Journal of Gastrointestinal Surgery 29 (2025) 102000

Contents lists available at ScienceDirect

Journal of Gastrointestinal Surgery

journal homepage: www.jogs.org

Original Article

The first international experience with histotripsy: a safety analysis of 230 cases

Chase J. Wehrle [a,*], Kevin Burns [b], Evan Ong [c], Allison Couillard [d], Neehar D. Parikh [e], Elaine Caoili [f], JaeKeun Kim [a], Federico Aucejo [a], Andrea Schlegel [a], Emily Knott [a], Paul Laeseke [d], J. Philip Boudreaux [g], Philipp von Breitenbuch [h], Mikhail Silk [i], Mohamed Alassas [c], Andrew Guzowski [j], Brian Fuller [b], Erica Knavel Koepsel [d], Brock Hewitt [k], Mishal Mendiratta-Lala [f], David C.H. Kwon [a]

[a] Division of Hepatopancreatobiliary Surgery and Liver Transplantation, Cleveland Clinic, Cleveland, OH, United States
[b] Department of Interventional Radiology, Mission Community Hospital, Los Angeles, CA, United States
[c] Division of Surgical Oncology, Swedish Health Services, Seattle, WA, United States
[d] Department of Interventional Radiology, University of Wisconsin – Madison, Madison, WI, United States
[e] Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, United States
[f] Division of Abdominal and Cross-Sectional Interventional Radiology, University of Michigan, Ann Arbor, MI, United States
[g] New Orleans Louisiana Neuroendocrine Tumor Specialists, Louisiana State University Health Center, New Orleans, LA, United States
[h] Department of Surgery, Sheikh Tahnoon Bin Mohammed Medical City, Al Ain, United Arab Emirates
[i] Division of Interventional Radiology, New York University Langone Health, New York, NY, United States
[j] Division of Hepatopancreatobiliary and Advanced Gastrointestinal Surgery, AdventHealth, Orlando, FL, United States
[k] Division of Surgical Oncology, New York University Langone Health, New York, NY, United States

ARTICLE INFO

Article history:
Received 9 January 2025
Received in revised form 8 February 2025
Accepted 15 February 2025
Available online 18 February 2025

Keywords:
Complications
Histotripsy
Liver cancer
Liver tumor
Safety

ABSTRACT

Background: Histotripsy is a novel, noninvasive, nonionizing, and nonthermal approach that uses focused ultrasound waves to treat liver tumors. This technology received a de novo Food and Drug Administration grant in late 2023. This study aimed to provide the first report on post-trial real-world clinical safety data.
Methods: Safety outcomes within 30 days of histotripsy were collected after obtaining Food and Drug Administration clearance (December 22, 2023 to July 26, 2024). All centers that performed histotripsy were invited to participate in this study. Complications requiring treatment were graded using the Clavien-Dindo classification and Comprehensive Complication Index (CCI).
Results: A total of 295 patients underwent histotripsy for 510 tumors at 18 centers. The treated liver tumor types included colorectal metastases (n = 140), neuroendocrine tumors (n = 46), hepatocellular carcinomas (n = 31), pancreatic tumors (n = 30), and breast metastases (n = 26). The most common numbers of tumors treated per procedure were 1 (n = 170), 2 (n = 69), and 3 (n = 37). All 8 liver segments were treated for tumors. Safety data were available for 230 patients from 9 centers. Of note, 12 of 230 patients (5.2%) experienced complications of any grade. Most patients (9 [75%]) had minor cases (Clavien-Dindo grade ≤ II). The median and mean CCIs were 0.00 (IQR, 0.00–0.00) and 0.00 (95% CI, 0.00–0.75). All 3 major complications (Clavien-Dindo grade > II [1.3%]) were death due to disease progression. All 3 patients underwent histotripsy with palliative intent for known advanced intra- and extrahepatic diseases.
Conclusion: To the best of our knowledge, this is the first study to report on the real-world therapeutic use of histotripsy for liver tumors. Histotripsy was well tolerated, with few overall complications and rare serious complications, indicating a safety profile that compares favorably with that of other liver-directed and surgical therapies for the treatment of liver tumors. Long-term follow-up data, including oncologic outcomes, were collected.

