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Review

Contrast-enhanced endoscopic ultrasound

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Compared to other imaging modalities, endoscopic ultrasound (EUS) has limitations in terms of image enhancement. However, with the availability of contrast agents in ultrasonography, EUS has evolved. Contrast-enhanced Doppler EUS (CD-EUS) enhances Doppler signals from vessels and is useful for characterizing lesions detected by EUS. Moreover, contrast-enhanced harmonic EUS (CH-EUS) with second-generation ultrasound contrast agents and a broad band transducer allows microvessels and parenchymal perfusion to be visualized. Vascularity can also be quantitatively analyzed during CH-EUS by generating a time-intensity curve. CE-EUS is useful for characterizing pancreatic lesions and can detect pancreatic adenocarcinomas with a sensitivity of 94% and a specificity of 89% as a result of the hypo-enhancement of these lesions. Indeed, CH-EUS is superior to multiple detector-computed tomography in terms of the differential diagnosis of small lesions that are ≤2 cm. CH-EUS complements EUS-guided fine-needle aspiration (EUS-FNA) as it identifies the EUS-FNA target and lesions with false-negative EUS-FNA findings. CH-EUS is also used to estimate the malignant potential of gastrointestinal stromal tumors and helps to differentiate between malignant and benign lymphadenopathy.

Key words: contrast-enhanced endoscopic ultrasound, endoscopic ultrasound, ultrasound contrast

DEVELOPMENT OF CONTRAST-ENHANCED ENDOSCOPIC ULTRASOUND

ENDOSCOPIC ULTRASOUND (EUS) imaging has been evolving since the first report on its utility in the diagnosis of digestive diseases.[1–3] Its development includes color and power Doppler, 3D imaging and electronic scanning, tissue harmonic, elastography and contrast enhancement.[4] However, compared to other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), EUS is limited in terms of characterizing lesions with contrast enhancement.

Hemodynamics of any area, both pathological and normal, needs to be evaluated for both blood flow in small vessels (2 or 3 mm in minimum diameter) and parenchymal microvasculature.[5] Contrast-enhanced endoscopic ultrasound (CE-EUS) was first reported by Kato *et al*., who used fundamental EUS with carbon dioxide gas.[6] The infusion of carbon dioxide gas through a catheter implanted into the celiac or superior mesenteric artery allowed vascularity to be depicted in EUS images. However, this technique was limited by the fact that the EUS had to be carried out during angiography examinations. EUS was then equipped with color and power Doppler mode to identify large vessels; this was particularly useful for avoiding vessels during EUS-guided fine-needle aspiration (EUS-FNA). However, whereas Doppler EUS can be used to assess whether target lesions have large vessels, it detects vessels with slow flow with poor sensitivity and cannot depict parenchymal perfusion.

The subsequent development of i.v. ultrasound contrast agents composed of microbubbles enabled us to carry out CE-EUS without having to carry out angiography.[7–9] Contrast-enhanced Doppler EUS increases the sensitivity to signals from vessels by generating pseudo-Doppler signals from microbubbles.[7–12] However, contrast-enhanced Doppler EUS suffers from artifacts such as blooming, in which vessels appear to be larger than they really are.[8–10] Recently, technological innovations in contrast-enhanced harmonic imaging have allowed microvessels and parenchymal perfusion to be visualized.[13,14] This allows lesions to be characterized more accurately.

INTRAVENOUS ULTRASOUND CONTRAST AGENTS

ULTRASOUND CONTRAST AGENTS consist of microbubbles of approximately 2–5 μm in diameter.[9,15] In addition to the back-scattering of the ultrasound signal, contrast microbubbles oscillate to sound pressure and have a

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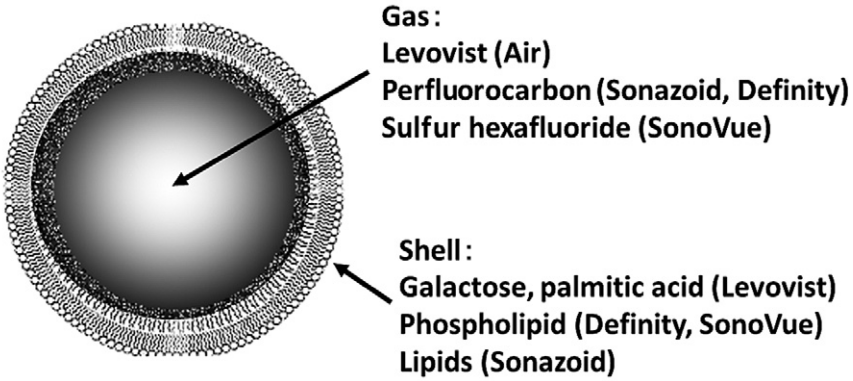

