Development of a contrast-enhanced ultrasound–guided high-intensity focused ultrasound system for coagulation of liver parenchyma

Alexander Tam, Kaizer Contreras, Fari Fall, MD, Adam Maxwell, PhD, Ji-Bin Liu, MD, Flemming Forsberg, PhD, Eli Vlaisavljevich, PhD, Allison Goldberg, MD, Tania Siu Xiao, MD, Cristina Kuon Yeng Escalante, MD, John R. Eisenbrey, PhD, *and* **George Koenig, DO***, Philadelphia, Pennsylvania*

BACKGROUND: The liver is the most common organ injured in blunt abdominal trauma and makes up roughly 5% of all trauma admissions. Current treatments are invasive and resource intensive, which may delay care. We aim to develop and validate a contrast-enhanced ultrasound (CEUS)–guided noninvasive tool to treat liver lacerations at the bedside.

METHODS: Two 1.8-MHz high-intensity focused ultrasound (HIFU) elements were coupled to a C1-6 diagnostic ultrasound probe and a Logiq E10 scanner (GE HealthCare, Waukesha, WI) using a custom enclosure for coregistered imaging and ablation. A phantom was created from polyacrylamide gel combined with thermochromic ink whose color changes above biological ablative temperatures (60°C). The HIFU wave was focused approximately 0.5 cm below the surface using a 50% duty cycle generating 11.9 MPa for 20, 30, 40, 50, and 60 seconds. Experiments were repeated on ex vivo chicken livers in a water bath. Finally, the livers of four live swine underwent up to six CEUS-guided treatments using parameters optimized from in vitro work.

RESULTS: Treatment of the phantom between 20 and 60 seconds produced ablation sizes from 0.016 to 0.4 cm^3. The relationship between time and size was exponential ($R^2 = 0.992$). Ablation areas were also well visualized on with ultrasound imaging. The ex vivo liver ablation size at 20 seconds was 0.37 cm^3, at 30 seconds was 0.66 cm^3, and at 100 seconds was 5.0 cm^3. For the in vivo swine experiments, the average ablation area measured 2.0 × 0.75 cm with a maximum of 3.5 × 1.5 cm. Contrast-enhanced ultrasound was used with the contrast agent Definity (Lantheus Medical Imaging, North Billerica, MA) for identification of lacerations and immediate postoperative evaluation of therapy.

CONCLUSION: These experiments demonstrate the feasibility of CEUS-guided transdermal HIFU ablation and the time-dependent size of ablation. This work warrants future investigations into using ultrasound to detect active bleeding and HIFU to coagulate grades III and IV liver laceration.

KEY WORDS: Abdominal trauma; contrast-enhance ultrasound; critical care; HIFU; liver laceration.

The liver is the most commonly injured solid organ in blunt abdominal trauma, making up roughly 5% of all trauma admissions with a 10% to 15% mortality rate primarily because of hemorrhage.[1] In recent decades, a paradigm shift toward nonoperative management (NOM) in hemodynamically stable patients has been driven by advancements in diagnostic imaging techniques and the refinement of interventional radiology procedures.[2] Arterial embolization has emerged as a pivotal intervention for achieving hemostasis in both acute and delayed hemorrhage. Nonoperative management has demonstrated substantial success across the spectrum of American Association for the Surgery of Trauma Organ Injury Scale grades, showcasing acceptable mortality rates, earlier hospital discharge, enhanced cost-effectiveness, and a reduction in intra-abdominal complications.[3] Despite the benefits of NOM, challenges persist, particularly in the context of grades III to V injuries. The decision to pursue NOM often relies on the surgeon's experience and ability to provide intensive management, leading to inconsistencies in patient selection and thus, the efficacy of NOM. In addition, a lack of standardized early follow-up protocols further compounds the complexity of managing these severe cases.[4] Operative management strategies, including resection-debridement, selective vascular ligations, and perihepatic packing, have been integral in cases where NOM has failed or been contraindicated.[5] In addition to operative management and NOM management, adjunctive interventions such as interventional radiology embolization may be used. Despite improvement in outcomes, there remain multiple complications associated with liver laceration, including biliary leak, pseudoaneurysm, and liver necrosis, some of which may be a consequence of the intervention rather than primary

Submitted: January 23, 2024, Revised: March 27, 2024, Accepted: May 6, 2024, Published online: May 23, 2024.