* Corresponding author.
E-mail address: wehrlec@ccf.org (C.J. Wehrle).

https://doi.org/10.1016/j.gassur.2025.102000

Introduction

Liver cancer is a major international health burden [1]. Histotripsy is a novel, noninvasive, nonionizing, and nonthermal treatment approach that uses focused ultrasound waves to create mechanical tissue disruption in liver lesions [2,3]. Such tumor disruption is created through rapidly growing and shrinking "bubble clouds" within the cellular cytoplasm that lead to mechanical cell lysis (Fig. 1) [4]. Since first described in 2006 in rabbit kidneys, experimental research has described the applications of histotripsy in

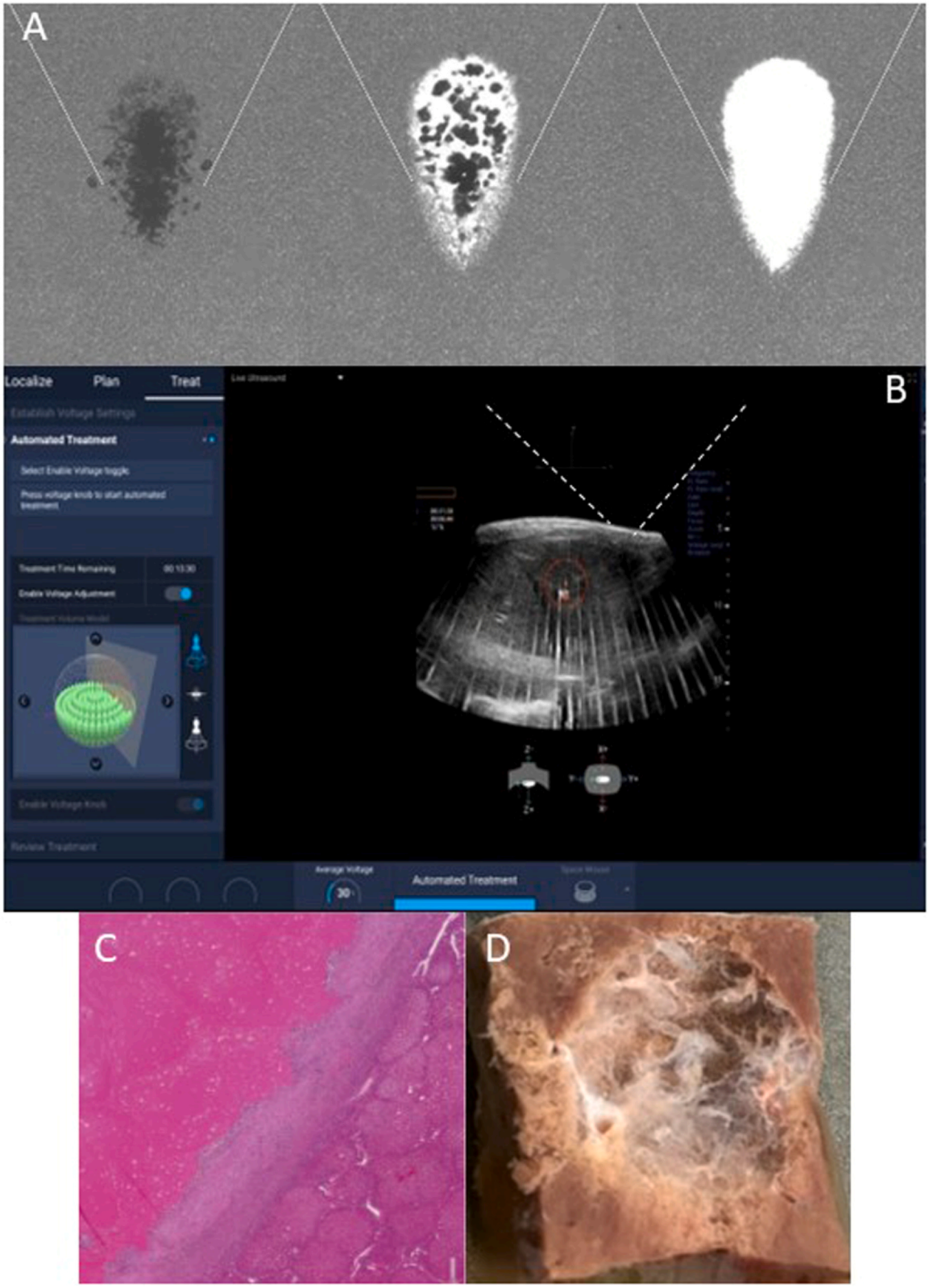

Figure 1. Mechanism and description of histotripsy. A, Electron microscopy image of the sample series demonstrating the precision of the bubble cloud. B, Screen capture of the ultrasound-based planning system during treatment. C, Hematoxylin and eosin stain of a resected tumor specimen after histotripsy. D, Gross image of a post-treatment cavity.

various organs, including the liver, pancreas, prostate, kidney, and brain [5–7].

Histotripsy was first used in humans in 2020, but only 3 studies (53 patients) have reported the clinical outcomes of histotripsy treatment of liver tumors to date [8–10]. Histotripsy has been marketed as a totally noninvasive procedure, which makes it an extremely safe procedure. Although initial data from 53 published patient data demonstrated a high rate of technical success and a low rate of procedure-related complications, the patient populations in these studies were highly selected on-trial cohorts [8–10]. It would be reasonable to presume that the widespread release of the technology would result in potentially riskier treatment approaches, such as treatment on or near major vascular or biliary structures or treatment closer to the bowel, both of which were avoided in the trial patients. Furthermore, patient comorbidities were highly regulated in trial settings and the safety of this technology has not been studied in a real-world population.

Other liver-directed, locoregional therapies (LRTs) have significant complication profiles, including bleeding, liver failure, infection, bile leak/biloma, and even death [11]. LRT remains the standard of care. However, these complications have been well explored, and thus, the risk-benefit profile can be discussed with patients and between providers as various approaches are considered [12–14]. Both surgery and LRT for liver tumors have evolved over time, and knowledge of safety profiles has been a crucial first step for each expansion, followed by novel applications of such technologies in various clinical settings [15–17]. Similarly, surgical studies continue to compare safety profiles between surgical approaches and combined LRT + surgical approaches, as we collectively follow Osler's first principle, "First, do no harm," striving for both the safest and most effective treatment option for each patient [17–20].

