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Review Article

Contrast-enhanced endoscopic ultrasound for pancreatobiliary disease

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ABSTRACT

Endoscopic ultrasound (EUS), with or without fine needle aspiration (FNA), has become an essential tool in the evaluation of pancreatobiliary diseases. Although conventional EUS is superior to multidetector computed tomography in tumor detection and staging, there are situations when characterization of various pancreatobiliary lesions remains difficult. Contrast-enhanced EUS (CE EUS) can further improve the detection and characterization of pancreatic solid lesions such as ductal adenocarcinoma, neuroendocrine tumor, or mass-forming autoimmune pancreatitis based on differences in the enhancement pattern of the target lesions. It is also useful in differentiating between mural nodules and mucous clots in pancreatic cystic neoplasms, and characterizing various lesions in the gallbladder and bile duct. CE EUS is complementary to FNA and has the potential to increase the diagnostic yield on the first FNA needle pass.

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Introduction

Endoscopic ultrasound (EUS) has become an indispensable tool in the evaluation of both benign and malignant pancreatobiliary diseases.^{1,2} When compared with computed tomography (CT), EUS has been shown to have higher sensitivity for detecting a pancreatic mass and tumor staging preoperatively in patients with suspected non-metastatic pancreatic cancer.^{3,4} However, despite its high spatial resolution, there are still situations when conventional EUS may be limited in its ability in characterizing various pancreatobiliary lesions. Examples of such challenging circumstances include differentiation of pancreatic adenocarcinoma from chronic focal pancreatitis, or differentiation of pancreatic adenocarcinoma from mass-forming autoimmune pancreatitis (AIP). Contrast-enhanced EUS (CE EUS) allows better evaluation of the vascularity and perfusion pattern of the target lesion and has become one of the novel advanced diagnostic techniques for improved characterization of both benign and malignant pancreatobiliary lesions.^{5,6} This article aims to review the current status of CE EUS applications in pancreatobiliary diseases.

Evolution of Contrast-Enhanced EUS

The fundamental principle of CE EUS involves the use of an ultrasound contrast agent composed of microbubbles with a lipid or albumin outer shell to highlight the microvasculature and perfusion pattern in the target lesion.^{5,6} In 1995, CE EUS was first performed by infusion of carbon dioxide gas as ultrasound contrast into the celiac or superior mesentery artery via a catheter.⁷ However, this form of CE EUS is relatively invasive and cumbersome to perform since angiographic technique is employed for ultrasound contrast infusion into specific vessels. On the other hand, CE EUS imaging performed with the fundamental B mode ultrasound after intravenous contrast injection was found to be suboptimal since the B mode ultrasound is inadequate in selectively detecting the signal from the contrast agent against the strong background echo intensity in the target tissue.⁵

As technology improves, CE EUS imaging techniques have evolved over time and can be performed with intravenous contrast agents by one of the two methods: contrast-enhanced Doppler EUS (CED EUS), or contrast-enhanced harmonic EUS (CEH EUS).⁵ The color Doppler or the power Doppler on electronic echoendoscopes is best used for visualization of vessels with rapid flow.⁵ On CED EUS, pancreatic ductal adenocarcinomas are

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usually observed as solid mass lesions with hypovascularity.^{5,8–10} The finding of a hypovascular pancreatic solid mass lesion on CED EUS was reported to be 83%–92% sensitive for adenocarcinoma.^{8–10} However, despite the promising results, images obtained by CED EUS often suffer from blooming artifacts (vessels looking bigger on power Doppler imaging when compared to B mode imaging), motion artifacts (generation of Doppler signals due to movement of the target tissue), and poor sensitivity for intra-lesional vessels with slow flow.^{5,8–10} On the other hand, intra-lesional slow-flowing vessels can be better demonstrated by contrast harmonic imaging without Doppler-related artifacts owing to its ability to detect the second harmonic signals of the contrast agents more strongly than the background signal of the target lesion.^{5,11–13} The technique of CEH EUS was made possible by the use of second generation ultrasound contrast agents such as SonoVue (Bracco Imaging, Milan, Italy) and Sonazoid (Daiichi-Sankyo, Tokyo, Japan), which can produce harmonic signals at lower acoustic power generated by the transducers on the modern electronic echoendoscopes.^{5,11–13} Contrast harmonic imaging technique has become the mainstay in modern CE EUS. The imaging characteristics and clinical applications of CEH EUS in pancreatobiliary diseases will be further discussed in the following sections.

