

Histotripsy For Liver Tumors: A Comprehensive Review

Swetha. M ¹, Dr. Alex Daniel Prabhu Arul Pitchai ², Phinekas Rajan.R ³, Dr. Jeffrey Skaria Joseph ⁴

¹ Ph.D, Research Scholar, Department of Radiology, Chettinad Academy of Research and Education, Kelambakkam

² Professor and HOD, Department of Radiology, Chettinad Academy of Research and Education, Kelambakkam

³ Lecturer, Faculty of Allied Health Science, Department of Radiology, Hindumission College of Allied Health Sciences

⁴ Associate Professor, Department of Radiology, Chettinad Academy of Research and Education, Kelambakkam

Corresponding Author :
Swetha M, Email id : swethamurugan3702m@gmail.com

Abstract

Purpose: Histotripsy is a non-thermal, non-invasive, focused ultrasound method that uses controlled acoustic cavitation to mechanically destroy tissues. With FDA approval in October 2023 for the treatment of liver tumors, histotripsy is rapidly being adopted as the first completely non-invasive method of liver ablation. This review summarizes the evidence for histotripsy in liver tumors and highlights the knowledge gaps that require further investigation.

Methods : A non-systematic search of PubMed and Google Scholar was conducted in June 2026 using keywords including histotripsy, acoustic cavitation ablation, hepatocellular carcinoma, liver metastases and HistoSonics Edison. Original peer-reviewed studies, clinical trials, systematic reviews and preclinical investigations relevant to histotripsy were included in this review.

Conclusion: The #HOPE4LIVER pivotal trials found a 95% technical success rate with a 7% major complication rate at 30 days. At one year, local tumor control was 63.4% by the primary assessment method and 90% by a post hoc reassessment. Remaining knowledge gaps include a lack of long-term (>1 year) and comparative effectiveness data, a tumor size limit of <3 cm, non-standardized imaging response criteria, unknown human immunological mechanisms, unclear dosing regimens, insufficient data from cirrhotic/high-risk patients, and undefined learning curves.

While histotripsy represents a well-founded scientific approach and a clinically promising technique for ablating liver tumors, there is still an immature body of literature lacking research integrity. There is a need for large prospective studies comparing various ablation techniques with long-term follow-up before histotripsy could be incorporated into clinical guidelines.

Keywords: Histotripsy; hepatocellular carcinoma; focused ultrasound; non-thermal ablation ; Immunologic cell death.

INTRODUCTION

Liver cancer, including both primary and secondary tumors, is among the most serious oncologic problems worldwide. Hepatocellular carcinoma (HCC) is one of the most frequent and dangerous malignancies, causing approximately 830,000 deaths annually. It develops almost exclusively on the background of chronic hepatic damage due to hepatitis B or C infection, alcohol-induced cirrhosis, or metabolic-associated steatohepatitis.[1,2] Hepatic insufficiency, increased risks of surgical intervention, and immunosuppressive microenvironment are among the major factors complicating therapy for HCC because of its close connection with cirrhosis.[3,4] Liver involvement caused by secondary dissemination of cancer originating in other organs is a supplementary issue since the liver becomes a primary place for hematogenous metastasis of various solid tumors.[5] Curative intent treatment of liver tumors is based on surgery, resection, and for selected patients with HCC, transplantation. However, such treatments are available for fewer than three out of ten patients at the time of diagnosis, due to competing requirements of inadequate hepatic functional reserve, bilobar/multifocal tumor, extensive vascular invasion, and surgical comorbidities.[6] The majority of patients need non-surgical approaches, including Thermal ablation – Radiofrequency ablation (RFA), Microwave ablation (MWA), Transarterial chemoembolization (TACE), Stereotactic body radiation Therapy, and increasingly immune checkpoint inhibitors.[7,8] Heat sink effect – the cooling of the treatment zone by high flow blood vessel nearby – is an inevitable consequence of thermal ablation, which leads to incomplete treatment, potential damage to biliary ducts as well as the surrounding tissues, and HCC larger than 3 cm – to a recurrence rate of more than 30 %.[9,10]

