Contrast-enhanced harmonic endoscopic ultrasonography in gallbladder cancer and pancreatic cancer

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[Review]

Contrast-enhanced harmonic endoscopic ultrasonography in gallbladder cancer and pancreatic cancer

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Abstract

Endoscopic ultrasonography (EUS) plays a major role in diagnosing gallbladder (GB) cancer and pancreatic cancer (PC). In cases of GB cancer, EUS allows for precise observations of morphology and wall layers. However, proficiency is required for the morphologic diagnosis of GB tumors. Therefore, contrast-enhanced harmonic EUS (CH-EUS) began to be performed to diagnose GB lesions. CH-EUS enables real-time observation of the hemodynamics of GB tumors. The enhanced patterns generated by CH-EUS improve precision in the diagnosis of such tumors.

PC appears as a hypoechoic mass on EUS. However, distinguishing between PC and mass-forming pancreatitis or focal autoimmune pancreatitis (AIP) is difficult via conventional EUS. CH-EUS allows for differentiating among these diseases (PC is hypoenhanced and heterogeneously enhanced, pancreatitis is isoenhanced, and a pancreatic neuroendocrine tumor is hyperenhanced). EUS-guided fine needle aspiration (EUS-FNA) also contributes to pathological diagnoses of pancreatic lesions. However, certain PC patients cannot be diagnosed via EUS-FNA. PC is heterogeneously enhanced on CH-EUS, and unenhanced regions have been reported to be areas of fibrosis or necrosis. CH-EUS-guided fine needle aspiration (CH-EUS-FNA) permits puncturing of the enhanced area while avoiding necrotic and fibrotic regions. Moreover, as CH-EUS findings have been quantitatively analyzed, a time-intensity curve (TIC) has become usable for diagnosing solid pancreatic lesions. CH-EUS-related techniques have been developed and increasingly utilized in the pancreaticobiliary area.

Introduction

Biliary tract cancer and pancreatic cancer (PC) have poor prognoses. More precise methods for diagnosing these diseases were desired. Endoscopic ultrasonography (EUS) has played an important role in diagnosing gallbladder (GB) cancer and PC[1-5)]. However, when EUS is used, GB cancer must be diagnosed morphologically, and it is difficult to differentiate between pancreatic inflammatory tumor-like lesions and PC[6,7)].

Recently, contrast-enhanced harmonic EUS (CH-EUS) was reported to be useful in diagnosing pancreaticobiliary diseases[8-27)]. In this report, we describe the efficacy of CH-EUS in diagnosing GB cancer and PC, including in experiments at our institution.

Contrast agent for ultrasound

Ultrasound contrast agents have been classified based on their ability to cross the pulmonary arterial bed and their motion under an ultrasound beam with a low mechanical index (MI) (Table 1)[28)].

Historically, Levovist (Schering, Berlin, Germany) was widely used for contrast-enhanced ab-

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Table 1. Ultrasound contrast agents

	Passes through the pulmonary arterial bed	Response MI	Diameter of microbubbles (μm)	Gas	Shell	Developer
Echovist®	×		99% < 12.0 95% < 8.0	Air	Galactose	Schering
Albunex®	○	High	4.3	Air	Albumin	MBI Mallinckrodt
Levovist®	○	High	2.0–4.0	Air	Galactose	Schering
Echogen®	○	Low	3.0–5.0	Perfluoropentane	Surfactant	Sonus Abbott
Optison®	○	Low	3.0–4.5	Perfluoropentane	Albumin	MBI Amersham Health
Definity®	○	Low	1.1–3.3	Perfluoropentane	Phospholipids	ImaRx, Bristol-Myers
ImavistTM	○	Low	5.0	Perfluoropentane	Phospholipids	Alliance
SonoVue®	○	Low	2.5	Sulfur hexafluoride	Phospholipids	Bracco
SonazoidTM	○	Low	3.0	Perflubutane	Lipids	GE Healthcare

MI, Mechanical index

dominal ultrasonography. Levovist features air surrounded by a galactose shell. When Levovist is used, enhanced images are created from harmonic signals received when microbubbles are destroyed by high MI ultrasound. Therefore, for continued observation, contrast agents must be repeatedly injected and destroyed.