Figure 1 Ultrasound contrast agents. First-generation ultrasound contrast agent (Levovist; Bayer Schering Pharma, Berlin, Germany) is composed of air, whereas second-generation ultrasound contrast agents (SonoVue [Bracco SpA, Milan, Italy], Sonazoid [Daiichi-Sankyo, Tokyo, Japan; GE Healthcare Milwaukee, WI, USA, and Definity [Lantheus Medical Imaging, Billerica, MA, USA]) are composed of other gasses.

variable asymmetrical diameter of between 2 and 10 μm.[15,16] As the microbubbles are given through a large peripheral vein, they do not leave the vascular system and pass through the lung circulation inducing contrast enhancement of the whole vascular system.[15,16] The first ultrasound contrast agent was Levovist (Bayer Schering Pharma, Berlin, Germany), which consists of microbubbles of air that are covered by galactose and palmitic acid (Fig. 1).[15] When used during transabdominal ultrasonography, Levovist depicts harmonic signals from microbubbles, thus allowing contrast-enhanced harmonic imaging.[17–20] However, contrast-enhanced harmonic imaging requires high acoustic power to oscillate or break the Levovist microbubbles. EUS is equipped with only a small transducer and the transmission signals from this transducer are too low to oscillate or break Levovist microbubbles. By contrast, second-generation ultrasound contrast agents, such as SonoVue (Bracco SpA, Milan, Italy), Sonazoid (Daiichi-Sankyo, Tokyo, Japan; GE Healthcare Milwaukee, WI, USA) and Definity (Lantheus Medical Imaging, Billerica, MA, USA) (which consists of microbubbles of gases other than air) (Fig. 1), can be oscillated or broken by lower acoustic power.[9,10,13,21] The development of the latter microbubbles thus promoted contrast-enhanced harmonic imaging in the field of EUS.[13,14,16,22,23]

CONTRAST-ENHANCED DOPPLER EUS

UNTIL RECENTLY, POWER Doppler and color Doppler were used for CE-EUS.[7,8,21,24–27] All types of ultrasound contrast agents induce phase shift (pseudo-Doppler signals), which enhances the Doppler signals from the vessels. Thus, infusing a contrast agent increases the sensitivity with which color and power Doppler imaging depicts Doppler signals from vessels.[10,11] However, contrast-enhanced Doppler EUS suffers from Doppler-related artifacts such as blooming. Recently, a novel type of directional power Doppler method called Directional eFLOW (Aloka Co., Ltd, Tokyo, Japan) was developed.[28] This method permits blood flow in minute vessels to be detected in more detail than can be achieved with conventional power or color Doppler (Fig. 2). In the directional eFLOW mode, fewer blooming artifacts are observed because broadband transmission is optimized and the real repeating frequency is increased.

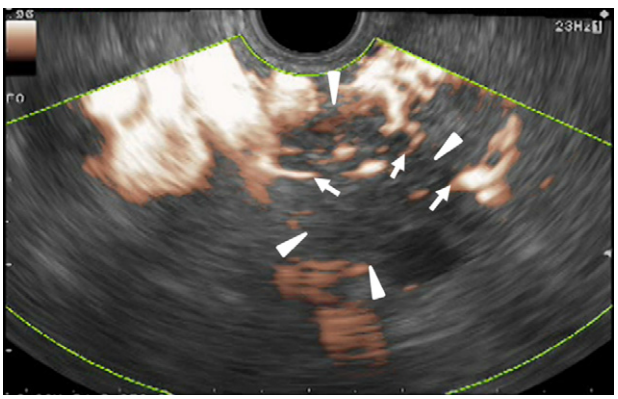

Figure 2 Contrast-enhanced directional eFLOW imaging in a pancreatic carcinoma. Endoscopic ultrasound with contrast-enhanced directional eFLOW imaging shows a hypoechoic tumor (arrowheads) at the pancreas head. Irregular vessels (arrows) are observed at the periphery of the tumor with fewer blooming artefacts. Color signals are fewer in the center of the tumor than in the periphery.

