic cyst fluid levels of amylase and tumor markers

	Serous cystadenoma	Mucinous cystic neoplasm	IPMN	Pseudocyst
Amylase	Low	Low	High	High
CEA	Low	High	High	Low
CA 72-4	Low	High	High	Low
CA 19-9	Variable	Variable	Variable	High
CA 125	Low	Variable	Low	Low

IPMN: Intraductal papillary mucinous neoplasia; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen.

Tumor markers other than CEA have also been used to analyze pancreatic cystic fluids sampled by EUS-FNA. These include CA19-9, CA125, and CA 72-4. The largest study to date that has examined the ability of multiple tumor markers in cystic fluid to detect benign and malignant mucinous cystic lesions in pancreatic cystic lesions found that mucinous cystic tumors had significant CA 72-4 levels and that this marker could detect mucinous or malignant cysts with a specificity and sensitivity of 95% and 80%, respectively[79].

Fluid obtained during FNA of pancreatic cysts could be sent for biochemical and cytological analysis, and tumor marker levels, which often determines the cyst type and the presence of malignancy[80-84]. A combined analysis of 11 studies[85,86] found that cytology from cyst fluid was diagnostic in 38% to 48% of cystic pancreatic neoplasms, and the Cooperative Pancreatic Cyst Study[84] determined the diagnostic accuracy to be 59% in this setting. When tumor markers, amylase testing and mucin staining are combined with cytological testing, the diagnostic accuracy increases to 80% or 90%[80-84] (Table 1). High levels of cyst fluid amylase are more often found in cysts that communicate with pancreatic ducts (pseudocysts and IPMN); a cyst fluid amylase level greater than 5000 U/L has a sensitivity and specificity of 61% and 58%, respectively, for distinguishing pseudocysts from other cystic neoplasms[86,87].

With regard to the complications associated with EUS-FNA of pancreatic cystic lesions, it has been reported that in 81 patients subjected to EUS-FNA, one developed an infected cystadenoma[88]. This patient did not receive prophylactic antibiotics before the procedure. The current standard of care for patients undergoing FNA of a pancreatic cystic lesion includes routine administration of antibiotics.

CONTRAST-ENHANCED EUS

While EUS is a diagnostic method that can detect small pancreatic lesions with high sensitivity, it remains difficult to differentially diagnose pancreatic lesions, especially malignant neoplasms in patients with chronic pancre-

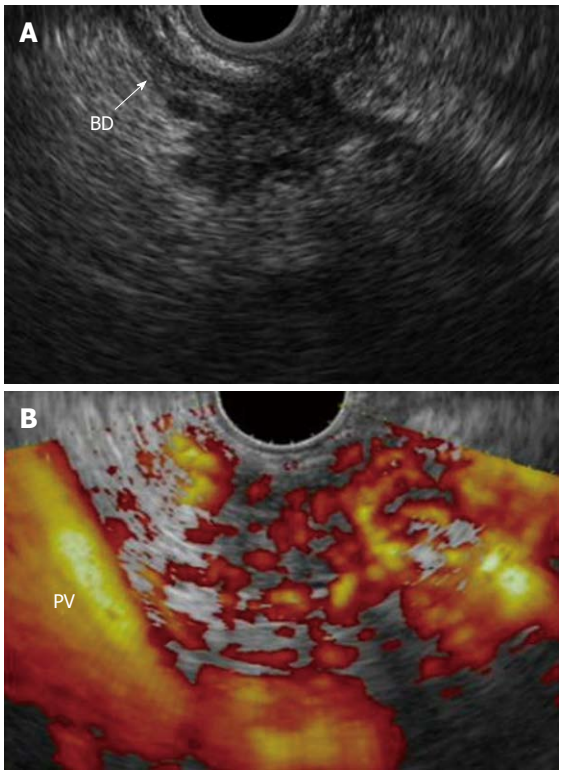

Figure 10 Focal chronic pancreatitis. A: EUS shows a mass with an irregular and inhomogeneous echo pattern at the head of the pancreas; B: Contrast-enhanced power Doppler EUS shows an isovascular nodule compared with the surrounding pancreatic tissue. BD: Bile duct; PV: Portal vein.

atitis[89]. The introduction of EUS-FNA has made this task easier, however, there are cases where the diagnosis is still difficult using EUS-FNA. These include cases where the EUS-FNA aspirant contains insufficient tumor material because the pancreatic tumor is small, and cases with severe chronic pancreatitis that make it difficult to see the borders of the lesion, thereby hampering the accurate insertion of the needle. Moreover, there are cases where a non-invasive diagnostic technique is needed because the patient is using anticoagulants. For these reasons, CE-EUS was developed.

Contrast-enhanced techniques provide information on vascularity and blood flow in normal and pathological tissues. CE-US has played an important role in clinical practice by aiding the differential diagnosis of diseases in a wide array of organs, including the liver, gallbladder, bile duct, pancreas, kidney, thyroid, and prostate. It has also helped to guide interventional procedures and to evaluate treatment responses after local therapies and chemotherapy[90-95].