Given the recent Food and Drug Administration (FDA) clearance, the safety profile of real-world histotripsy application is of immediate clinical relevance. This study aimed to report the first large-scale international safety data on liver histotripsy since the FDA de novo grant in October 2023.

Methods

This international retrospective cohort study included adult (age ≥ 18 years) patients who underwent histotripsy of ≥1 liver lesion after device approval (HistoSonics Edison System, HistoSonics) from December 22, 2023 (the first case performed after clearance), to July 26, 2024, and with ≥30 days of follow-up. Patients were excluded if they had undergone histotripsy before FDA clearance or were aged < 18 years. The primary purpose of this study was to report the short-term safety profile of liver histotripsy. This study was approved by the institutional review board and conducted according to the Declaration of Helsinki. Consent was waived.

All centers that had performed histotripsy in an off-trial manner as of the date of collection (N = 18) were invited to participate in the study by direct contact with the primary investigators in an attempt to receive data on all cases performed at the time of data collection. No center was precluded from participating in the study to prevent any intentional bias. Of the 18 centers, 9 elected to participate, representing 79% of the cases performed nationwide. The total number of cases was determined on the basis of a request from the device manufacturer.

Treatment information was obtained in a deidentified fashion from an educational database that supported the quality implementation of the technology. Complications were determined using an investigator-developed survey that was sent directly to all providers performing the procedure. All reported complications within 30 days of treatment and subsequent treatments or interventions were recorded. In addition, any death within 30 days was recorded along with the cause of death. Complications were graded according to the Clavien-Dindo classification and the Comprehensive Complication Index (CCI) [21,22].

Complications were self-reported, and each center was asked to provide details on the complications and how they were managed using a standardized data collection form. Complications were graded according to the Clavien-Dindo and CCI methodologies to standardize complications based on their management using previously validated systems for multicenter studies.