However, second-generation contrast agents are used today. In particular, SonoVue (Bracco, Milan, Italy) and Sonazoid (GE Healthcare, Little Chalfont, United Kingdom) have been used for pancreaticobiliary CH-EUS. These microbubbles of contrast agents resonate under low MI ultrasound without being destroyed. Thus, second-generation contrast agents have allowed for the prolonged observation of enhancement effects.

Methods of CH-EUS

In our hospital, the endoscopes and ultrasonic equipment used for CH-EUS are GF-UCT260 and GF-UE260 ultrasound gastrovideoscopes (Olympus Medical Systems, Tokyo, Japan), the ProSound α-10 ultrasound system (Aloka, Tokyo, Japan), and the EU-ME2 ultrasound processor (Olympus Medical Systems, Tokyo, Japan). Ideally, patients are adequately sedated with midazolam or another agent prior to endoscope insertion. After target lesions are visualized on the monitor in the B and extended pure harmonic detection (ExPHD) modes, 0.015 mL/kg of the contrast medium (16 μg of Sonazoid in 2 mL of distilled water) is injected. Subsequently, the target lesions are evaluated in the arterial and early venous phases that occur approximately 90 seconds after these lesions are enhanced[15,29].

CH-EUS using first-generation enhancing agents for GB cancer

Several investigators have previously described the superiority of EUS relative to abdominal ultrasonography (US) for diagnosing neoplastic GB lesions (adenomas and adenocarcinomas)[1,2,30,31]. However, these reports did not intend to imply that EUS can only be used to diagnose GB adenocarcinomas. The efficacy of CH-EUS for diagnosing GB malignant lesions has also been reported. In 1997 and 1998, Hirooka *et al.*[8,10] observed that the visualization of GB adenocarcinoma was enhanced by the contrast medium Albunex, a first-generation enhancing agent (Table 1). In those studies, 11 GB adenocarcinoma patients (91.7%) exhibited enhancement effects, but such effects were not observed for patients with adenosquamous carcinoma or cholesterol polyps.

CH-EUS using second-generation enhancing agents for GB cancer

Recently, the differentiation of GB lesions via CH-EUS with second-generation enhancing agents (SonoVue or Sonazoid) has been reported. In these reports, GB polyps were diagnosed based on enhanced patterns.

Choi *et al.*[13] and Park *et al.*[14] described the efficacy of CH-EUS with the contrast medium SonoVue. Choi *et al.*[13] reported that irregular vessels observed via CH-EUS were useful in the diagnosis of malignant polyps, with a sensitivity and a specificity of

90.3% and 96.6%, respectively. Furthermore, perfusion defects observed via CH-EUS could be used to efficiently diagnose malignant polyps, with a sensitivity and a specificity of 90.3% and 94.9%, respectively. In addition, when using SonoVue and the same procedures, Park *et al.*[14] found that 80% (8/10) of GB adenocarcinomas were heterogeneously enhanced and that 75% of GB adenomas (6/8) were homogeneously enhanced.

In Japan, Sonazoid is used as the second-generation contrast agent for EUS for pancreaticobiliary or other abdominal diseases[11,15,24-26,32-35]. Imazu *et al.* performed CH-EUS with Sonazoid and reported finding inhomogeneously enhanced patterns that indicated malignant GB wall thickening. In that report, the sensitivity, specificity and accuracy for conventional EUS vs CH-EUS for diagnosing malignant GB wall thickening were 83.3% vs 89.6%, 65.0% vs 98.0% ($p<0.001$) and 73.1% vs 94.4% ($p<0.001$), respectively. Specificity and accuracy for GB wall thickening were significantly higher for CH-EUS than for conventional EUS. We retrospectively reviewed the efficacy of CH-EUS for diagnosing large (>10 mm) malignant and benign GB-protruding lesions[17]. In that review, the sensitivity, specificity, and malignant accuracy of CH-EUS were 100% (7/7), 94.1%, (16/17) and 95.8% (23/24), respectively. Cases treated at our hospital are presented in Figure 1.

CH-EUS for PC

CH-EUS using SonoVue or Sonazoid has been used to diagnose solid pancreatic lesions (SPLs)[18,19,21,24,26,27,36]. CH-EUS can be utilized to clearly visualize SPL microvasculature and blood flow of the pancreatic parenchyma. PC has been observed as a hypoenhanced heterogeneous tumor on CH-EUS[18,19,24,26,27] (Figure 2).