From the Sidney Kimmel Medical College (A.T.), Thomas Jefferson University, Philadelphia, Pennsylvania; Applied Physics Laboratory (K.C., A.M.), University of Washington, Seattle, Washington; Department of Surgery (F. Fall, G.K.), and Department of Radiology (J.-B.L., F. Forsberg, T.S.X., C.K.Y., J.R.E.), Thomas Jefferson University, Philadelphia, Pennsylvania; Department of Biomedical Engineering and Mechanics (E.V.), Virginia Polytechnic Institute and State University, Blacksburg, Virginia; and Department of Pathology (A.G.), Thomas Jefferson University, Philadelphia, Pennsylvania.

This study was presented at the Western Trauma Association 53rd Annual Meeting in Snowmass, Colorado on March 01, 2024.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for correspondence: George Koenig, DO, Department of Surgery, Thomas Jefferson University, 1100 Walnut St, 5th Floor, Philadelphia, PA 19107; email: George.Koenig@jefferson.edu.

DOI: 10.1097/TA.0000000000004397

injury.[6] This nuanced clinical landscape encourages the development of minimally invasive tools to address moderate and severe liver lacerations. Furthermore, such tools could be adaptable to low-resource or austere settings, where management options are limited or not immediately available.

Noninvasive ultrasound surgery using high-intensity focused ultrasound (HIFU) has been explored for treatment of various tumors including liver cancer as an alternative to resection or invasive locoregional therapies. However, these methodologies generally use short pulses (1–3 seconds) and can require hours of treatment time to generate ablation patterns.[7] Prior preclinical work has demonstrated the ability of HIFU to coagulate soft tissue lacerations in solid organs, including in the liver.[8] Although promising, this approach lacked imaging guidance, a necessity for the noninvasive treatment of lacerations in the trauma setting. B-mode ultrasound guidance has demonstrated poor intraprocedural assessment of therapeutic efficacy, and while oncologic applications have used magnetic resonance imaging guidance to circumvent this issue,[9] these systems do not provide the real-time visualization of blood flow, which is required for achieving hemostasis of lacerations noninvasively. These methods have proved ineffectual in trauma settings.

One attractive solution for HIFU guidance in the trauma setting is the use of contrast-enhanced ultrasound (CEUS), which has already been used to evaluate treatment efficacy in the oncology space.[10] Contrast-enhanced ultrasound uses intravenous contrast agents consisting of 1- to 8-μm gas-filled microbubbles that create nonlinear responses to ultrasound waves because of acoustic impedance mismatch and bubble oscillation.[11] Because of their confinement within the blood stream, this approach provides real-time visualization of blood perfusion on ultrasound. The technique is well validated for visualization of liver lesions and has also demonstrated value within trauma surgery.[12] Consequently, CEUS guidance may be an ideal approach for guiding HIFU for coagulation of liver lacerations in the trauma setting.[13] This article describes the initial hardware development and demonstration of proof of concept in vitro and in vivo application of CEUS-guided HIFU for coagulating liver tissue.

PATIENTS AND METHODS

A custom 3D-printed enclosure was created to house two 1.8-MHz HIFU elements with a focal depth of 6 cm. Simulations of the beam width were predicted to be 2.4 × 1.8 × 7.4 mm with a focal pressure gain of 31, indicating that the probe would have excellent overall control within the treatment area. The HIFU elements were coupled to a diagnostic ultrasound C1-6