Histotripsy

Histotripsy is a novel, noninvasive, nonionizing, and nonthermal treatment modality currently approved by the FDA for the treatment of primary and secondary liver tumors. FDA clearance was approved in October 2023, and the first case was subsequently performed in December 2023 [23]. Histotripsy uses ultrasound waves that induce rapid oscillations in the target tissue. This generates acoustic cavitation through microbubbles in the target tissue. The procedure requires no incision and is performed under general anesthesia.

Statistics

Descriptive statistics were used to analyze the study population. Continuous variables were presented as means and SDs or medians and IQRs. Categorical variables were presented as counts and percentages. Categorical variables were analyzed using the chi-square test or Fisher exact test. Continuous variables were analyzed using the Mann-Whitney *U* test.

Results

At the time of publication, nontrial histotripsy was performed at 18 centers, of which 295 patients underwent histotripsy for 510 liver tumors. The most commonly treated tumor types were colorectal metastases (n = 140), neuroendocrine tumors (n = 46), hepatocellular carcinomas (HCCs; n = 31), pancreatic tumors (n = 30), and breast metastases (n = 26) (Fig. 2). The numbers of tumors treated per procedure were 1 (n = 170), 2 (n = 69), and 3 (n = 37). Tumors in all 8 liver segments were treated (Table 1 and Fig. 3).

An electron microscopy image of the sample series demonstrating the precision of the bubble cloud and an ultrasound-based planning system screen capture during treatment are presented in Fig. 1. In addition, hematoxylin and eosin staining of a resected tumor specimen after histotripsy and gross imaging of a post-

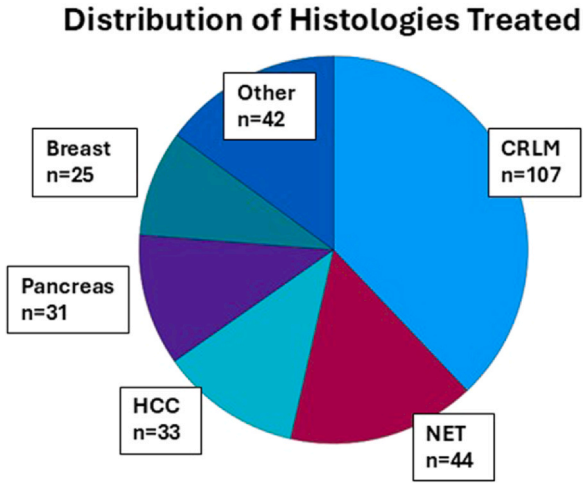

Figure 2. Treated lesions by liver segment. CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; NET, neuroendocrine tumor.

Table 1
Information for included patients.

Variable	Total (N = 230)
Age, y	60 (58–67)
Male sex, n (%)	94 (41.0)
Number tumors treated, n (%)	
1	170 (58.0)
2	69 (23.0)
3	37 (13.0)
> 3	19 (6.0)
Size of tumor treated, cm	2.85
Tumor type/primary tumor site, n (%)	
Colorectal	117 (40.0)
Hepatocellular carcinoma	31 (11.0)
Neuroendocrine tumor	46 (16.0)
Cholangiocarcinoma	23 (8.0)
Breast	26 (9.0)
Pancreatic	30 (10.0)
Other	22 (7.0)
Time of treatment, min	22.6
Liver segments treated, n (%)	
I	9 (2.0)
II	60 (12.0)
III	140 (27.0)
IVA/B	99 (19.0)
V	79 (15.0)
VI	96 (18.0)
VII	29 (6.0)
VIII	8 (2.0)
	Outcomes of histotripsy (N = 230)
Any complication, n (%)	12 (5.2)
No complication, n (%)	218 (94.8)
Clavien-Dindo grade, n (%) [21]	
I	5 (2.2)
II	4 (1.7)
III	0 (0.0)
IV	0 (0.0)
V	3 (1.3)
CCI (points), median (IQR) [22]	0 (0–0)
Readmission, n (%)	6 (2.6)

CCI, Comprehensive Complication Index.