In 2008, Kitano *et al.* reported that on CH-EUS with SonoVue, hypovascular and heterogeneous images were observed for 80% (4/5) of malignant pancreatic lesions and isovascular images were ob-

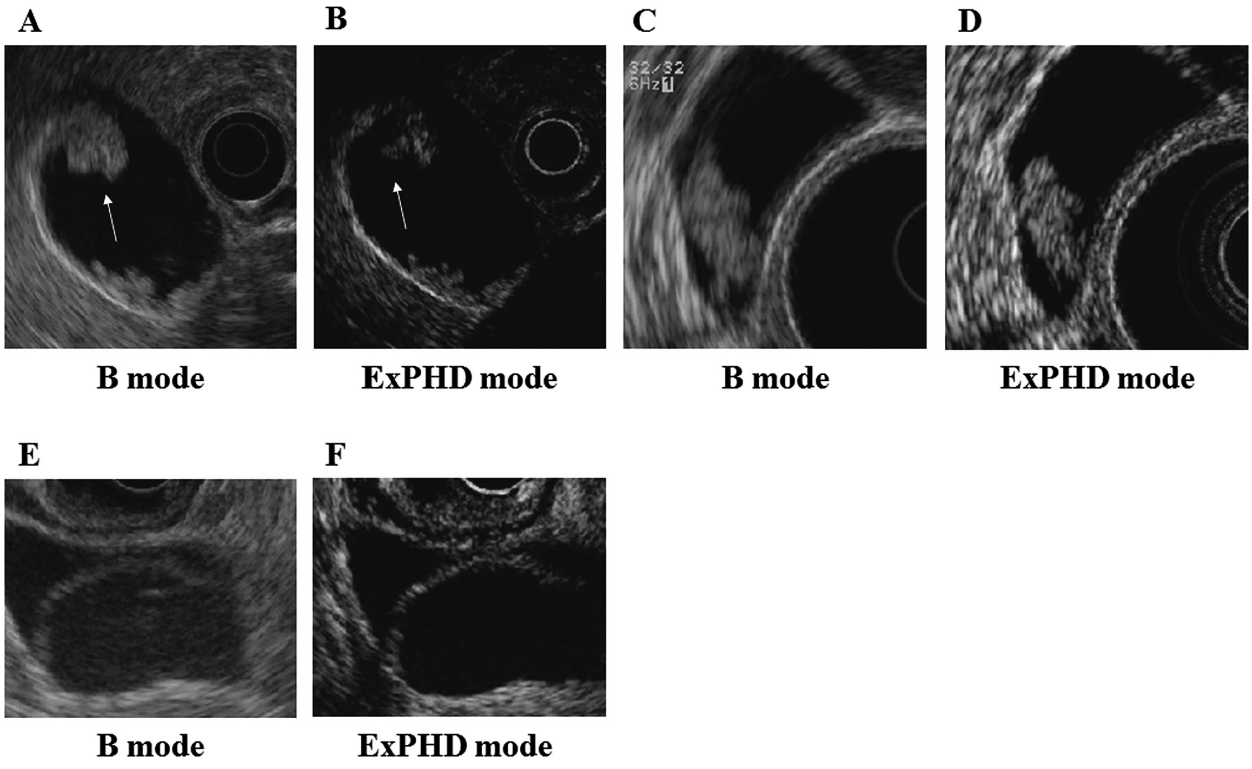

Fig. 1. Enhanced pattern of contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) for gallbladder (GB) lesions.
A. GB cancer was detected in a B-mode image.
B. After contrast agent (Sonazoid) injection, GB cancer was enhanced heterogeneously in an extended pure harmonic detection (ExPHD)-mode image.
C. GB adenoma was detected in a B-mode image.
D. After contrast agent (Sonazoid) injection, GB adenoma was enhanced homogeneously in an ExPHD mode image.
E. GB cyst was detected in a B-mode image.
F. After contrast agent (Sonazoid) injection, a GB cyst was not enhanced in an ExPHD-mode image.

