Endoscopic high-intensity focused US: technical aspects and studies in an in vivo porcine model (with video)

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Background: High-intensity focused US (HIFU) is becoming more widely used for noninvasive and minimally invasive ablation of benign and malignant tumors. Recent studies suggest that HIFU can also enhance targeted drug delivery and stimulate an antitumor immune response in many tumors. However, targeting pancreatic and liver tumors by using an extracorporeal source is challenging due to the lack of an adequate acoustic window. The development of an EUS-guided HIFU transducer has many potential benefits including improved targeting, decreased energy requirements, and decreased potential for injury to intervening structures.

Objective: To design, develop, and test an EUS-guided HIFU transducer for endoscopic applications.

Design: A preclinical, pilot characterization and feasibility study.

Setting: Academic research center.

Patients: Studies were performed in an in vivo porcine model.

Intervention: Thermal ablation of in vivo porcine pancreas and liver was performed with EUS-guided focused US through the gastric tract.

Results: The transducer successfully created lesions in gel phantoms and ex vivo bovine livers. In vivo studies demonstrated that targeting and creating lesions in the porcine pancreas and liver are feasible.

Limitations: This was a preclinical, single-center feasibility study with a limited number of subjects.

Conclusion: An EUS-guided HIFU transducer was successfully designed and developed with dimensions that are appropriate for endoscopic use. The feasibility of performing EUS-guided HIFU ablation in vivo was demonstrated in an in vivo porcine model. Further development of this technology will allow endoscopists to perform precise therapeutic ablation of periluminal lesions without breaching the wall of the gastric tract.

Abbreviations: H&E, hematoxylin and eosin; HIFU, high-intensity focused US; NADH-d, nicotinamide adenine dinucleotide diaphorase.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this article. This work was supported by NIH grants 1R01CA154451, 1K01EB015745, and Washington State Life Sciences Discovery Fund (3292512).*

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0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2014.12.019

Received July 29, 2014. Accepted December 4, 2014.

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High-intensity focused ultrasound (HIFU) is a promising noninvasive technology in which high-amplitude US waves are focused inside the human body to thermally ablate or mechanically disrupt the tissue at the focus without affecting surrounding tissues. The thermal ablation effect of HIFU has been used to coagulatively necrose or cauterize tissue[1] and applied in the treatment of benign and malignant tumors including pancreatic cancer[2-4] and liver cancer.[5,6] Recent studies also found that the mechanical effects of HIFU (eg, acoustic cavitation) can enhance targeted drug delivery[7-9] and stimulate a systemic antitumor immune response[10,11] in cancer patients with liver[12] and pancreatic[13] tumors, among others. However, targeting these tumors by using an extracorporeal source can be challenging due to the lack of an acoustic window. Bowel gas, intestinal loops, and ribs are major obstacles that reflect and/or absorb HIFU energy. As a result, the US waves are redistributed or absorbed before they reach the target and may not cause the desired bioeffects and may result in adverse effects on the intervening tissues. Burning of the abdominal wall and necrosis of the ribs are also common adverse effects of extracorporeal HIFU ablation.[14]

It has been long acknowledged that an endoscopic device that would integrate an HIFU transducer and an EUS imaging probe would be a safer and more efficient alternative to extracorporeal HIFU in the ablation of periluminal lesions.[1,15] Such an EUS-guided HIFU device would bring many potential benefits including improved targeting, decreased energy requirements, and decreased potential for injury to intervening structures. The aim of this study was to demonstrate the feasibility of precise ablation of the pancreas and liver by a prototype EUS-guided HIFU device in tissue-mimicking gel phantoms, ex vivo tissues, and in vivo porcine model.

METHODS

EUS-HIFU setup

The EUS-guided HIFU apparatus consisted of a custom-built spherically curved HIFU transducer (12-mm diameter with a 35-mm radius of curvature) integrated with a 10-MHz EUS imaging probe (BF-Y0044; Olympus Medical System Corp, Tokyo, Japan). The HIFU transducer (SU121; Sonic Concepts, Bothell, Wash) operated at 3.73 MHz (Fig. 1A). The dimensions of the focal area at the −6-dB level were 28 × 1.6 mm. The HIFU transducer and the imaging probe were tightly fitted into a metal housing and were aligned so that the focus of the HIFU transducer appeared at the depth of 2.4 cm from the EUS probe and was centered laterally. The metal housing was covered by a thin latex sheath that was sealed, to be filled with degassed water for US coupling (Fig. 1B). The water balloon was contained inside a specially designed plastic cover and could be inflated and deflated by using 2 water channels on the side of the metal housing. The plastic cover ensured the frontal distention of the water balloon to control the depth of the HIFU focus in tissue. The full bending capability of the distal end of the endoscope was maintained (Fig. 1C).

The HIFU transducer was powered by a function generator (AFG 3022B; Tektronix, Beaverton, Ore) and a 400-W power amplifier (ENI 400B; ENI, Rochester, NY), and the peak electric power used in all experiments was 150 W. This power level resulted in the focal acoustic waveform shown in Figure 2, as measured by a fiberoptic probe hydrophone (FOPH 2000; RP Acoustics, Leutenbach, Germany) in water. The peak compressional and peak rarefactional pressures were 17 MPa and 9 MPa, respectively. Most importantly, the focal waveform contained a shock front, ie, a sharp increase in the pressure resulting from nonlinear propagation effects of the acoustic waves. The shock fronts are known to result in much more rapid and localized heat deposition compared with linear US waves so that the boiling temperature of water (100°C) can be reached in a matter of milliseconds.[16] As demonstrated in both ex vivo and in vivo tissues, the resulting vapor bubble is clearly visible as a hyperechoic region on B-mode US and can be efficiently used for therapy monitoring. The waveform shown in Figure 2 would allow reaching the boiling temperature at the focus within 134 ms, according to theoretical estimations.[17] Therefore, the following HIFU pulsing protocol was chosen: 0.1-s pulse duration, 0.2-s pulse repetition period, and total exposure duration of 30 s.

Gel phantoms and ex vivo tissues

Visual observation of thermal lesion formation was first performed by using tissue-mimicking transparent gel phantoms. The gel phantoms were composed of 5% wt/vol polyacrylamide hydrogels and 7% wt/vol bovine serum albumin that becomes optically opaque when thermally denatured.[18] To characterize the lesion formation in ex vivo tissue, ex vivo bovine liver tissue was obtained from an abattoir on the same day as experiments. The tissue was cut into samples to fit in a custom-designed tissue holder and degassed in a desiccant chamber before experiments. During the experiment, the endoscopic device was placed so that the HIFU focus was 15 mm deep below the surface for both gel phantoms and ex vivo tissue. The tissue samples were then bisected and photographed to observe gross damage to the tissue.

In vivo porcine model

To test the device in an in vivo setting, a pig model was chosen because of its similarity to the human digestive anatomy. The in vivo studies were performed in 5 pigs to demonstrate the feasibility of targeting and creating lesions. The animal protocol was approved by the University of Washington Institutional Animal Care and Use Committee. Before each experiment, the animal was anesthetized