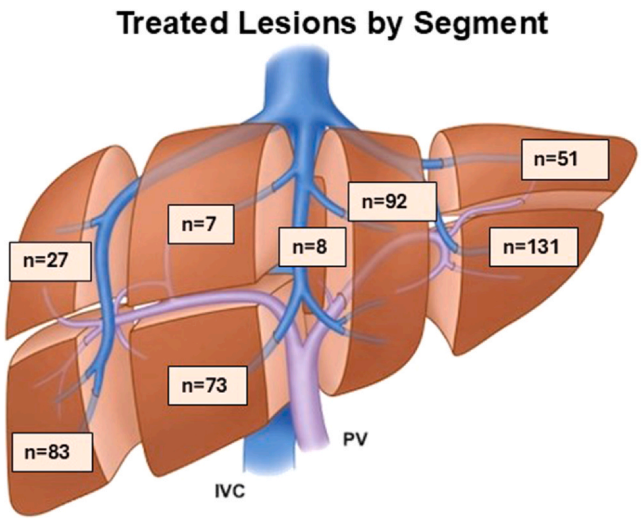

Figure 3. Treated lesions by histologic subtype. IVC, inferior vena cava; PV, portal vein.

treatment cavity are presented in Fig. 1 demonstrating the precision of the device for treating the intended area without affecting the surrounding tissue.

Safety data were reported for 230 patients treated at 9 centers. The median age at treatment was 60 years (IQR, 58–67), and 41% of patients (n = 94) were male. Of these patients, 12 were reported to experience complications, whereas 218 (94.8%) reported no complications. None of the patients required interventions for complications directly related to histotripsy. In addition, 6 patients (2.6%) required readmission within 30 days of admission. Of note, 1 case of readmission was procedure related.

The severity of such postsurgical events was graded using the Clavien-Dindo classification as grade I (5 [2.2%]), II (4 [1.7%]), or V (3 [1.3%]). The rate of major complications (Clavien-Dindo grade > II) was 1.3% (n = 3), and all 3 major complications were death due to malignancy progression (HCC, HCC + cholangiocarcinoma, and colorectal liver metastasis). All 3 patients had known intra- and extrahepatic diseases before treatment, and histotripsy was performed for palliative purposes. Therefore, these complications were considered unrelated to the device and simply the progression of the natural history of the disease. It is unknown whether histotripsy affects disease progression in such patients.

Clavien-Dindo grade I complications included skin irritation treated with topical agents (n = 4) and fluid overload requiring diuresis (n = 1). Grade II complications included portal vein thrombosis requiring anticoagulation (n = 3) and acute kidney injury treated medically (n = 1). Complications were recorded along with age, sex (assigned at birth), treatment histology and intent, comorbidities, complication treatment, and eventual outcome (Table 2).

The overall median CCI was 0.00 (IQR, 0.00–0.00). In addition, the mean CCI across cases was 0 (95% CI, 0.00–0.75). The distribution of the CCI was similar across centers (P =.092).

Discussion

To the best of our knowledge, this is the first comprehensive study to report on the real-world safety profile of histotripsy. Most importantly, the rate of major complications was low within 30 days (1.3%). In addition, the rates of both readmission and nonmajor complications were low. This can provide reassurance that histotripsy is safe as more is learned about the optimal use of this approach for liver tumors.

Histotripsy is a new procedure with clinical data currently available in a limited number of uniquely selected trial patients [8,10,24]. Before this study, there were no reports of postmarket outcome data for histotripsy, although the recently published #HOPE4LIVER trial demonstrated safety in a tightly controlled trial setting [10]. Thus, the safety profile has not been established in real-world practice. In the first 230 clinical cases performed worldwide, there was a low rate of complications within 30 days of the procedure, including the treatment of complex central lesions in the caudate and perihilar regions. Of note, the readmission rates were low, and the procedure was performed as an extended recovery intervention (discharge within 24 h) without interruption of systemic therapy or anticoagulation in most centers.