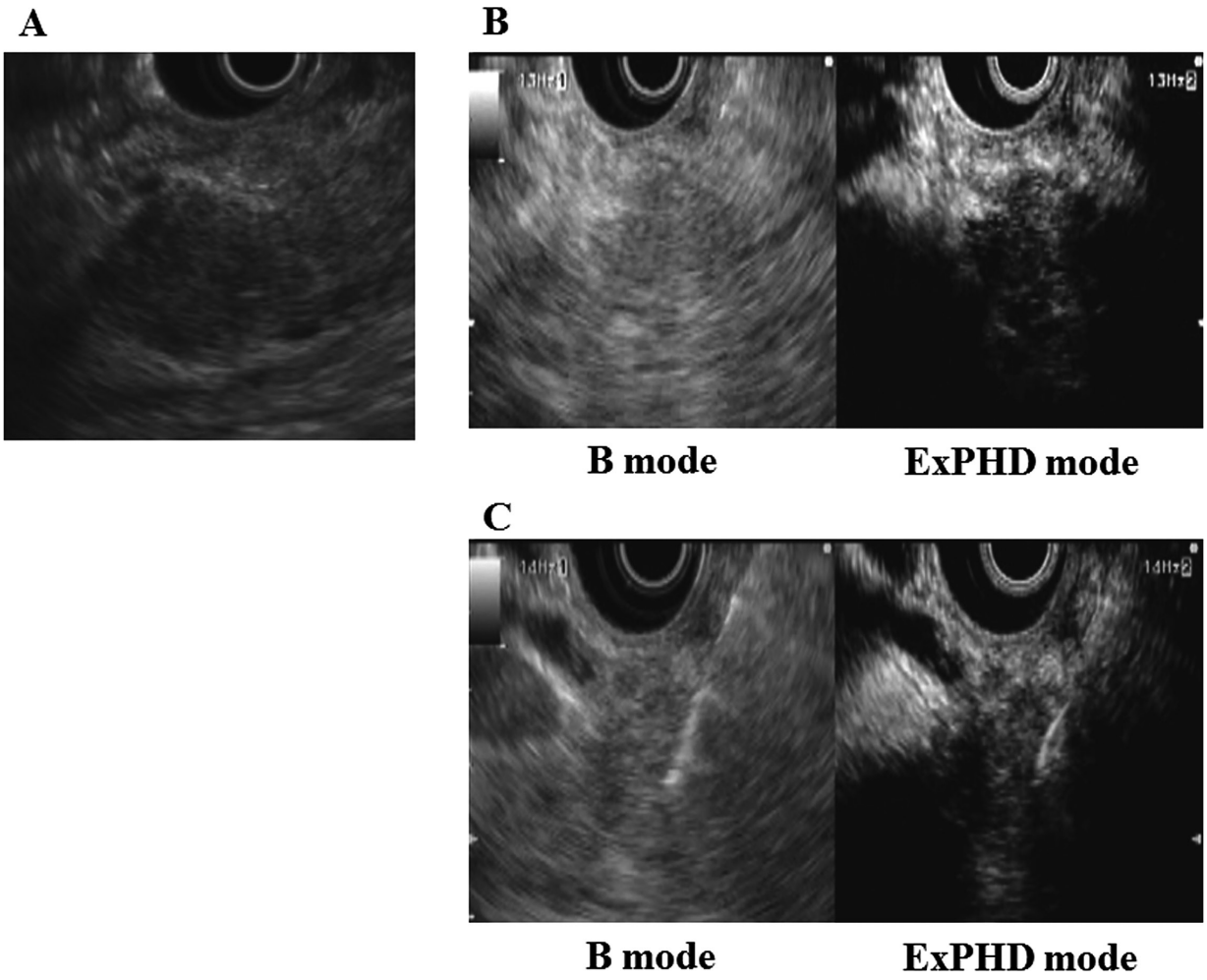

Fig. 2. Enhanced pattern of pancreatic cancer (PC) on contrast-enhanced harmonic EUS (CH-EUS) and CH-EUS-guided fine needle aspiration (CH-EUS-FNA).
A. PC was imaged using B mode.
B. (Left : B mode ; right : extended pure harmonic detection (ExPHD) mode) CH-EUS was performed and visualized using ExPHD mode. PC was hypoenhanced and enhanced heterogeneously on CH-EUS.
C. (Left : B mode ; right : ExPHD mode) Fine needle aspiration was performed in the enhanced region of PC.

served for 100% (3/3) of pancreatitis lesions[18]. In 2010, Fusaroli *et al.* stated that hypoenhanced and inhomogeneous images on CH-EUS with Sono-Vue were a good identifier for diagnosing pancreatic adenocarcinoma. In 2014, Park *et al.* found that 57 out of 62 pancreatic adenocarcinomas produced hypoenhanced images on CH-EUS with Sono-Vue, which had a sensitivity of 92%, a specificity of 68% and an accuracy of 82%[27].