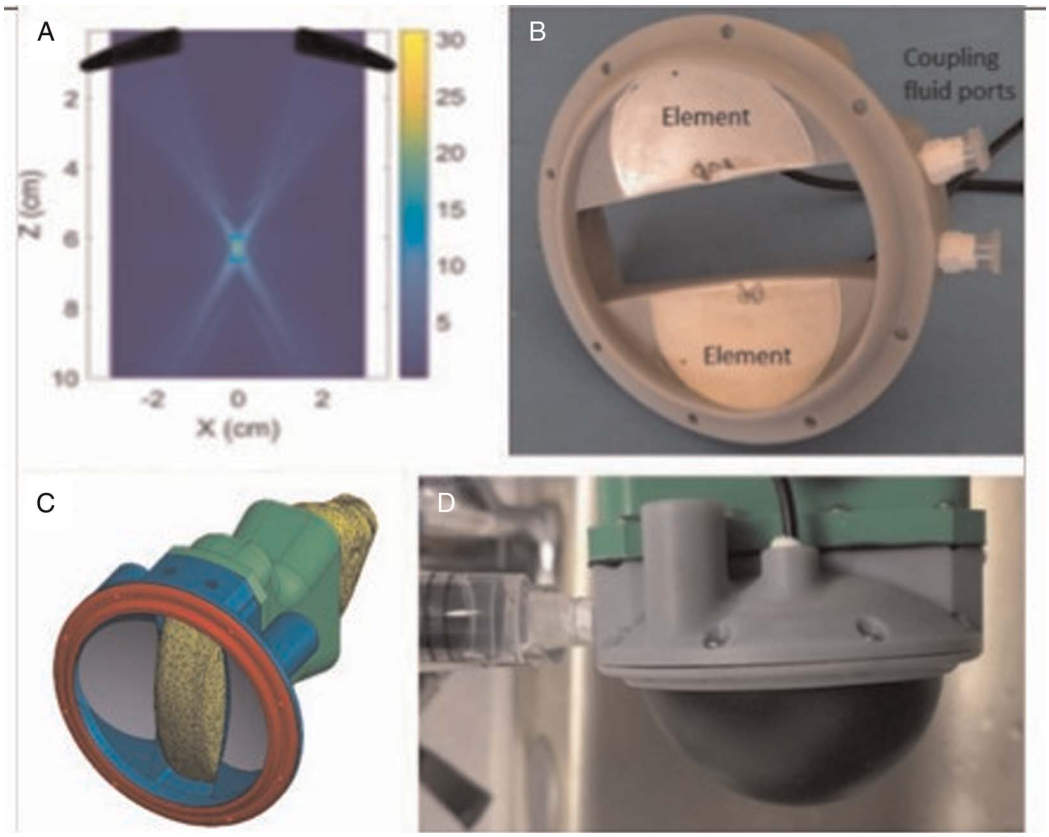

Figure 1. Ultrasound housing and HIFU simulation. (*A*) Simulation of HIFU field showing a focal area (used for laceration hemostasis) at a depth of 6 cm. (*B*) Fabricated probe assembly showing the location of HIFU elements and fluid coupling fluid ports. (*C*) Design of composite HIFU and CEUS transducer showing both components without the flexible membrane. (*D*) Complete assembly transducer containing C1-6 transducer with fluid filled membrane extended.

curvilinear probe operated by a Logiq E10 scanner (GE HealthCare, Waukesha, WI) for coregistered imaging and ablation. A schematic of this assembly is shown in Figure 1. The incorporation of the imaging transducer provides an ability to visualize the nonlinear harmonic signal from microbubble contrast agents.

For in vitro experiments, a tissue-mimicking thermochromic (TMTC) phantom was created from polyacrylamide gel combined with Kromagen thermochromic ink that changes color above biological ablative temperatures (60°C). This TMTC phantom possessed the same density, thermal conductivity, and thermal diffusivity as reported values of human soft tissue.[14] The TMTC phantom was placed in a water bath, and the HIFU was focused approximately 0.5 cm below the surface of the phantom using a 50% duty cycle, 1.81-MHz sinusoidal pulse generated by an HP8116A pulser/function generator (Germany) amplified by a 50-dB amplifier (3100 L; ENI, Rochester NY). Time to cavitation and ablation was explored at peak negative pressures of 5.9, 8.5, 10.1, and 11.9 MPa. Cavitation lesions were observed on B-mode ultrasound at 10.1 MPa and 11.9 MPa at 90 seconds and 45 seconds, respectively. Hence, 11.9 MPa was chosen to conduct further experiments on the TMTC phantom with exposure times varying from 10, 20, 30, 40, 50, to 60 seconds. Dispersion patterns were measured in B-mode and compared with the color-changing pattern seen on the cross-section of the TMTC phantom. Experiments were repeated on ex vivo chicken livers submerged in water baths with exposure times lasting 20 and 30 seconds. Finally, a linear ablation pattern was created from four 25-second pulses resulting in 100 seconds of total exposure time.

