Exploring Boiling Histotripsy for Hepatocellular Carcinoma: A Translational Perspective

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Introduction

Background: Hepatocellular carcinoma (HCC) remains the leading cause of cancer-related death worldwide, with particularly poor outcomes in cirrhotic patients where liver function preservation is critical. Traditional thermal ablation techniques (RFA, MWA) create coagulative necrosis that may compromise remaining hepatic function and have limited applicability in complex anatomical locations.

Technology Overview: Boiling histotripsy (BH) represents a paradigm shift in liver tumor treatment - the first FDA-approved (October 2023) non-thermal, non-invasive ablation technology. Unlike thermal methods, BH uses millisecond high-intensity focused ultrasound (HIFU) pulses to create mechanical tissue disruption through controlled acoustic cavitation.

Clinical Need: Cirrhotic HCC patients require treatment modalities that preserve liver function while achieving complete tumor destruction. BH offers unique advantages including real-time ultrasound visualization, structure-sparing ablation, and documented hepatic regeneration potential.

Methods

This educational exhibit presents a case-based review of BH as a non-invasive therapeutic modality for HCC. The exhibit synthesizes available preclinical and early clinical studies, highlighting procedural technique, imaging guidance, and treatment parameters. Current literature is examined to illustrate clinical applications, safety considerations, and emerging evidence from ongoing trials. Future directions for translating BH into routine HCC management are explored, with an emphasis on expanding its clinical utility in cirrhotic liver settings.

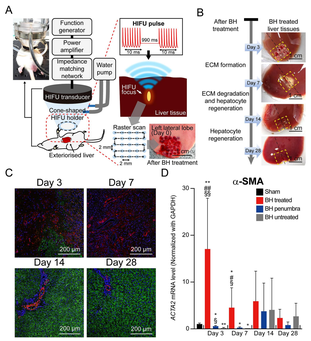

Figure 1. (Heo et al.) Experimental method and regeneration of hepatocytes with degradation of fibroblasts after the BH treatment. (A) A schematic diagram of the experimental setup for performing boiling histotripsy in rat's liver in vivo. The HIFU transducer was placed on the exteriorized liver tissue and a 10 ms-long HIFU pulse with a pulse repetition frequency of 10 Hz was used. The HIFU focus was moved by raster scan resulting in the production of a number of BH lesions in the liver over the area of 1.44 cm2 (1.2 cm×1.2 cm). The photo of the in vivo experimental setup was adapted from Supplementary Fig. S5. The photo of the BH treated liver was adapted from Supplementary Fig. S1. (B) Morphological observation of the liver tissue on days 3, 7, 14 and 28 after the BH treatment. The yellow outlined boxes and black dot lines indicate BH-treated regions and cross section lines for histological observation. (C) Representative IHC staining images of fibroblasts and hepatocytes in the cross-sectioned BH-treated liver tissues. Hepatocytes were immunostained with Asgr1 antibody (green), and fibroblasts were immunostained with α-SMA antibody (red). Nuclei were counterstained with DAPI (blue). (Scale bar, 200 μm; magnification, 100×) (D) Expression mRNA levels of α-SMA. n=5 for Sham, n=3 for Day 3 and 7, n=4 for Day 14, and n=5 for Day 28. Data are presented as means±standard deviation (SD) of individual values. One-way analysis of variance (ANOVA) followed by post-hoc Tukey's test was used.