Given the novel mechanism behind histotripsy vs other commonly used LRTs for liver tumors, initial safety evaluation is both crucial and challenging. The toxicity rates with histotripsy in our study compared favorably with those of possible alternative liver-directed therapies, including chemoembolization/radioembolization, external beam radiation, and surgery. The pooled incidence rates of mortality and overall complications within 30 days after any form of LRT for liver cancer were > 2% and > 12%, respectively [25,26]. The reported complications after 4 common approaches (transarterial embolization [TAE], transarterial chemoembolization [TACE], transarterial radioembolization [TARE], and ablation) included postembolization syndrome (TAE and TACE), liver abscess (TAE, TACE, and TARE), liver biloma (TAE, TACE, and TARE), bleeding (ablation), and liver failure (TARE and TACE) [11]. We observed no evidence of any of these complications in this study, which represents a potential advantage of histotripsy. However, different spectrums of complications were observed in our cohort. These complications were generally minor (a potentially positive signal), although there were 3 cases of disease progression and death. These cannot be causally

Table 2
Detailed description of all reported complications within 30 days, including treatment and ultimate outcomes.

Patient	Age (y), sex	Histology treated; treatment intent	Comorbidities before treatment	Complication	Clavien-Dindo grade	Treatment	Outcome
1	51, male	CRLM; palliative	Previous PE, HTN	Skin blister/rash	I	Skin ointment (bacitracin)	Resolution
2	52, female	PDAC; palliative	Depression/anxiety	Skin blister/rash	I	Skin ointment (bacitracin)	Resolution
3	80, male	PDAC; palliative	Hyperlipidemia, HTN	Skin blister/rash	I	Skin ointment (bacitracin)	Resolution
4	64, female	CRLM; palliative	Depression/anxiety	Skin blister/rash	I	Skin ointment (bacitracin)	Resolution
5	62, male	HCC; curative	Hepatic fibrosis, ascites	Fluid overload/CHF exacerbation	I	Diuretics	Resolution
6	74, male	HCC; curative	HLD, HTN, obesity, BPH, previous CVA	Portal vein thrombosis	II	Oral anticoagulation	Resolution
7	43, male	CRLM; palliative	Previous DVT/PE	Portal vein thrombosis	II	Oral anticoagulation	Resolution
8	67, female	Breast; curative	Asthma, HLD, mixed HLD	Portal vein thrombosis	II	Oral anticoagulation	Resolution
9	58, female	Metastatic NET; palliative	None	Acute kidney injury	II	Diuretics, IV fluids, potassium binders	Resolution
10	85, male	HCC; palliative	ETOH cirrhosis (compensated), obesity, HTN, DVT	Disease progression, death	V	–	Death
11	56, male	Mixed HCC and CCA; palliative	Active hepatitis C infection, cirrhosis	Disease progression, death	V	–	Death
12	49, male	CRLM; palliative	Ascites, asthma	Disease progression, death	V	–	Death

BPH, benign prostatic hyperplasia; CCA, cholangiocarcinoma; CHF, congestive heart failure; CRLM, colorectal liver metastasis; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ETOH, alcohol; HCC, hepatocellular carcinoma; HLD, hyperlipidemia; HTN, hypertension; IV, intravenous; NET, neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma; PE, preeclampsia.
Patients 10 to 12 had known advanced intra- and extrahepatic malignancies before treatment, which was performed with palliative intent.

attributed to histotripsy, although studies will need to carefully report such findings to ensure that they remain isolated cases related to the disease rather than the procedure itself.

Therefore, the preliminary findings regarding histotripsy-related complications, readmission rates, and mortalities confirm that this procedure has a similar safety profile. The management of histotripsy surrounding biliary stents is an ongoing debate and has been well-described in other LRT modalities. Of note, 1 case of sepsis was noted in #HOPE4LIVER after histotripsy in proximity to the endobiliary stents. Therefore, providers may consider prophylactic antibiotics in such cases.