All in vivo work was performed under Institutional Animal Care and Use Protocol 22-10-592. The animal research reporting of in vivo experiments guidelines were used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/D853). Proof of concept trials to evaluate the beam's ability to induce cavitation and distortion were conducted in a live swine model. Four swine livers were treated transdermally in a closed abdomen model. The swine were sedated with 2 to 5 mg/kg of Telazol and placed under general endotracheal anesthesia using Isoflurane or Sevoflurane (2–4%). The contrast agent Definity (Lantheus Medical Imaging, North Billerica, MA) was infused at a rate of 8 mL/min (concentration, 5 mL in 100 mL of saline). Each swine underwent a maximum of six ablation treatments with and without contrast enhancement. Peak negative pressures of 5.9, 8.5, 10.1, and 11.9 MPa were generated using 1.81-MHz HIFU pulses at 50% duty cycle. In vivo treatment stopped when cavitation was seen on B-mode ultrasound. Ablation lesions were visualized and measured in coded harmonic imaging, B-mode ultrasound, and gross specimen pathology.

RESULTS

In Vitro Results

For the 10-second exposure, no color change was found throughout the TMTC phantom. For between 20 and 60 seconds treatment of the phantom, teardrop-shaped ablation patterns were created ranging from 0.016 cm^3 to 0.4 cm^3 as demonstrated in Figure 2*B*. The relationship between time and size was found to be exponential ($R^2 = 0.992$, near perfect correlation). Ablation areas were also well visualized on B-mode ultrasound immediately after treatment (Fig. 2*A*). In smaller lesions (less than 0.075 cm^3), there was a 35% ± 10% decrease in the ablation size measured grossly by TMTC phantom color change compared with the cavitation pattern measured on ultrasound, but in more extensive lesions (>0.075 cm^3), the areas only differed by 9% ± 4%. The ex vivo liver ablation size after 20 seconds was 0.37 cm^3, increasing to 0.66 cm^3 at 30 seconds and 5.0 cm^3 at 100 seconds. Necrosis was demonstrated on visual inspection (Fig. 3).

In Vivo Results

Cavitation lesions were not achieved below 8.5 MPa in vivo. Gas formation was apparent on B-mode imaging at 10.1 MPa after approximately 90 seconds and at 11.9 MPa