CONTRAST-ENHANCED HARMONIC EUS

WHEN THE ULTRASOUND contrast agents receive a certain range of acoustic power, they produce a second harmonic component.[10,11,29,30] The second harmonic component from microbubbles is much higher than that from

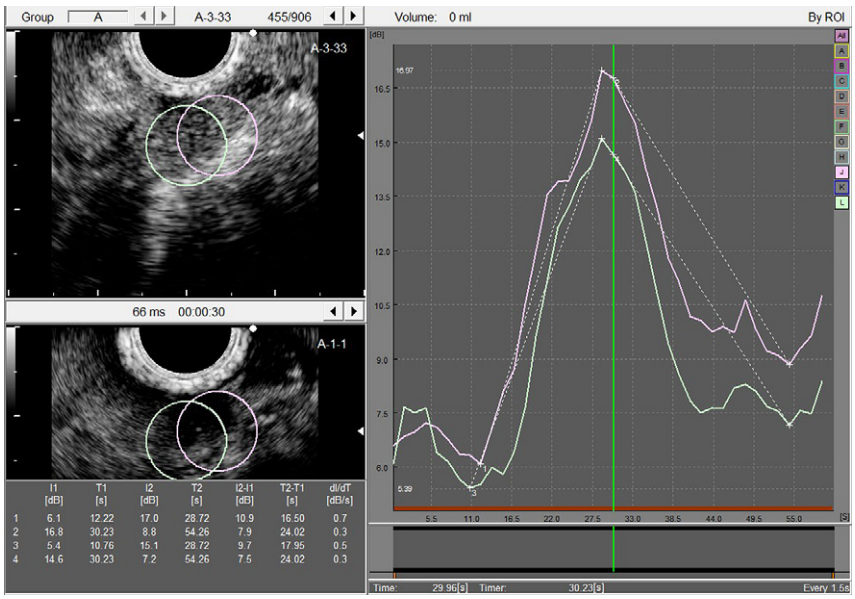

Figure 3 Time–intensity curve of echo intensity in a pancreatic carcinoma. Time-course of the echo intensity in the colored circle is measured.

the tissue. Contrast-enhanced harmonic EUS selectively depicts the second harmonic component, which results in selective visualization of microbubbles.[10,11,29,30] Compared to Doppler imaging, which depicts vessel flow, contrast-enhanced harmonic imaging depicts the microbubbles themselves.[10,11,14] Thus, contrast-enhanced harmonic imaging can visualize fine vessels with slow flow. This technology allows microvessels to be visualized as well as parenchymal perfusion.[14] Moreover, by measuring the time-course of echogenicity intensity (time–intensity curve), vascularity can be quantitatively analyzed (Fig. 3).[5,31–34]

CE-EUS FOR PANCREATIC DISEASES

ENDOSCOPIC ULTRASOUND HAS an advantage over other imaging methods in obtaining high-resolution images of the pancreas, which is a highly sensitive method for the diagnosis of pancreatic tumors.[35–37] However, EUS has been limited in the characterization of some lesions in the pancreas. Evaluation of vascularity using contrast agents is one of the candidates to improve the ability to characterize pancreatic lesions depicted by EUS.[5,9,16,22,30] The finding of a hypoenhancing mass was a sensitive and accurate identifier of patients with adenocarcinoma, which was more accurate in the diagnosis than finding a hypoechoic lesion using standard EUS ($P < 0.001$).[38] A recent meta-analysis on CE-EUS that analyzed reports on both contrast-enhanced Doppler and contrast-enhanced harmonic EUS showed that this method differentially diagnoses pancreatic adenocarcinomas with a pooled sensitivity and specificity of 94% and 89%, respectively.[39] This article also showed that the detection of a hypoenhanced lesion is an accurate predictor of pancreatic adenocarcinoma. However, this article included results of both CD-EUS and CH-EUS.[39] As described previously, CD-EUS has a limitation in the depiction of small vessels with slow flow and depicts artifacts such as blooming. Therefore, CD-EUS fails to evaluate the vascularity of some tumors, such as those of small size and adjacent to large vessels. In contrast, CH-EUS allows visualization of microvasculature, which results in detailed observation of intratumoral structure and characterization of difficult cases (Fig. 4).[14,40] Indeed, hypovascularity as a sign of ductal carcinomas in CH-EUS obtained a sensitivity of 89–95% and a specificity of 64–89%.[38,40,41] Particularly, CH-EUS was significantly more accurate than CT in diagnosing small ductal carcinomas of ≤2 cm ($P < 0.034$).[41] The sensitivity and specificity in diagnosing pancreatic carcinomas with EUS are 91% and 94%, respectively, whereas those values with CT are 71% and 92%, respectively.[41]