Contrast-Enhanced EUS in Pancreatobiliary Diseases

Solid mass lesions of the pancreas

Although conventional EUS is superior to CT in detecting a pancreatic solid lesion and tumor staging, characterization of various types of solid lesions, especially small lesions, may still be challenging. Solid pancreatic lesions can be better characterized based on the difference in enhancement pattern of the target lesion on CE EUS.^{11–13} The enhancement pattern of solid mass lesions can be classified as non-enhancement, hypo-enhancement, iso-enhancement, and hyper-enhancement on CE EUS.¹⁴

Majority of the pancreatic ductal adenocarcinomas are depicted as hypo-enhanced lesions on CE EUS (Fig. 1).^{14,15} In a recent meta-analysis including 5 studies with CED EUS and 7 studies with CEH EUS, a hypo-enhanced pattern on CE EUS has both high pooled sensitivity of 94% (95% confidence interval [CI], 0.91–0.95) and high specificity of 89% (95% CI, 0.85–0.92) for pancreatic ductal adenocarcinoma.¹⁶ In a study with 277 solid pancreatic lesions, CEH EUS was found to be superior to contrast enhanced multidetector CT in characterizing lesions < 2 cm.¹⁴ In the same study, combining CEH EUS with EUS fine needle aspira-

tion (FNA) would increase the overall sensitivity in diagnosing pancreatic ductal adenocarcinoma from 92.2% by EUS FNA alone to 100%.¹⁴ CE EUS was shown to better demonstrate the depth of invasion and presence of vascular invasion in pancreatobiliary cancers. In the study with 26 cases of surgically resected pancreatobiliary cancers, CEH EUS was found to be more accurate in T-staging when compared to conventional EUS (91.4% vs 69.2%, $P < 0.05$).¹⁷

Pancreatic neuroendocrine tumors (PNET) on the other hand were most commonly found to be hyper-enhanced on CE EUS due to the vascular nature of the lesion (Fig. 2).^{5,14} When compared with multidetector CT and transabdominal ultrasound, CE EUS was shown to be more sensitive in detecting a PNET.¹⁸ The finding of hyper-enhancement on CE EUS has a sensitivity of 78.9%–95.1% for PNET.^{14,18} Benign lesions of the pancreas, such as inflammatory lesions are often iso-enhanced on CE EUS.⁵ In the study of 277 solid pancreatic lesions, 36 out of the 46 cases (78.2%) of inflammatory pseudotumors displayed iso-enhancement on CEH EUS (Fig. 3).¹⁴ In another study, 8 out of 8 cases (100%) of AIP were found to have an iso-enhanced, homogeneous pattern on CEH EUS.¹⁹

Cystic neoplasms of the pancreas

In the recently updated 2012 international consensus guidelines for the management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas, an enhancing solid component and a non-enhancing mural nodule are considered a high-risk stigmata of malignancy and a worrisome feature, respectively.²⁰ However, differentiation between a mucous clot and a mural nodule may be difficult on conventional EUS. CE EUS is helpful in this regards since a true mural nodule would display enhancement after contrast injection while a mucous clot would be shown as an avascular structure.^{13,21} Four types of mural nodules have been described based on CE EUS features: low papillary nodule (type I), polypoid nodule (type II), papillary nodule (type III), and invasive nodule (type IV).²² In the study with 84 resected IPMNs, type III and type IV mural nodules were most commonly associated with malignancy among the four mural nodule types.²² In another study with 50 branch duct IPMNs diagnosed by CT and EUS, the diagnostic accuracy for mural nodule increases to 98% when both conventional EUS and CE EUS were used.²³

Fig. 1. Contrast-enhanced harmonic endoscopic ultrasound (CEH EUS) showing the typical hypo-enhancement pattern in a small pancreatic ductal adenocarcinoma (arrows). (A) Conventional B-mode EUS imaging. (B) CEH EUS imaging.