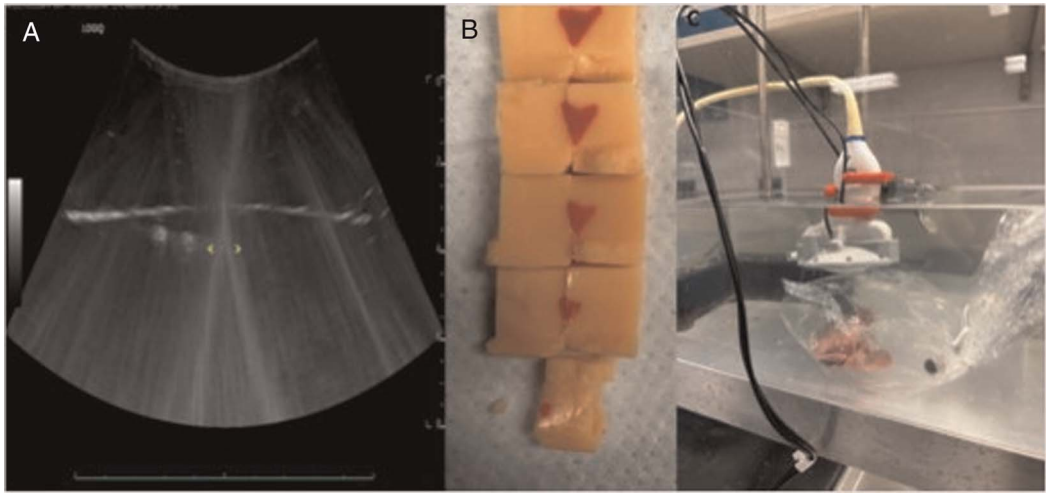

Figure 2. In vitro phantom results. (*A*) Diagnostic B-mode ultrasound image of the in vitro TMTC phantom submerged within a water bath during HIFU ablation with focal target 0.5 cm inferior to phantom edge. (*B*) Cross-sectional slices of the thermochromic phantom with ablation times of 60, 50, 40, 30, and 20 seconds, from top to bottom. (*C*) Degassed and deionized water bath containing HIFU housing targeting an ex vivo chicken liver.

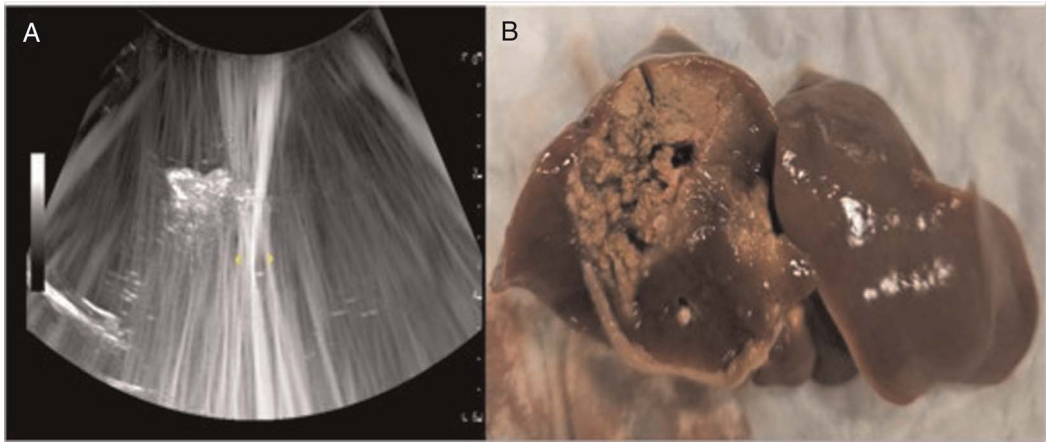

Figure 3. In vitro chicken liver results. (*A*) Diagnostic ultrasound image during HIFU ablation with focus targeted approximately 1 cm below the liver surface. (*B*) Cross-sectional slices of ex vivo liver with total ablation time of 100 seconds (five 20-second burst moved linearly across the liver edge).

within 45 seconds. No gross visually significant difference in ablation size was observed with or without the presence of ultrasound contrast. An example of these treated areas is presented in Figure 4. Average ablation areas on explant tissue were approximately 2 × 0.75 cm, which matched well with our initial beam profiles. The largest treated area was 3.5 × 1.5 cm, which was attributed to cavitation in the tissue because of proximity to a larger vessel. Measurements on both grayscale and CEUS were compared with treatment areas on pathology. Both imaging modes matched well with quantification of the specimens, although improved correlation was observed using CEUS ($R^2 = 0.81$ [strong linear correlation] vs. $R^2 = 0.42$ [moderate linear correlation]). Mild skin burns were observed in some treated areas and attributed to air between the transducer face and skin surface when the treated area was near a nipple. These results demonstrate that CEUS-guided HIFU can be used to coagulate areas noninvasively and accurately within the liver and provide real-time feedback on active vascularity.

DISCUSSION

The experiments demonstrate the feasibility of CEUS-guided transdermal HIFU ablation with a goal of eventual noninvasive, CEUS-guided HIFU treatment of liver lacerations. Prior work has demonstrated the feasibility of using HIFU to coagulate grades III to IV liver lacerations in a swine model, but this approach relied on suboptimal image guidance.[15–17] Contrast-enhanced ultrasound has many advantages including real-time identification of bleeding relative to conventional B-mode or Doppler ultrasound.[18,19]