With respect to pancreatic neuroendocrine tumors, most heterogeneous hypoechoic areas and anechoic areas corresponded to hemorrhage or necrosis on pathological examination, which was the most significant factor for malignancy. They were identified as filling defects in CD-EUS and were more clearly recognized than in conventional EUS.[26] Recent articles on quantitative analyses using a time–intensity curve with CH-EUS revealed that the values of maximum intensity,[33] accumulated intensity during observation,[34] intensity reduction rate,[32] and the ratio between the uptake inside the mass and the uptake of the surrounding parenchyma[31] are

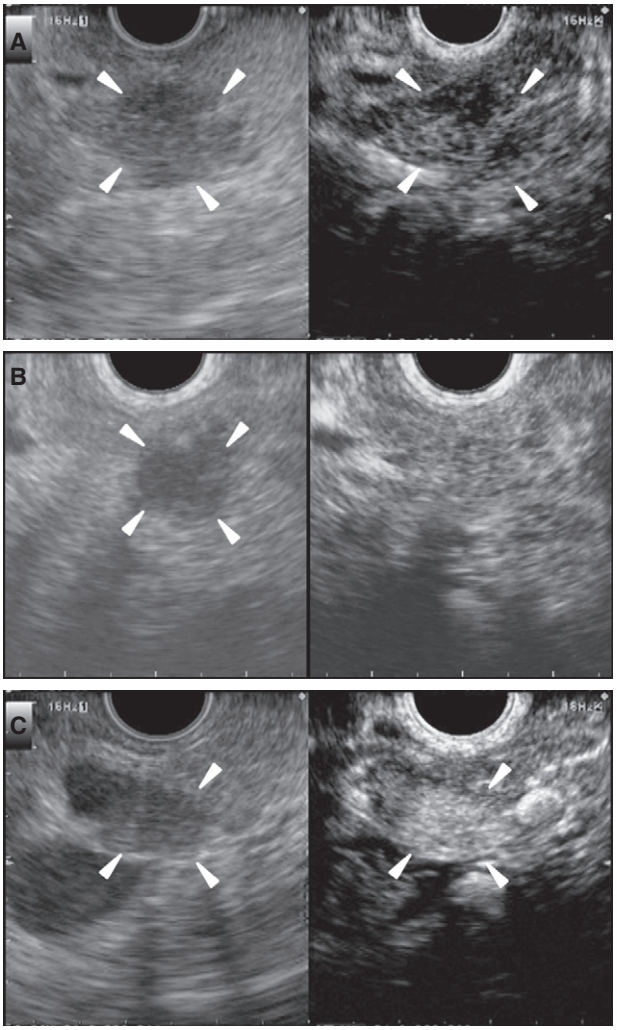

Figure 4 Typical contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) images of pancreatic tumors. (a) Ductal carcinoma with hypoenhancement. Conventional EUS (left) shows a hypoechoic area (arrowheads) of 15 mm in diameter at the pancreas tail. CH-EUS (right) indicates that the area has hypoenhancement (arrowheads) compared with the surrounding tissue. (b) Inflammatory pseudotumor with isoenhancement. Conventional EUS (left) shows a hypoechoic area (arrowheads) of 9 mm at the pancreas body. CH-EUS (right) indicates homogeneous enhancement in this area similar to the surrounding tissue; a margin is not observed. (c) Neuroendocrine tumor with hyperenhancement. Conventional EUS (left) shows a hypoechoic mass (arrowheads) of 9 mm in diameter at the pancreas body. CH-EUS (right) indicates that enhancement (arrowheads) in the mass is higher than in the surrounding tissue.