Histotripsy is a mechanism-based focused ultrasound therapy platform is being developed over more than two decades at the University of Michigan for precise, non-invasive mechanical tissue ablation.[11,12] Histotripsy does not use heating of the tissue, like traditional thermal ablation, but creates a controlled cavitation in the tumor, leading to the conversion of tissue to acellular fluid using solely mechanical energy without any ionizing radiation and without any heating of the tissue.[13] The HistoSonics Edison System became the first liver ablation device to

get FDA clearance by a wholly non-invasive approach in October 2023, becoming a landmark in oncologic locoregional therapy.[14]

By mid-2024, more than a thousand patients have undergone histotripsy treatment in academic and community facilities worldwide.[15] Early results from the landmark #HOPE4LIVER pivotal study indicate the technical feasibility and short-term safety of the modality.[16,17] However, the scientific literature is still in infancy. The follow-up periods were too short, no comparative trials against existing ablation technologies were conducted, and many physical, clinical, and technical issues require clarification. This review critically assesses the current state of knowledge on histotripsy, including cavitation biophysics, preclinical immunological studies, and pivotal/post-marketing trials, and identifies the research gaps that needed to be addressed for histotripsy to gain a recommended place in the algorithm of liver oncology treatment.

METHODS

A non-systematic search of PubMed and Google Scholar was performed using the advanced search keywords “histotripsy, acoustic cavitation ablation, hepatocellular carcinoma and liver metastases” in June 2026, which was not limited by date or study type. All titles and abstracts were individually screened to include articles that evaluated the role of histotripsy including diagnosis, prognosis and therapeutics in humans. The citations of these shortlisted articles were further analyzed to include additional relevant articles.

Biophysical Mechanisms of Histotripsy

Acoustic Cavitation as the Therapeutic Mechanism

The unique characteristic that makes histotripsy distinct from all prior ablation techniques is its complete reliance on mechanical damage caused by acoustic cavitation without significant input from heat energy.[13,18] Unlike traditional focused ultrasound, RFA and MWA, which depend on the application of heat, histotripsy operates outside this framework.

Histotripsy uses short bursts of high-intensity focused ultrasound pulses at duty cycles of less than 1%, ensuring that the average power does not cause any temperature increase in the tissues. The peak pressure values in the focal point – with negative pressure amplitudes of 15-30 MPa depending on the mode – exceed the tensile strength of gas nanobubbles native to tissues.[19,20] The bubbles form, grow up to hundreds of micrometres within microseconds, and then implode through inertia. The effects of this imploding process, including microjet formation at the asymmetric interface of the bubble, compressive shock waves radiating outwardly, and extreme shear stress are sufficient to destroy the plasma membrane, cytoskeleton, and extracellular matrix elements at the focus.[21,22](Figure 1) This leads to the formation of a tissue homogenate – an acellular liquid containing subcellular pieces, that is gradually reabsorbed by the immune system and lymphatics over days, leaving a liquid-filled space.

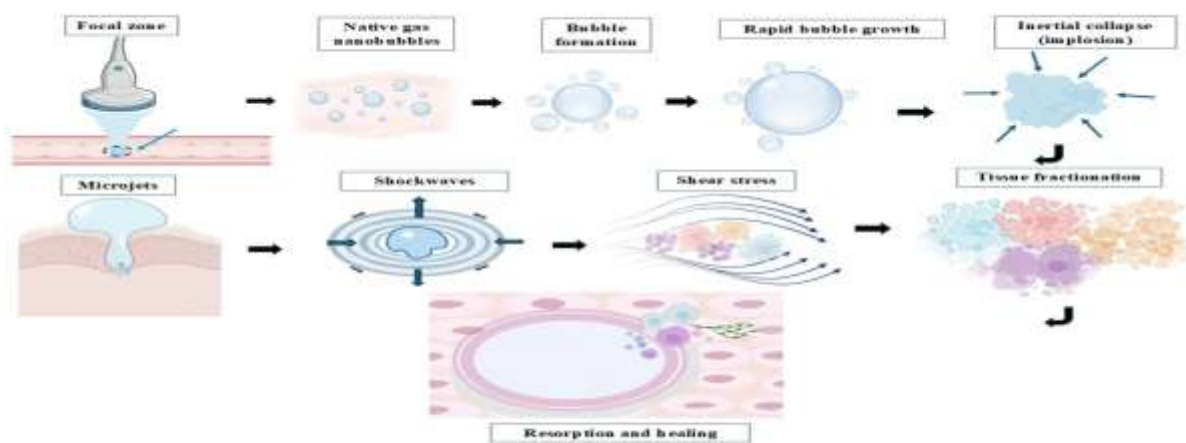


Figure 1: Mechanism of histotripsy-induced acoustic cavitation. Focused ultrasound generates cavitation, producing microjets, shockwaves, and shear stresses that mechanically fractionate tissue, followed by gradual resorption and healing. Created in <https://BioRender.com>