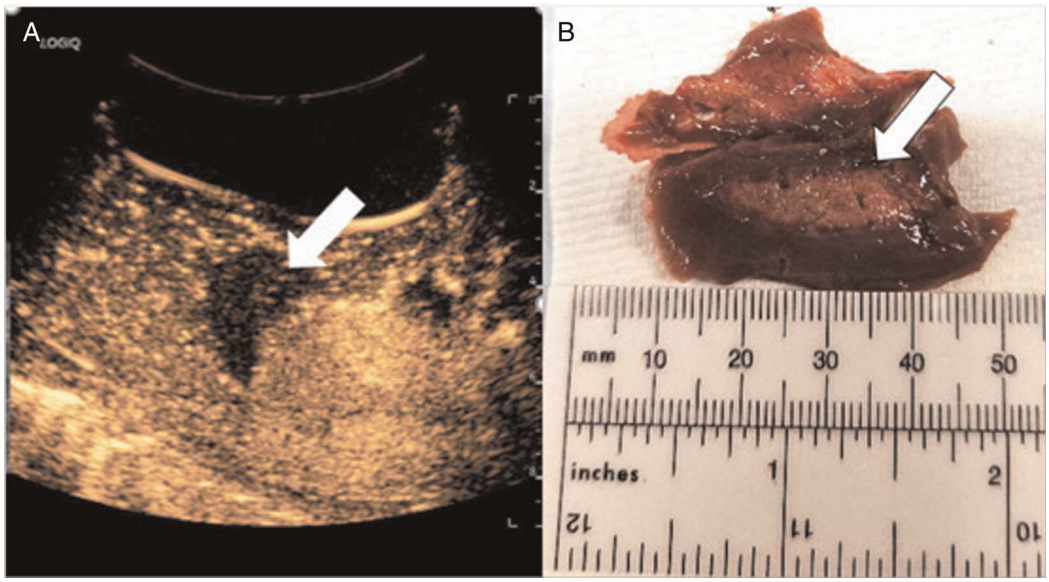

Figure 4. In vivo swine results. (*A*) A HIFU treatment lesion (white arrow) in the liver on CEUS. The lack of contrast signal indicates destroyed vascularity within the treated area. (*B*) A treated lesion (white arrow) within a liver specimen. The overall area of ablation was measured to 2.0 × 0.75 cm, which matched well with CEUS and the simulated beam profile.

Data from this study demonstrated that coagulation can be created in a time efficient manner comparable with the operative hemostasis time previously reported for porcine livers[20] and that changes in vascularity within the liver parenchyma can be monitored in real time using CEUS. Further work will be performed to identify if the larger in vivo ablation area of 3.5 × 1.5 cm near a vessel is reproducible. We theorize that this is due to gas expansion of blood causing increased cavitation pressures and may be beneficial during ablation of active hemorrhage. While harmonic imaging modes required for CEUS were prone to noise during HIFU treatment, immediate posttreatment imaging with CEUS proved more accurate for quantifying coagulated areas than standard B-mode. These results demonstrate the potential of CEUS-guided HIFU to noninvasively identify and coagulate active liver lacerations with immediate postprocedure evaluation.

AUTHORSHIP

K.C., F.F., A.M., F.F., E.V., J.R.E., and G.K. contributed in the study design. A.T., F.F., J.-B.L., F.F., J.R.E., and G.K. contributed in the data collection. A.T., A.G., T.S.X., C.K.Y., and J.R.E. contributed in the data analysis. A.T., K.C., A.M., E.V., and J.R.E. contributed in the data interpretation. A.T., J.R.E., and G.K. contributed in the writing. A.T., J.R.E., and G.K. contributed in the critical revision.

ACKNOWLEDGMENT

This study received funding from Focused Ultrasound Foundation.

DISCLOSURE

Conflict of Interest: Author Disclosure forms for all authors have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D854).

I, Dr. George Koenig, attest on behalf of all authors that we had full access to the data of the study, conducted all data analyses independently from the funding entity, and take complete responsibility for the integrity and accuracy of the data reported in the manuscript.