Finally, given the novelty of this technology and its relatively rapid expansion, we aim to discuss our insights into the learning curve for newer technologies. We acknowledge that this is our intuition rather than being strictly evidence based. In general, histotripsy is limited in its ability to target lesions in the air and bone: air typically from bowel gas and bone secondary to the ribs. For new providers, lesions in the inferior part of the left lobe (segments III and IVb) are the easiest, followed in the next difficulty "tier" by segments II, IVa, and V. We recommend providers pick 5 to 10 easier cases to ensure early success while building their practice. As shown in Fig. 2, lesions in all areas have been targeted, which has been achieved primarily through transcostal approaches. These approaches are performed with the patient in a lazy lateral position with a water bath on the patient's rib cage. In addition, many centers elect to perform screening transabdominal ultrasound in the clinic setting with both abdominal radiology and surgery present to assess feasibility, particularly as experience grows. Finally, providers less familiar with abdominal ultrasound may consider collaborating with experienced providers, either those specifically performing more histotripsy cases or those simply performing the initial cases jointly with radiology colleagues to assist with targeting.

This study has some limitations, including lack of oncologic outcomes, use of concomitant/adjuvant therapies, and short follow-up. Future studies should evaluate the treatment response to histotripsy, recurrence, and progression-free survival. Although these results are early, they demonstrate that new multidisciplinary users (surgery and interventional radiology) have effectively treated multiple tumor types within the liver with few major complications to date. The practice patterns vary widely among institutions. We attempted to standardize data collection across institutions using the Clavien-Dindo scale and CCI. However, as with any multicenter study, there are potential biases introduced with data collection from multiple centers. With only 12 total complications, we could not comment on the combined histotripsy and systemic therapy. Our study is retrospective but lacks a comparator arm for surgery, LRT, or no intervention, which makes comparisons, particularly in the discussion, purely speculative to previously published research. Furthermore, there is no ability to infer the causality between the treatment approach and complication profiles, particularly when considering other potential treatment approaches. Institutional- and investigator-sponsored studies are being initiated to formally explore the implementation of histotripsy in various settings and in combination with chemotherapy and immune therapies.

Conclusion

Our report highlights the ability of histotripsy to safely treat multiple tumor types in all segments of the liver with few acute complications. In addition, our early histotripsy results for the treatment of liver tumors compare favorably with those of other liver-directed treatments.

Funding

This study did not receive any funding.

Author contributions

This study was conceptualized and conducted under the direction of DCH Kwon. Data collection and analysis were performed by each physician at their institution and collated centrally by CJ Wehrle. Manuscript drafting was performed by CJ Wehrle and DCH Kwon. All authors critically reviewed the manuscript.

Declaration of competing interest

DCHK is a paid consultant at HistoSonics. PL is a consultant, shareholder, and research support at HistoSonics and a consultant at Johnson & Johnson. EK is a medical advisory board member at Boston Scientific. The other authors declare no competing interests.

Conference information

This work was presented as a late-breaking/high-impact trial podium presentation at the 2024 American College of Surgeons Clinical Congress, San Francisco, California, October 22, 2024.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gassur.2025.102000.

References

[1] GBD US Health Disparities Collaborators. Burden of liver cancer mortality by county, race, and ethnicity in the USA, 2000-19: a systematic analysis of health disparities. Lancet Public Health 2024;9(3):e186–98.

[2] Roberts WW, Hall TL, Ives K, Wolf JS, Fowlkes JB, Cain CA. Pulsed cavitational ultrasound: a noninvasive technology for controlled tissue ablation (histotripsy) in the rabbit kidney. J Urol 2006;175(2):734–8.

[3] Worlikar T, Hall T, Zhang M, Mendiratta-Lala M, Green M, Cho CS, et al. Insights from in vivo preclinical cancer studies with histotripsy. Int J Hyperthermia 2024;41(1):2297650.

[4] Khokhlova VA, Fowlkes JB, Roberts WW, Schade GR, Xu Z, Khokhlova TD, et al. Histotripsy methods in mechanical disintegration of tissue: towards clinical applications. Int J Hyperthermia 2015;31(2):145–62.

[5] Lake AM, Hall TL, Kieran K, Fowlkes JB, Cain CA, Roberts WW. Histotripsy: minimally invasive technology for prostatic tissue ablation in an in vivo canine model. Urology 2008;72(3):682–6.

[6] Yeats E, Lu N, Stocker G, Komaiha M, Sukovich JR, Xu Z, et al. In vivo cavitation-based aberration correction of histotripsy in porcine liver. IEEE Trans Ultrason Ferroelectr Freq Control 2024;71(8):1019–29.