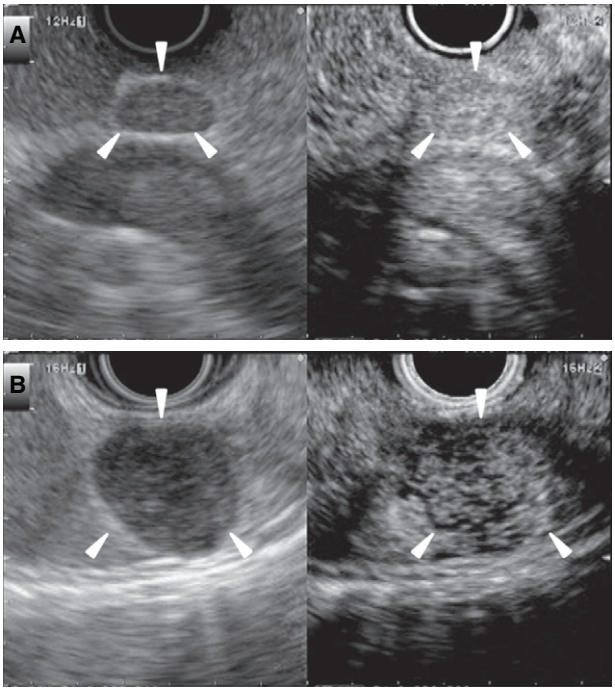

Figure 5 Typical contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) images of lymphadenopathy. (a) Reactive lymphadenopathy with homogeneous enhancement. Conventional EUS (left) shows a lymph node of 10 mm in diameter (arrowheads). CH-EUS (right) indicates that the lymph node has homogeneous enhancement (arrowheads). (b) Metastatic lymphadenopathy with heterogeneous enhancement. Conventional EUS (left) shows a lymph node of 15 mm in diameter (arrowheads). CH-EUS (right) indicates that the lymph node has heterogeneous enhancement (arrowheads).

useful for discrimination of carcinomas from autoimmune pancreatitis, pseudotumors and neuroendocrine tumors. CH-EUS is also used for T staging of pancreatobiliary carcinomas. CH-EUS is superior to tissue harmonic EUS without contrast enhancement in T staging.[42] In particular, CH-EUS more clearly depicts invasion of the portal vein.

CE-EUS FOR DIGESTIVE TRACT DISEASES

WHEN CH-EUS WAS carried out in subepithelial tumors, the time–intensity curve revealed that echo intensity in gastrointestinal stromal tumors (GIST) was significantly higher than that in benign tumors such as lipomas.[43] In addition, CH-EUS allows visualization of vessels flowing from the periphery to the center of GIST (Fig. 5).[43,44] All high-grade malignancy GIST possess these irregular vessels.[44] CH-EUS depicted these irregular vessels in all high-grade malignancy GIST, whereas CT depicted

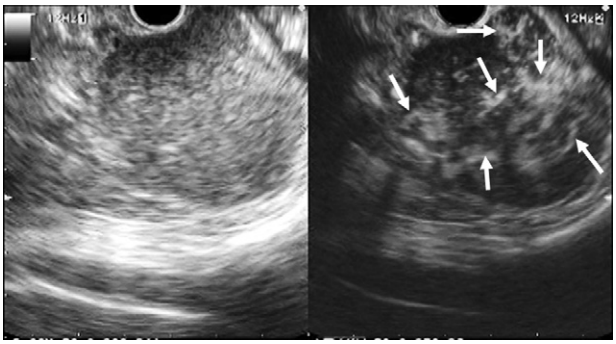

Figure 6 Typical contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) image of gastrointestinal stromal tumor with high-grade malignancy. Conventional EUS (left) shows a submucosal tumor of 50 mm in diameter. CH-EUS (right) indicates that the tumor has irregular vessels (arrows).

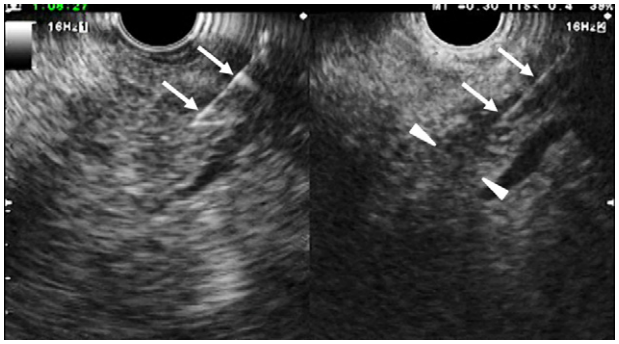

Figure 7 Fine-needle aspiration (FNA) guided by contrast-enhanced harmonic endoscopic ultrasound (CH-EUS). CH-EUS (right) reveals a tumor with hypoenhancement (arrowheads), whereas conventional EUS does not (left). FNA can be carried out under the guidance of CH-EUS. Arrows indicate a needle.