Results

- Preclinical studies using BH have demonstrated complete hepatic regeneration without fibrosis formation in porcine liver models. Heo et al. showed progressive tissue healing with fibroblast activation by day 3, blood vessel formation by day 14, and full architectural restoration by day 28 following BH treatment (Figure 1).
- A recent study performed by Joung et al. demonstrated that BH treatment significantly reduced liver fibrosis in both the treated penumbra and identical liver lobe compared to untreated controls. BH-treated regions showed increased hepatocyte-specific marker expression and improved serological liver function markers without notable adverse effects (Figure 2).
- Histological analysis revealed that BH creates precise mechanical tissue fractionation while preserving critical hepatic structures including blood vessels and bile ducts. Unlike thermal ablation methods, BH reduced tissue to subcellular debris (<0.1 μm) without coagulative necrosis or heat sink effects.
- Real-time ultrasound monitoring during BH treatment showed distinct hyperechoic cavitation during active treatment followed by hypoechoic ablation zones, enabling precise treatment control and verification of tissue destruction boundaries. This imaging capability allows for safe treatment near critical structures in anatomically complex cirrhotic livers.
- The results of these studies establish BH's unique regenerative and anti-fibrotic properties, positioning it as a promising translational approach for cirrhotic HCC patients where liver function preservation is critical, with next steps focusing on first-in-human clinical trials and treatment parameter optimization.

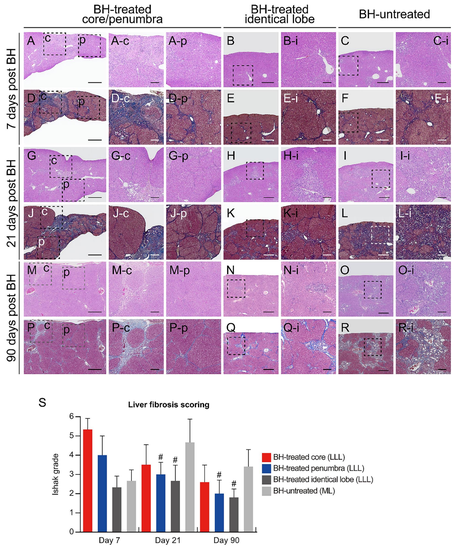

Figure 2. (Joung et al.) Cross sectional images of the fibrotic liver tissues after BH treatment. (A–R) Histological images of (A–C, G–I, M–O) haematoxylin and eosin (H&E) or (D–F, J–L, P–R) Masson's trichrome stained liver tissues collected on days 7, 21, and 90 after the BH treatment. (A, D, G, J, M, P) BH-treated region in the left lateral lobe (LLL). (B, E, H, K, N, Q) The BH-unaffected region in the BH-treated LLL. (C, F, I, L, O, R) BH–untreated median lobe (ML). (Scale bar, 1 mm). Images (c), (p), and (i) show the highlighted areas in (A to R, square with broken lines) at higher magnifications. (Scale bar, 250 μm; magnification ×100). c: BH-treated core, p: BH-treated penumbra. (S) Liver fibrosis index score for each region of fibrotic liver samples at days 7, 21, and 90 after the BH treatment. n=6 for sham, n=6 for Day 7, n=5 for Day 21, n=3 for Day 90. All values are shown as mean ± standard deviation (SD, # P<0.05 vs. BH-untreated (ML) of each time point)

Discussion

- BH is becoming a more promising technique as a non-invasive management option for cirrhotic HCC patients, offering more benefits and fewer risks compared to traditional thermal ablation and surgical treatments.
- One of the intriguing aspects of the preclinical studies is BH's ability to promote hepatic regeneration without fibrosis formation. This result suggests that more refinement in treatment parameters and clinical translation are necessary to better harness BH's regenerative potential. However, this also opens new areas of research regarding how BH can be tailored for patients with existing liver cirrhosis and compromised hepatic function.
- In addition to the direct ablation of tumor tissue, BH's potential to preserve liver architecture while promoting regeneration is an interesting area for future exploration as it could provide a dual benefit for cirrhotic patients who require both tumor control and liver function preservation. Creating this approach could potentially improve outcomes in patients with HCC and underlying cirrhosis.
- Next steps in research should focus on first-in-human clinical trials, optimizing treatment parameters for cirrhotic liver tissue, and conducting safety studies to assess BH's efficacy in patients with compromised liver function.

References

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