Contrast-enhanced harmonic endoscopic ultrasound: Future perspectives

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Contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) can be applied as not only unprecedented new imaging method but also the treatment of cancer in the future. We provided a review article on the future of CH-EUS, especially in terms of targeted endoscopic ultrasound fine-needle aspiration (EUS-FNA), evaluation of chemotherapy, molecular imaging, local drug delivery, and local ablation in this section.

APPLICATION TO THE TARGETED ENDOSCOPIC ULTRASOUND FINE-NEEDLE ASPIRATION

Conventional endoscopic ultrasound (EUS) sometimes fails to depict margins and the structure of the target for EUS-FNA. CH-EUS helps identification of these subtle lesions [Figure 1]. Fusaroli *et al.* examined ninety patients who were suspected of having pancreatic solid neoplasm.[1] CH-EUS allowed detection of small lesions in seven patients who had uncertain standard EUS findings and targeted EUS-FNA was performed on these lesions. Seicean *et al.* evaluated diagnostic accuracy of EUS-FNA with CH-EUS for solid tumors in the pancreas. They avoided nonenhanced parts for the target during EUS-FNA with CH-EUS. The sensitivity of EUS-FNA with CH-EUS (83.9%) was higher than that with conventional EUS (73.2%), although these values did not differ significantly.[2] Sugimoto *et al.* compared the diagnostic yield of EUS-FNA and CH-EUS in the diagnosis of solid pancreatic lesions. In their report, fewer needle passes were required to obtain samples from solid pancreatic lesions using CH-EUS than conventional EUS during EUS-FNA.[3]

Romagnuolo *et al.* evaluated whether CH-EUS is a useful modality for selection of the EUS-FNA target.[4] Liver hemangioma was confirmed by CH-EUS before EUS-FNA and resulted in avoiding EUS-FNA. Moreover, in another case, mediastinal cystic lesion was confirmed as solid lesion by CH-EUS. In these cases, management changed significantly. CH-EUS is also helpful for determining the lymph nodes that should be subjected to EUS-FNA [Figure 2]. Miyata *et al.* reported that CH-EUS was useful for differentiating malignant from benign lymph nodes in patients with pancreatobiliary carcinomas.[5]

Thus, CH-EUS before EUS-FNA is a useful modality for targeted EUS-FNA in terms of detecting the target,

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avoiding necrotic tissue and/or vascular structures in the target and selecting the most suspicious target of malignancy.

APPLICATION TO THE EVALUATION OF CHEMOTHERAPY

The evaluation of chemotherapy in patients with pancreatic carcinoma is commonly performed by measurement of tumor size. However, the evaluation of tumor size reduction rate was sometimes difficult on the fundamental B-mode ultrasonography because the tumor margin was unclear. On the other hand, the hypovascular area was clearly depicted on the perfusion image of contrast-enhanced harmonic imaging and changes in tumor size could be easily evaluated.[6]

Changes in vascularity of the tumor under contrast-enhanced transabdominal ultrasonography are also employed for evaluating the effectiveness of chemotherapy.[7] Using contrast-enhanced EUS, vascularity can be more precisely visualized to identify its changes earlier during chemotherapy [Figure 3a and b]. Abundant intratumoral blood flow indicated a significantly better response and this change in the intratumoral blood flow after chemotherapy were related to the prognosis.[7] Yamashita *et al.* performed CH-EUS on 39 patients with unresectable pancreatic cancer and showed that both progression-free survival and overall survival were significantly longer in patients with abundant intratumoral blood flow than patients without it ($P = 0.037$ and $P = 0.027$, respectively).[8] They discussed that tumors with abundant intratumoral vessels were chemosensitive because drugs penetrated tumors through vessels.

On the other hand, Masaki *et al.* assessed tumor vascularity of pancreatic cancer using contrast-enhanced transabdominal ultrasonography before systemic chemotherapy.[9] They revealed that the median survival was longer in patients who had avascular tumors compared with patients who had vascular tumors and multivariate analysis showed that tumor vascularity was a significant, independent factor.

Thus, contrast enhancement with transabdominal ultrasonography or EUS is useful for evaluation of prognosis of pancreatic cancer after chemotherapy as well as before chemotherapy.

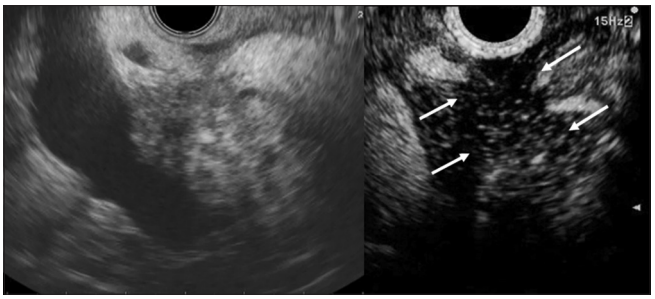

Figure 1. A case of unclear isoechoic pancreatic cancer in the pancreatic head. Conventional endoscopic ultrasound (left image) does not show the edge of the tumor clearly. Contrast-enhanced harmonic endoscopic ultrasound (right image) shows the tumor (arrows) as hypo-enhancement with clear margin to the surrounding tissue