Fig. 2. Contrast-enhanced harmonic endoscopic ultrasound (CEH EUS) showing the typical hyper-enhancement pattern in a pancreatic neuroendocrine tumor. (A) Conventional B-mode EUS imaging. (B) CEH EUS imaging.

Fig. 3. Contrast-enhanced harmonic endoscopic ultrasound (CEH EUS) showing the iso-enhancement pattern of an inflammatory pseudotumor in autoimmune pancreatitis (arrows). (A) Conventional B-mode EUS imaging. (B) CEH EUS imaging.

Lesions of the bile duct and gallbladder

Bile duct wall thickening causing biliary stricture can result from benign inflammatory disease or malignancy. CE EUS is an option for further characterization of bile duct wall thickening and biliary stricture when brush cytology during endoscopic retrograde cholangiopancreatography or cholangioscopy with/without biopsy results are inconclusive. The finding of a hypo-enhanced pattern on a thickened bile ductal wall is most suggestive of malignancy, while enhancement of the thickened bile duct wall was reported to be more commonly associated with inflammatory condition.^{6,24,25}

CEH EUS has been studied in the characterization of benign and malignant gallbladder polyps.^{26,27} In a study of 87 patients, a homogeneous enhancement pattern on CEH EUS was 75.0% sensitive and 66.6% specific in distinguishing gallbladder adenomas from cholesterol polyps, whereas a heterogeneous enhancement pattern was more commonly seen in cholesterol polyps on CEH EUS.²⁶ In another study of 93 patients with gallbladder polyps larger than 10 mm, the finding of irregular intratumoral vessels or perfusion defects on CEH EUS were found to be highly sensitive (93.5%) and specific (90.0%) predictors for malignant gallbladder polyps.²⁷

CEH EUS guided FNA

In addition to better characterization of pancreatobiliary lesions by their respective enhancement patterns, CEH EUS has the potential to reduce the number of passes required for diagnosis. In a randomized study of 40 patients comparing CEH EUS guided FNA and conventional EUS FNA, while the overall diagnostic sensitivity and accuracy for malignancy were not significantly different between the CEH EUS FNA group and the conventional EUS FNA group (90% vs 85%, $P = 0.50$), there was a higher frequency for the CEH EUS FNA group to obtain sufficient sample on one needle pass for diagnosis when compared to the conventional EUS FNA group (60% vs 25%, $P = 0.027$).²⁸ Further studies would be needed to evaluate the optimal role of CEH EUS guided FNA in clinical practice.

Quantitative measurements in CEH EUS

While most studies on CE EUS have described qualitative contrast enhancement pattern of the target lesion, quantitative evaluation by CEH EUS can be performed by generation of time-intensity curve (TIC).^{13,19} In the study of 91 pancreatic lesions (48 pancreatic ductal adenocarcinoma, 27 mass-forming pancreatitis and AIP, 16 PNET with CEH EUS) using Sonazoid as contrast agent, the echo intensity reduction rate from the peak at 1 minute

was found to be the greatest in pancreatic ductal adenocarcinoma, followed by mass-forming pancreatitis, AIP, and PNET ($P < 0.05$).²⁹ The diagnostic accuracy increased to 94.7% when TIC was combined with EUS.²⁹ In another study with 8 AIP and 22 pancreatic ductal adenocarcinomas evaluated by CEH EUS using Sonazoid, the peak intensity and maximum intensity gain of the suspected mass lesion of AIP were demonstrated to be significantly higher than those of pancreatic ductal adenocarcinoma.¹⁹

Conclusion

The technology and indications of CE EUS have evolved over time. When compared with conventional EUS, CE EUS has been shown to improve detection and characterization of both benign and malignant pancreatobiliary lesions. CE EUS is complementary to FNA and has the potential to reduce the number of passes required for diagnosis.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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