[7] Lu N, Hall TL, Choi D, Gupta D, Daou BJ, Sukovich JR, et al. Transcranial MR-guided histotripsy system. IEEE Trans Ultrason Ferroelectr Freq Control 2021;68(9):2917–29.

[8] Vidal-Jove J, Serres X, Vlaisavljevich E, Cannata J, Duryea A, Miller R, et al. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. Int J Hyperthermia 2022;39(1):1115–23.

[9] Vidal-Jove J, Serres-Creixams X, Ziemlewicz TJ, Cannata JM. Liver histotripsy mediated abscopal effect-case report. IEEE Trans Ultrason Ferroelectr Freq Control 2021;68(9):3001–5.

[10] Mendiratta-Lala M, Wiggermann P, Pech M, Serres-Créixams X, White SB, Davis C, et al. The #HOPE4LIVER single-arm pivotal trial for histotripsy of primary and metastatic liver tumors. Radiology 2024;312(3):e233051.

[11] Zane KE, Cloyd JM, Mumtaz KS, Wadhwa V, Makary MS. Metastatic disease to the liver: locoregional therapy strategies and outcomes. World J Clin Oncol 2021;12(9):725–45.

[12] Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734–9.

[13] Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, et al. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009;10(11):1111–8.

[14] Poon RTP, Fan ST, Tsang FHF, Wong J. Locoregional therapies for hepatocellular carcinoma: a critical review from the Surgeon's perspective. Ann Surg 2002;235(4):466–86.

[15] Kumar P, Wehrle CJ, Sun K, Jiao C, Panconesi R, Zhang M, et al. Combining liver-directed and immunotherapy in advanced hepatocellular carcinoma: a review and future directions. Surg Oncol Insight 2024;1(4):100100.

[16] Wehrle CJ, Fujiki M, Schlegel A, Uysal M, Sobotka A, Whitsett Linganna M, et al. Intensive locoregional therapy before Liver Transplantation for colorectal cancer liver metastasis: a novel pre-transplant protocol. Liver Transpl 2024;30(12):1238–49.

[17] Wehrle CJ, Raj R, Maspero M, Satish S, Eghtesad B, Pita A, et al. Risk assessment in liver transplantation for hepatocellular carcinoma: long-term follow-up of a two-centre experience. Int J Surg 2024;110(5):2818–31.

[18] Wehrle CJ, Woo K, Raj R, Chang J, Stackhouse KA, Dahdaleh F, et al. Comparing outcomes of minimally invasive and open hepatectomy for primary liver malignancies in patients with low-MELD cirrhosis. J Gastrointest Surg 2023;27(11):2424–33.

[19] Ozair A, Collings A, Adams AM, Dirks R, Kushner BS, Sucandy I, et al. Minimally invasive versus open hepatectomy for the resection of colorectal liver metastases: a systematic review and meta-analysis. Surg Endosc 2022;36(11):7915–37.

[20] Berardi G, Ivanics T, Sapisochin G, Ratti F, Sposito C, Nebbia M, et al. Minimally invasive versus open liver resections for hepatocellular carcinoma in patients with metabolic syndrome. Ann Surg 2023;278(5):e1041–7.

[21] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–13.

[22] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258(1):1–7.

[23] Trumbore M. Focused ultrasound system for non-thermal, mechanical tissue ablation U.F.a.D.A. (FDA). Editor; 2023.

[24] Vidal-Jové J, Serres-Creixams X, Ziemlewicz TJ, Cannata JM. Liver histotripsy mediated abscopal effect—case report. IEEE Trans Ultrason Ferroelectr Freq Control 2021;68(9):3001–5.

[25] Viveiros P, Riaz A, Lewandowski RJ, Mahalingam D. Current state of liver-directed therapies and combinatory approaches with systemic therapy in hepatocellular carcinoma (HCC). Cancers (Basel) 2019;11(8):1085.

[26] Curley SA, Marra P, Beaty K, Ellis LM, Vauthey JN, Abdalla EK, et al. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. Ann Surg 2004;239(4):450–8.