them in only 31%.[44] These results suggest that CH-EUS can be applied for estimation of the malignant potential of GIST.[44]

Differential diagnosis of malignant from benign lymphadenopathy is challenging for radiologists and gastroenterologists. CD-EUS is reported to be useful for differential diagnosis of malignant from benign lymphadenopathy. On CD-EUS, filling defect is a typical feature of malignant lymphadenopathy with a sensitivity of 100% and a specificity of 86.4%.[27] When CH-EUS was used for the diagnosis of intra-abdominal lesions of undetermined origin, 96.3% of malignant lesions exhibited heterogeneous enhancement, whereas 75% of benign lesions exhibited homogeneous enhancement (Fig. 6).[45] Thus, these techniques can be applied for N staging of digestive tumors.

CE-EUS FOR EUS-FNA

CONVENTIONAL EUS SOMETIMES fails to depict pancreatic tumors in cases with chronic pancreatitis, diffusely infiltrating carcinoma or a recent episode of acute pancreatitis.[46] In such cases, the target of EUS-FNA cannot be identified. Because contrast-enhanced harmonic EUS clearly depicts subtle lesions that conventional EUS cannot identify, it can be used to identify the target of EUS-FNA (Fig. 7).[38,41,47] It can also be used to identify a specific site within an otherwise clearly visible lesion that would be more suitable than other sites for EUS-FNA.[48] Identification and avoidance of an avascular site in a lesion may help avoid sampling necrotic areas (Fig. 8).

Two articles have reported that contrast-enhanced harmonic EUS is as sensitive as EUS-FNA and thus may be complementary to EUS-FNA, particularly with respect to the

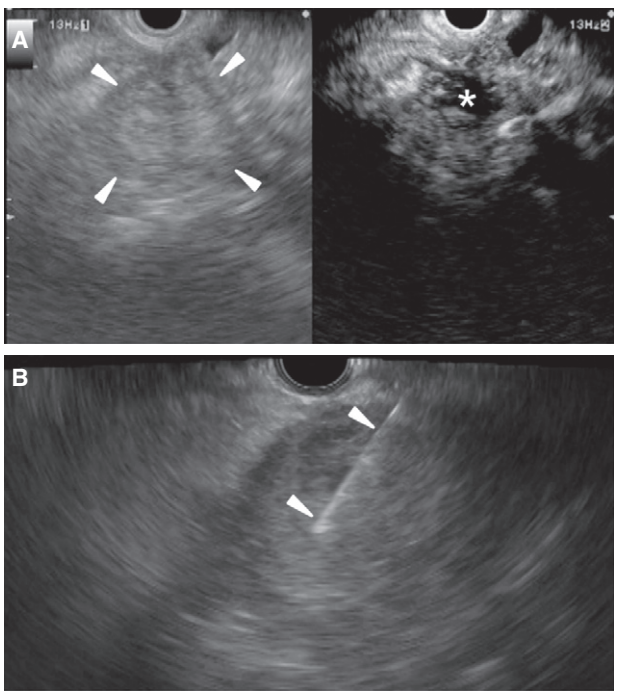

Figure 8 Contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) images of pancreatic carcinoma with a necrotic area. (a) Conventional EUS (left) shows a tumor of 35 mm in diameter (arrowheads) at the pancreas head. CH-EUS (right) identifies an avascular site (asterisk) at the center of the tumor. (b) EUS-fine-needle aspiration is carried out at the periphery of the tumor. Arrowheads indicate a needle.

identification of pancreatic adenocarcinomas with false-negative EUS-FNA findings.[40,41] EUS-FNA is sometimes difficult to carry out because of intervening vessels or anticoagulation treatment. In such cases, CE-EUS could be a

useful substitute.[49] CE-EUS might also help assess lymph nodes that cannot be accessed by EUS-FNA because of an intervening tumor or help eliminate the waste of time and risk in carrying out EUS-FNA at a second site.[49]

CONCLUSIONS

CONTRAST-ENHANCED EUS IS useful for characterization of tumors in the digestive organs. By elimination of Doppler-related artifacts, contrast enhanced harmonic EUS allows visualization of microvasculature and parenchymal perfusion, which leads not only to improved characterization of EUS-detected lesions, but also to identification of small tumors, estimation of malignant potential, as well as tumor staging. Contrast-enhanced harmonic EUS also complements EUS-FNA as it clearly depicts the target of EUS-FNA and identifies tumors with false-negative EUS-FNA findings.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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