Applications of contrast-enhanced harmonic endoscopic ultrasound on biliary, focal liver lesions and vascular diseases

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INTRODUCTION

Contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) is an emerging technique used in many gastrointestinal disorders. CH-EUS has not only improved diagnostic performance in numerous pathological conditions but has also changed the status of EUS in some gastrointestinal disorders. Innovations continue to expand the capabilities of CH-EUS and push the boundaries of its indications. This review focuses on new potential indications of CH-EUS.

NOVEL APPLICATIONS OF CONTRAST-ENHANCED HARMONIC ENDOSCOPIC ULTRASOUND

Gallbladder

The enhancement process of the gallbladder on CH-EUS is classified as early phase (10–30 s after contrast injection) and late phase (31–180 s after contrast injection), as the blood supply of the
gallbladder is entirely arterial. The late phase persists for a short time compared to that of liver lesion.\[2\] While conventional EUS is one of the most common imaging investigations for diagnosing gallbladder diseases, it is often insufficient for determining the nature of complicated gallbladder diseases. This limitation of conventional EUS is mainly due to its poor ability to depict microvasculature in gallbladder diseases. Thus, CH-EUS can be applied to overcome the limitations of conventional EUS, as it can depict the hemodynamics in micro-and macro-circulations.

The use of CH-EUS in differentiating gallbladder polyps and gallbladder carcinoma has been studied previously.\[3,4\] A differential diagnosis between adenomas and cholesterol polyps is important because adenomas have the potential to develop into cancer over time. According to the study by Park et al., the sensitivity and specificity of CH-EUS for differentiating adenoma from cholesterol polyp was based on enhancement pattern were 75% and 67%, respectively [Figure 1a].\[4\] Choi et al. investigated the value of CH-EUS for determining the malignant potential of gallbladder polyps >10 mm.\[3\] The identification of irregular tumor vessels and perfusion defects aided to differentiate malignant gallbladder polyps from benign ones, with a sensitivity and specificity of 94% and 93%, respectively [Figure 1b].\[3\] Motionless sludge ball in the gallbladder occasionally mimics gallbladder polyp or cancer on EUS.\[8\] CH-EUS can very easily depict biliary sludge as avascular lesions in the gallbladder [Figure 1c] and the biliary tract, whereas it depicts apparent vessels in a gallbladder polyp and carcinoma.\[3\] Imazu et al. evaluated the utility of CH-EUS in differentiating gallbladder wall thickening and found that an inhomogeneous enhancement pattern is strongly predictive of a malignancy.\[8\]

**Bile duct lesions**

Bile duct wall thickening is a common feature in both benign and malignant bile duct lesions such as sclerosing cholangitis and cholangiocarcinoma. Studies suggested that homogeneous contrast enhancement in the biliary tract corresponds to nonneoplastic changes of the bile duct as in cholangitis.\[7\] In pancreatobiliary malignancies, accurate preoperative T-staging is important to guide the optimal treatment strategy. Although conventional EUS has been used widely in the diagnosis and T-staging of pancreatobiliary malignancies, the accuracy of EUS for vascular invasion appears to be lower than has previously been reported.\[8\] Tumor margin and the interface between tumor and vessel have been clearly demonstrated with contrast enhancement.\[9\] Imazu et al. compared the accuracy of EUS and CH-EUS for preoperative T-staging in 26 patients who underwent surgery.\[9\] CH-EUS was significantly better than EUS for T-staging, with an overall accuracy of 92% and 69%, respectively.\[9\] The depth of invasion and vascular involvement could be demonstrated more clearly with CH-EUS compared to EUS.\[9\]

**Focal liver lesions**

Ultrasound is suitable for liver imaging, and EUS provides very good imaging of the left lobe of the liver and a significant portion of the right lobe of the liver. Due to the dual blood supply system of the liver, CH-EUS is divided into arterial phase (<30 s from contrast injection), portal phase (30–120 s), and late phase (>120 s). On contrast enhancement imaging, arterial hyperenhancement and late-phase contrast washout indicate hepatocellular carcinoma, and peripheral rim-like hyperenhancement and the subsequent washout often indicate metastatic liver cancer.\[10\] The typical enhancement patterns of hemangioma are peripheral nodular hyperenhancement and sustained enhancement in the late phase.\[10\] Many studies have shown that compared with computed
tomography (CT), CH-EUS is able to achieve the same or even superior characterization of focal liver lesions.\textsuperscript{11}

**Visceral vascular diseases**

EUS can assess the large-caliber vasculatures adjacent to the gastrointestinal tract. Color Doppler EUS helps detect abnormal blood flow, along with flow direction and velocity within the vessel. The injection of ultrasound contrast agents (UCAs) can enhance the depiction of vascular flow and help to describe the vascular structure clearly.\textsuperscript{12} Paik et al. demonstrated the value of CH-EUS in assessing visceral vascular disease. CH-EUS provides real-time angiography-like depiction of the vasculature and allows the accurate diagnosis of visceral vascular disease. A total of 12 patients with suspected visceral vascular disease on CT scan were included in the study.\textsuperscript{12} EUS accurately identified all the visceral vascular lesions of 11 patients, and one patient with suspicious superior mesenteric artery (SMA) dissection on CT was proven to be normal by EUS.\textsuperscript{12} CH-EUS showed intimal flap and flow within the true lumen of celiac axis, suggesting that what was presumed to be a periarterial soft tissue cuffing was actually organization of the false lumen [Figure 2].\textsuperscript{12} While the focal stenosis of a visceral artery is not described on color Doppler EUS, it can be seen on CH-EUS [Figure 3].\textsuperscript{12} Moreover, the stenotic area could be measured by using Doppler EUS. Two patients in the study underwent surgical thrombectomy and angioplasty because of total occlusion of SMA on CH-EUS.\textsuperscript{12} The simultaneous assessment of morphologic and hemodynamic information using color Doppler EUS and CH-EUS would be useful in determining optimal management strategy in mesenteric artery dissection. CH-EUS has also been used in the hemodynamic assessment of esophageal varices.\textsuperscript{13}

**Treatment response evaluation**

Recent research has focused on the potential of EUS-guided local ablation for treating pancreatobiliary tumor. In these local therapies, the tumor is not eradicated, but is devascularized or coagulated. Therefore, it is important to evaluate the local treatment response and detect residual viable tumor. Conventional EUS does not provide any reliable information regarding the efficacy of ablative treatment. When EUS is used as the imaging modality for guiding intervention, the addition of UCAs can provide useful information.\textsuperscript{14,15} The pretreatment assessment of tumor vascularity to compare pre- and post-ablation patterns at the end of ablation treatment is mandatory. The typical imaging that indicates complete ablation is the disappearance of any previously visualized intra-lesional enhancement on CH-EUS.\textsuperscript{14} The size of the nonperfused volume of the necrosis achieved can be compared with the size of the pretreatment volume of the tumor. In addition, CH-EUS can be used as a complement to CT or magnetic resonance imaging for conducting pretreatment assessments of vascularity and treatment responses.\textsuperscript{14}

**CONCLUSIONS**

CH-EUS provides improved characterizations of various gallbladder and bile duct lesions. Its applicability has expanded to focal liver lesions and visceral vascular disease. Novel applications include assessing treatment...
response after local therapies. The advent of CH-EUS has greatly enhanced the usefulness of EUS and even changed the status of EUS in clinical practice. The role of CH-EUS is continuously evolving and it is expected that its use will be expanded further in the future.

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There are no conflicts of interest.

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