Variant Mechanisms and the HistoSonics Edison Platform

The three operation modes of histotripsy mechanisms have been defined based on the pulse structure and route to the cavitation threshold.[23] Intrinsic-threshold histotripsy uses ultrashort high-pressure ultrasound pulses (>25–30 MPa) to generate dense cavitation bubble clouds, producing sharply demarcated mechanical tissue ablation.[24] Shock-scattering histotripsy employs multi-cycle ultrasound pulses (3–20 cycles, 15–25 MPa), where shock-wave interactions with microbubbles amplify cavitation, resulting in dense bubble cloud formation. This mechanism forms the basis of the HistoSonics Edison System.[25,26](Figure 2)



Figure 2: The HistoSonics Edison System, the first FDA-cleared clinical histotripsy platform for liver tumor ablation. Created in <https://BioRender.com>

The HistoSonics Edison System (HistoSonics Inc., Minneapolis, MN, USA)— the sole FDA-cleared clinical histotripsy device and platform underpinning all published human liver data — delivers treatment transcutaneously through a robotic positioning arm under continuous B-mode ultrasound guidance, without skin-breach or vascular access requirements.[27]

Structural Selectivity: Vessels, Bile Ducts, and Fibrous Stroma

Another key aspect of cavitation-based ablation is its ability to selectively disrupt parenchymal and tumor cells without affecting the different structures in the ablation target. The collagen-rich matrix of blood vessels, bile duct basement membrane of the epithelium, and fibrous scaffolds of stromata show acoustic impedance and physical properties allowing relative protection from cavitation-mediated disruption.[28] In both animal studies and first human trials, intact major branches of portal and hepatic veins and bile ducts passing through the area of ablation have always been reported, whereas such complications as heat sink effect, biliary strictures, and wall coagulative necrosis have been described after thermal ablation in similar anatomical zones.[29,30]

Thus, owing to selective tissue disruption, histotripsy can potentially be applied for the ablation of centrally located perivascular or peri-hilar tumors that are dangerous with thermal methods ; however, there are not enough prospective data in humans on this issue.

Clinical Workflow and Treatment

The histotripsy procedure is performed using the HistoSonics Edison System, a robotically positioned platform in which the therapy transducer is co-housed with a diagnostic ultrasound probe within a single treatment head, permitting real-time visualisation of the target and continuous monitoring of the cavitation bubble cloud throughout sonication.[9,13,14,27] Candidate selection is guided by pre-procedural cross-sectional imaging (contrast-enhanced CT or MRI), performed within approximately one week of the planned procedure, to confirm tumour number, size and location within the device's validated treatment envelope, together with confirmation of an adequate acoustic window free of overlying bowel gas, lung, or bone.[16,31] In the pivotal #HOPE4LIVER trials,

eligible patients had up to three hepatic tumours, each ≤ 3 cm in greatest dimension, who had exhausted, declined, or were unsuitable for standard-of-care locoregional or systemic therapy.[16] The treatment head is coupled to the abdominal wall over the target, the ablation volume is outlined with a peripheral margin around the visualised tumour, and mechanical pulses are delivered under continuous sonographic guidance until the entire planned volume has been treated, most often as a single outpatient or short-stay session rather than a staged multi-visit protocol.[31,32]

Immediate post-procedural cross-sectional imaging is obtained within 36 hours (Fig 4) to confirm technical success, defined as complete coverage of the intended ablation volume, with further structured follow-up incorporating clinical assessment and contrast-enhanced imaging at 30 days and, in trial protocols, at 90 days, six months, and annually thereafter.[16,17,33](Figure 3) Because histotripsy produces a finite liquefactive lesion without a coagulative rim, most patients recover with early ambulation and a short observation period, and the reported adverse-event profile has been dominated by transient procedural pain rather than the delayed vascular, biliary, or thermal-injury complications occasionally described after radiofrequency or microwave ablation.[29,30,33]