REFERENCES

1. Cothren CC, Moore EE. Hepatic trauma. *Eur J Trauma Emerg Surg*. 2008; 34(4):339–354.
2. Piper GL, Peitzman AB. Current management of hepatic trauma. *Surg Clin North Am*. 2010;90(4):775–785.
3. Letoublon C, Morra I, Chen Y, Monnin V, Voirin D, Arvieux C. Hepatic arterial embolization in the management of blunt hepatic trauma: indications and complications. *J Trauma*. 2011;70(5):1032–1037.
4. Ryce AL, Somasundaram A, Duszak R, Newsome J, Majdalany BS, Johnson J-O, et al. Contemporary management of blunt liver trauma: an analysis of the Trauma Quality Improvement Program Registry (2007–2019). *J Vasc Interv Radiol*. 2023;34(8):1441–1450.e4.
5. Tinkoff G, Esposito TJ, Reed J, Kilgo P, Fildes J, Pasquale M, et al. American association for the surgery of trauma organ injury scale I: spleen, liver, and kidney, validation based on the national trauma data bank. *J Am Coll Surg*. 2008;207(5):646–655.
6. Coccolini F, Coimbra R, Ordonez C, Kluger Y, Vega F, Moore EE, et al. Liver trauma: WSES 2020 guidelines. *World J Emerg Surg*. 2020;15(1):24.
7. Zhou Y-F. High intensity focused ultrasound in clinical tumor ablation. *World J Clin Oncol*. 2011;2(1):8.
8. Vaezy S, Zderic V. Hemorrhage control using high intensity focused ultrasound. *Int J Hyperthermia*. 2007;23(2):203–211.
9. Jolesz FA, McDannold N. Current status and future potential of MRI-guided focused ultrasound surgery. *J Magn Reson Imaging*. 2008;27(2):391–399.
10. Leslie T, Ritchie R, Illing R, Ter Haar G, Phillips R, Middleton M, et al. High-intensity focused ultrasound treatment of liver tumours: post-treatment MRI correlates well with intra-operative estimates of treatment volume. *Br J Radiol*. 2012;85(1018):1363–1370.
11. Delaney LJ, Isguven S, Eisenbrey JR, Hickok NJ, Forsberg F. Making waves: how ultrasound-targeted drug delivery is changing pharmaceutical approaches. *Mater Adv*. 2022;3(7):3023–3040.
12. Tester BE, Liu JB, Eisenbrey JR, Koenig G. Emerging applications of contrast-enhanced ultrasound in trauma. *Adv Ultrasound Diag Ther*. 2022; 6(2):39.
13. Eisenrey JR, Gabriel H, Savsani E, Lyshchik A. Contrast-enhanced ultrasound (CEUS) in HCC diagnosis and assessment of tumor response to locoregional therapies. *Abdom Radiol*. 2021;46(8):3579–3595.
14. Negussie AH, Partanen A, Mikhail AS, Xu S, Abi-Jaoudeh N, Maruvada S, et al. Thermochromic tissue-mimicking phantom for optimisation of thermal tumour ablation. *Int J Hyperthermia*. 2016;32(3):239–243.
15. Bailey MR, Maxwell AD, Reed JA, Kreider W, Khokhlova VA, Zderic V, et al. Dual frequency high intensity focused ultrasound to accelerate hemostasis. *J Acoust Soc Am*. 2004;116(4_Supplement):2560–2560.
16. Haar GT, Coussios C. High intensity focused ultrasound: physical principles and devices. *Int J Hyperthermia*. 2007;23(2):89–104.
17. Burgess S, Zderic V, Vaezy S. Image-guided acoustic hemostasis for hemorrhage in the posterior liver. *Ultrasound Med Biol*. 2007;33(1):113–119.
18. Catalano O, Aiani L, Barozzi L, Bokor D, De Marchi A, Faletti C, et al. CEUS in abdominal trauma: multi-center study. *Abdom Imaging*. 2008; 34(2):225–234.
19. Thorelius L. Emergency real-time contrast-enhanced ultrasonography for detection of solid organ injuries. *Eur Radiol*. 2007;17(S6):107–111.
20. Paternò VA, Bisin A, Addis A. Comparison of the efficacy of five standard topical hemostats: a study in porcine liver and spleen models of surgical bleeding. *BMC Surg*. 2020;20(1):215.