Several studies that assessed the utility of CE-EUS for diagnosing pancreatic tumors were reported recently[23,96-100]. One of these was our study comparing the ability of power Doppler EUS (PD-EUS), CE-EUS with power Doppler mode using first generation US contrast agent (Levovist), and contrast-enhanced helical CT (CE-CT) to diagnose small pancreatic tumors[23]. PD-EUS and CE-EUS allowed the pancreatic tumors to be classified according to their density of vessels relative to the vascularity of the surrounding pancreatic tissue, namely as, hypovascular, isovascular, and hypervascular (Figures 10 and 11): For small pancreatic tumors that were ≤ 2 cm, the sensitivity with which PD-EUS, CE-EUS and CE-CT differentiated ductal carcinoma from other tumors was 50%, 83.3% and 11%, respectively. Thus, CE-EUS was significantly more sensitive than PD-EUS and CE-CT, which suggests that CE-EUS is particularly useful for differentially diagnosing, pancreatic tumors, especially small pancreatic tumors. However, such Doppler ultrasonography with contrast enhancement has several limitations, including blooming artifacts, poor spatial resolution, and low sensitivity to slow flow[96-99]. Indeed, in our study, these limitations

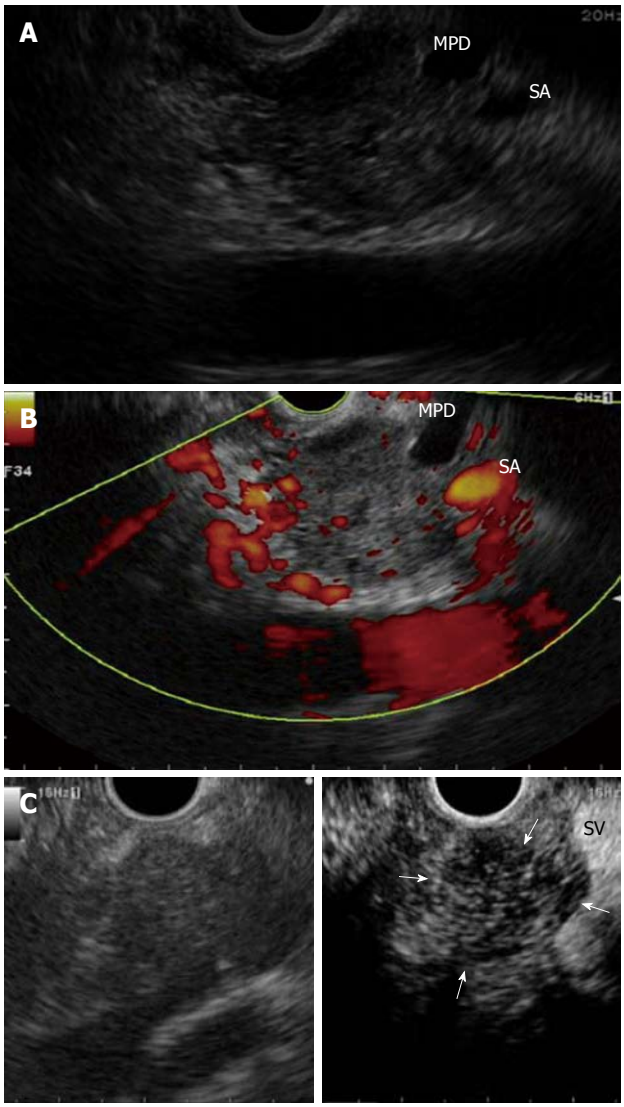

Figure 11 Pancreatic adenocarcinoma. A: EUS shows a heterogeneous hypoechoic mass with irregular margins at the body of the pancreas and tail side main pancreatic duct enlarged due to the infiltrating mass; B: Contrast-enhanced power Doppler EUS shows a hypovascular nodule compared with the surrounding pancreatic tissue; C: Contrast-enhanced harmonic EUS showing a clear margin and hypovascular nodule compared with surrounding pancreatic tissue (arrows) without blooming artifact such as that found with Doppler imaging. Left: B-mode imaging; Right: Contrast imaging. MPD: Main pancreatic duct; SA: Splenic artery.

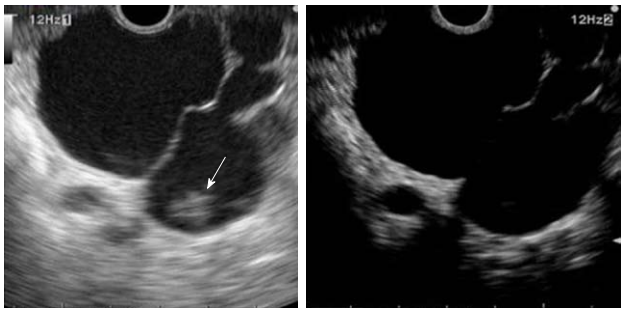

Figure 12 IPMN of side branch type. Left (B-mode image): The nodule (arrow) in dilatation of the side branch cannot be distinguished between sediment and tumor by B-EUS; Right (contrast image): Contrast-enhanced harmonic EUS reveals that this nodule is sediment.

prevented vascularity from benign evaluated in 7.8% of all patients, of whom 22.2% had carcinomas that were ≤ 2 cm in diameter.