In 2012, Kitano *et al.* described findings obtained when using CH-EUS with Sonazoid to assess small (≤2 cm in diameter) SPLs[26]. In this report, small pancreatic ductal carcinomas (n=67) appeared as hypoenhanced lesions, and the sensitivity and specificity of the tested imaging approach were 91.2% and 94.4%, respectively. This approach was superior to multidetector-row computed tomography (which had a sensitivity of 70.6% and a specificity of 91.9%). Furthermore, these researchers reported sensitivities of 90.6% and 92.2% for CH-EUS and EUS-guided fine needle aspiration (EUS-FNA), respectively, in patients who underwent surgical resection of tumors (n=91), although sensitivity increased to 100% if findings for both procedures were considered.

CH-EUS-guided fine needle aspiration (CH-EUS-FNA) for SPLs

EUS-FNA is used to collect biopsy samples from many organs throughout the digestive tract and is useful for diagnosing SPLs[37-40]. The reported diagnostic accuracy, sensitivity, and specificity of EUS-FNA for SPLs are 85-89.4%, 82-94.7%, and 100%,

respectively[41-43]. However, certain SPL patients could not be diagnosed via EUS-FNA. In 2015, Hou *et al.* described findings obtained using CH-EUS-FNA with Sono-Vue[44]. They punctured SPLs after they had confirmed these lesions' enhanced patterns and retrospectively analyzed 58 cases involving CH-EUS-FNA and 105 cases involving EUS-FNA. Sufficient biopsy specimens were more frequently obtained in the CH-EUS group (96.6%) than in the EUS-FNA group (86.7%).

As mentioned above, PC appears as hypoenhanced heterogeneous tumors on CH-EUS. Unenhanced areas reportedly reflect necrosis and fibrosis[45]. Therefore, we performed CH-EUS-FNA by puncturing the enhanced region of SPLs[33] (Figure 2). In our report, sufficient biopsy samples were obtained with a single needle pass for 60% (12/20) of the CH-EUS-FNA group compared with 25% (5/20) of the conventional EUS-FNA group (P=0.027). In many cases, when EUS-FNA is performed, four needle passes are needed to obtain sufficient biopsy samples[46]. In all reports about pancreatic tumor seeding associated with EUS-FNA, multiple needle punctures were performed[47-51]. CH-EUS-FNA is expected to require a minimal number of needle passes.

Quantitative evaluation of CH-EUS for SPLs

In the reports described above, enhanced patterns were judged subjectively. However, as CH-EUS findings for SPLs have been subjected to objective quantitative analyses, a time-intensity curve (TIC) has been determined.

In 2011, Matsubara *et al.* observed that the rate of echo intensity reduction from the peak at one minute was greatest for PC, followed by mass-forming pancreatitis, autoimmune pancreatitis (AIP), and pancreatic neuroendocrine tumors[24]. The reported sensitivity, specificity, and accuracy of EUS with a TIC were 95.8%, 92.6%, and 94.7%, respectively. In 2012, Imazu *et al.* reported that peak intensity and maximum intensity gain were significantly higher for AIP than for PC[25].

In 2015, Saftoiu *et al.* described TIC analysis with an artificial neural network classification model for diagnosing PC and chronic pancreatitis[52]. The sensitivity, specificity, positive predictive value, and negative predictive value for this approach were 94.64%, 94.44%, 97.24%, and 89.4%, respectively.

Conclusion

CH-EUS has been reported to be extremely effective in the diagnosis of pancreaticobiliary diseases. The combination of CH-EUS with EUS-FNA recently began being utilized ; furthermore, techniques to quantitatively evaluate enhancement effects, such as determination of a TIC, have been performed. Procedures related to CH-EUS play a major role in the pancreaticobiliary field.

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