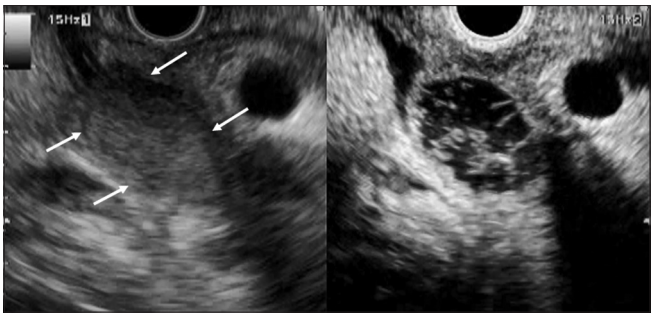

Figure 2. A case of metastatic lymph node from pancreatic cancer. Conventional endoscopic ultrasound (left image) shows low-echoic lymph node surrounding with common bile duct (arrows). Contrast-enhanced harmonic endoscopic ultrasound (right image) shows the lesion is enhanced heterogeneously that indicates a malignant lymph node. Therefore, endoscopic ultrasound fine-needle aspiration was performed in this lymph node for T-staging of pancreatic cancer before surgery

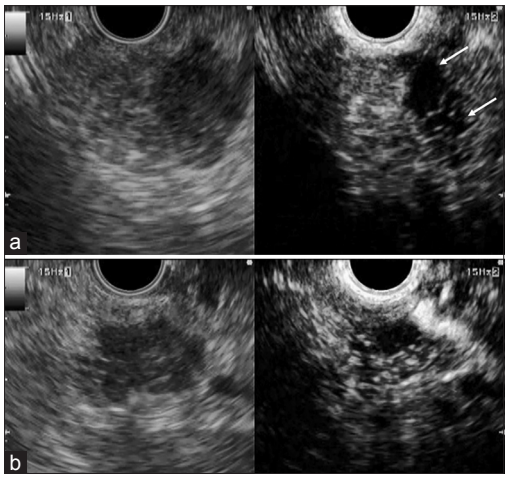

Figure 3. A case of pancreatic cancer. (a) Endoscopic ultrasound images before chemotherapy. Conventional endoscopic ultrasound (left image) shows low-echoic mass in the pancreatic head. Contrast-enhanced harmonic endoscopic ultrasound (right image) is showing the avascular area in the tumor (arrows). (b) Endoscopic ultrasound images after chemotherapy. Avascular area decreased on contrast-enhanced harmonic endoscopic ultrasound (right image)

APPLICATION TO MOLECULAR IMAGING

Microbubbles that have high affinity to specific molecules may visualize sites of inflammation, angiogenesis, and cancer to obtain more disease-specific information. Leveraging the natural pathway of leukocyte rolling on inflamed vascular endothelial cells, a clinically translatable, dual-targeted contrast agent specific for the leukocyte adhesion molecules P- and E-select in has been shown to enable accurate quantification of inflammation in animal models of chemically induced colitis and ileitis.[10,11]

Vascular endothelial growth factor receptor type 2 (VEGFR2), which is a well-studied molecular marker overexpressed on angiogenic vascular endothelial cells of cancer, is visualized by ultrasonography using VEGFR2-targeted ultrasound microbubbles in models for breast cancer, pancreatic adenocarcinoma, and colon carcinoma, and applied to monitoring response to their anticancer therapy.[12-18]

More recently, Bachawal *et al.* reported that expression of B7-H3 (CD276), a member of the B7 family of ligands for T-cell coregulatory receptors, is more selectively observed in tumor vessels of breast cancer, compared with VEGFR, suggesting the use of B7-H3–targeted ultrasound molecular imaging can be used for more selective tumor detection.[19]

If these molecular-targeted ultrasound microbubbles are applied to clinical practice, they can also be applied to the field of EUS, facilitating characterization of conventional EUS-detected lesions.

APPLICATION TO LOCAL DRUG DELIVERY

Bioactive substances can be attached to or incorporated into microbubble shells. High ultrasound energies destroy the microbubbles, followed by changes in capillary and cell membrane permeability in the immediate vicinity, facilitating tissue, and cell penetration by loaded bioactive substances.[20] The major limitation of systemic chemotherapy is undesirable side effects in healthy tissues. Focusing the ultrasound field at the target tissues improves not only the efficacy but also the selectivity of the treatment to avoid its side effects. Ultrasound-targeted microbubble destruction following the administration of a novel doxorubicin-loaded or plasmid DNA-loaded, microbubble formulation has the potential to dramatically improve local therapies by enhancing the delivery of these cytotoxic agents to malignant tissues, and significantly decreased the tumor growth of cancer models.[20,21]

APPLICATION TO LOCAL ABLATION

CH-EUS can be useful to evaluate the effectiveness of local ablation for pancreatic cancer. Giday *et al.* assessed local effects of intra-pancreatic alcohol injection and the utility of CH-EUS for its monitoring in a porcine model.[22] They revealed that alcohol injection caused focal pancreatic necrosis and was seen by CH-EUS as an avascular area. Microbubble oscillation by ultrasound beam generates heat as a result of friction with surrounding structures and their decompression. The release of heat to the surrounding tissues causes local damage.[23,24] High powered ultrasound waves cause acoustic cavitation of microbubbles, consisting of fast microbubbles growth, and expansion followed by their ultimate collapse, which results in irreversible damage to intact cells and a nondestructive increase in membrane permeability.[23,24] Recently, phase-change nanodroplets (PCNDs) are reported to exert as a sensitizer on efficient induction of mechanical effects of pulsed high-intensity focused ultrasonography.[25] Using colon tumor tissues, PCND enhanced mechanical tissue fractionation by pulsed high-intensity focused ultrasonography. This combination can be a new candidate for the treatment of locally advanced cancer. Although current EUS transducers produce too low acoustic power to affect tissue integrity exposed by its ultrasound waves, a specific echoendoscope which produces, high powered ultrasound waves would allow the local ablation using ultrasound contrast agents.

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Conflicts of interest
There are no conflicts of interest.

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