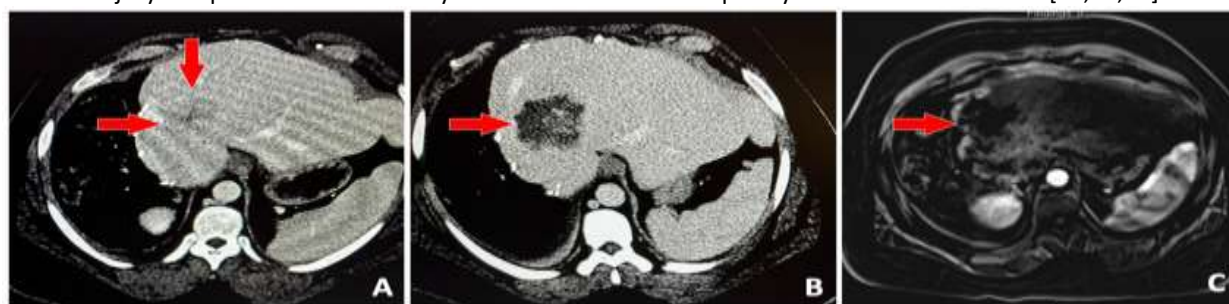


Figure 3: Histotripsy of a colorectal liver metastasis. (A) Baseline CT shows the 3.5-cm lesion. (B) CT on post-procedure day 1 shows no enhancement in the treated region. (C) MRI at 1 month shows no viable tumor. (Reproduced under CC BY 3.0 license from: Paramythiotis D, Tsavdaris D, Tsavdaris G, Hatzidakis A, Psarras K, Mekras A, Georgiades C, Michalopoulos A. Surgery Without Scalpel: Histotripsy as a Non-Invasive and Non-Thermal Modality for Liver Tumor Ablation. J Clin Med. 2025;14(18):6391.)

Preclinical Evidence

Technical Feasibility and Ablation Characterisation

The underlying basis of experimental histotripsy for liver oncology has been systematically developed over more than 15 years of dedicated preclinical research. Critical proof-of-principle studies by Xu et al. from the University of Michigan showed that transcutaneous and ultrasound-guided ablation of the liver was possible in porcine and rodent models, resulting in discrete and homogeneous acellular zones without damage to adjacent tissues.[11,34] (Figure 4)



Figure 4: Timeline(2000-2024) of key preclinical,clinical, and regulatory milestones in histotripsy development for

liver tumors, from foundational cavitation research to FDA clearance and post market data. Created in <https://BioRender.com>

Vlaisavljevich et al. subsequently established that ablation zones were subject to predictable resorption and regeneration of normal parenchyma surrounding the area without any subsequent fibrosis.[35] Histopathological findings were uniform in demonstrating a characteristic profile: a liquefied acellular cavity with a sharp interface with viable parenchyma – distinctly different from the gradual necrotic-to-viable transition seen with thermal therapies.[36,37] The proof-of-concept of tumor ablation using histotripsy was achieved subsequently by Worlikar et al. in subcutaneous HCC xenograft models with a custom-made 1MHz transducer, while its translational utility for orthotopic tumor treatment has been demonstrated in rats, achieving ablation across the intact abdominal wall under sonography guidance.[28,38]

Immunostimulatory Effects: Preclinical Data

Of all biological mechanisms underlying histotripsy, its potential for eliciting an antitumor immune response has yielded the most promising scientific translational hypothesis (Fig 6).[39,40] The key immunological study using histotripsy involved an orthotopic immunocompetent McA-RH7777 rat HCC and delivered subcomplete ablation to cover 50-75% of the tumor volume.[41] While leaving part of the tumor untouched, complete local tumor remission was noted in nine out of 11 treated rats without any sign of intrahepatic tumor metastases up until 12 weeks of observation, while all untreated controls had progressed to euthanasia in one to three weeks. Both local tumor control and survival were significantly better in the histotripsy group ($p < 0.0001$), while the increased presence of immune cells infiltrating the tumor in treated animals suggested that immune-mediated tumor remission occurred.[41]