Hocke *et al*[100] evaluated the ability of CE-EUS with power Doppler mode using SonoVue, a second generation US contrast agent, to differentiate inflammation from pancreatic carcinoma on the basis of the perfusion characteristics of the microvessels. For this study, chronic pancreatitis without neoplasm was defined as the lack of detectable vascularization or the regular appearance of vessels both before and after the injection of SonoVue, and the detection of both arterial and venous vessels in the contrast-enhanced phase. Malignancy was defined as the lack of detectable vascularization before the injection of SonoVue, the irregular appearance of arterial vessels after the injection of SonoVue, and the absence of venous vessels in the lesion. In patients with chronic pancreatitis, combined conventional B-mode and power Doppler EUS diagnosed pancreatic cancer with a sensitivity and specificity of 73.2% and 83.3%, respectively, whereas CE-EUS with power Doppler had a sensitivity and specificity of 91.1% and 93.3%, respectively. Thus, CE-EUS is highly useful for the differential diagnosis of pancreatic cancer.

CONTRAST-ENHANCED HARMONIC EUS

Kitano *et al*[101] recently developed an echoendoscope with a broad-band transducer and an imaging mode specifically for CEH-EUS. This technology can detect signals from microbubbles in vessels with a very slow flow without Doppler-related artifacts and can be used to characterize tumor vascularity in the pancreas (Figure 11C). Second-generation US contrast agents such as SonoVue and Sonazoid, harmonic signals at low acoustic powers and thus are suitable for EUS imaging at low acoustic powers[102,103]. CEH-EUS successfully creates novel perfusion images and the vascular structures of pancreatic lesions (Figure 12). This CEH-EUS mediated evaluation of the microvasculature of pancreas lesions is expected to improve the differential diagnosis of pancreatic disease in the near future.

OTHER DIAGNOSTIC EUS ADAPTED PROCEDURES

IDUS

The list of indications of EUS is growing, which has forced gastroenterologists to think outside the lumen. Technological advances in EUS imaging has led to the development of IDUS mini propes for the evaluation of the pancreatobiliary tree and periductal structures. In the evaluation of patients with pancreatic duct stenosis, IDUS can be used to distinguish malignant strictures, allow for the early detection of small pancreatic adenocarcinomas, assist in local staging and to determine resectability[104,105]. IDUS may also be useful for the localization of pancreatic neuroendocrine tumors not visualized by other imaging modalities[104-106]. In the evaluation of IPMN, IDUS is used to determine malignant disease and disease extent before surgery. IDUS and pancreatoscopy had a reported combined sensitivity, specificity and accuracy of 91%, 82% and 88%, respectively[107].

EUS-elastography

EUS-elastography can assess tissue hardness by measuring its elasticity which might provide clinical utility in the diagnosis of pancreatic disorders. Tissue elasticity studies can provide information on both its pattern and distribution. EUS-elastography has introduced a new form of pathologic analysis, that is, tissue elasticity. This parameter appears to correlate with the malignant potential of the lesions. Importantly, the image of EUS elastography indicates the relative value in a region of interest (ROI), so the same lesion might display different colors in a different ROI. This is a limitation of EUS-elastography. The other is the distribution of tissue elasticity. With the prototype image analysis software, we can now capture and analyze features of real-time tissue elastography by using computer software. Theoretically, this will limit interpretation bias and provide a measure of pattern distribution that is constant and independent, regardless of ROIs[108]. More studies and greater experience are needed before it has a place in our diagnostic armamentarium.

Tridimensional-EUS

Tridimensional (3D)-EUS certainly facilitates anatomical interpretation of the images in the pancreatobiliary area, as well as vascular landmarks used for staging and assessment of resectability. The method might be feasible for the assessment of venous invasion and venous compression in focal pancreatic masses, in both chronic pancreatitis and pancreatic cancer[109]. The acquisition of 3D volume allows a retrospective assessment and slicing of the reconstructed cube, with accurate depiction of focal masses, even if missed on the initial real-time evaluation. However, further progress of the technology is still necessary.

CONCLUSION

EUS is established as a most accurate method for stag-

ing malignancies of the pancreas, particularly small pancreatic lesions. EUS-FNA also allows safe tissue sampling of pancreatic tumors. EUS and EUS-FNA are now indispensable for the management of pancreatic tumors. In addition, we have recently been able to use various new EUS adapted technologies such as CE-EUS and CEH-EUS in clinical practice, which are helpful in the differential diagnosis of pancreatic tumors, especially small pancreatic tumors. Further improvements in EUS technology are expected to provide more useful modalities for the detection and diagnosis of pancreatic tumors.

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