The basic premise is that histotripsy retains the conformational integrity of native antigens, while mechanical membrane rupture does not denature the proteins, unlike thermal denaturation. In other words, the release of tumor-associated antigens (TAAs) takes place in their native and biologically active form.[42] Damage-associated molecular patterns (DAMPs) such as HMGB1, translocated calreticulin, and heat shock proteins activate the innate immune cells, cause dendritic cell maturation, and prime CD8⁺ cytotoxic T lymphocytes for antitumor immunity.[43,44] Bilateral tumor murine models yielded evidence for systemic immune propagation in the form of regression of an untreated contralateral lesion following the ablation of one lesion, the so-called 'abscopal' effect, potentiated by simultaneous administration of a checkpoint inhibitor targeting anti-CTLA-4.[45,46] Quantification of antigen release showed a dose-response correlation between the treatment and immunogenic antigen release.[42,47](Figure 5) Importantly, all these data are exclusively from immunocompetent murine studies using transplantation of syngeneic tumors and do not reflect the cirrhotic, immunologically tolerized environment of HCC patients; thus, human-specific clinical investigations are required.

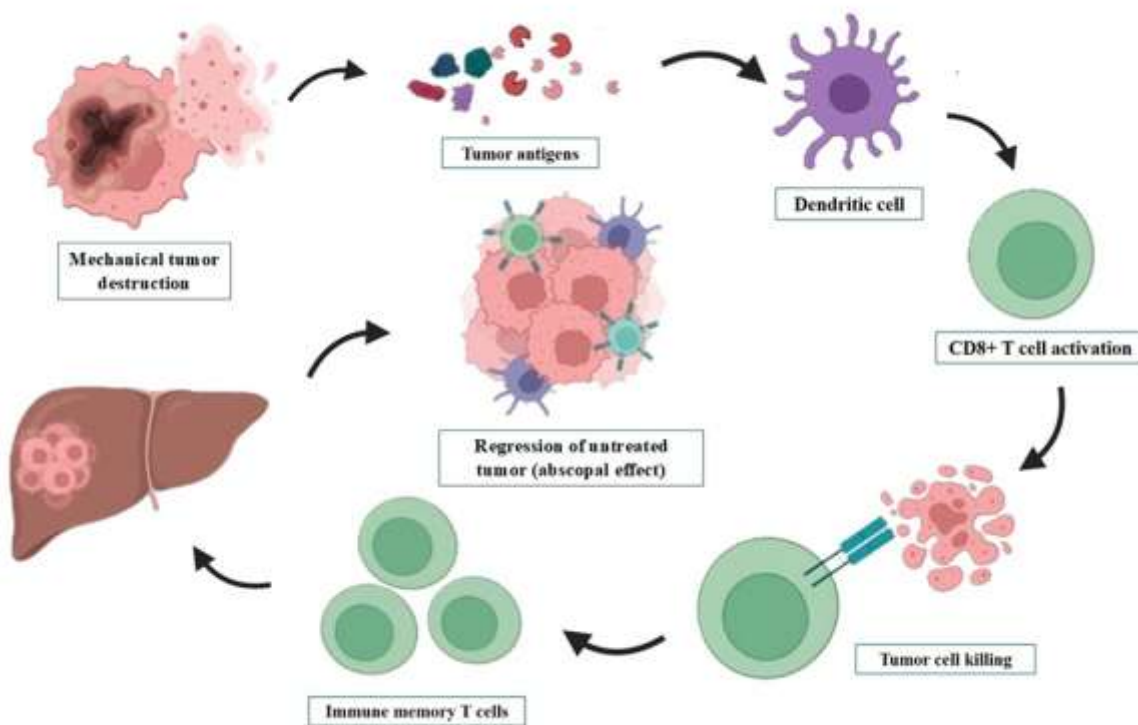


Figure 5: Proposed mechanism of histotripsy-induced antitumor immune response. Mechanical tumor destruction releases tumor antigens, activating dendritic cells and CD8⁺ T cells, resulting in tumor cell killing, immune memory, and a potential abscopal effect. Created in <https://BioRender.com>

Clinical Evidence: First-in-Human through Post-Clearance Data

First-In-Human Feasibility Study: The THERESA Trial

Initial human study employing histotripsy for the treatment of hepatic tumours is presented by Vidal-Jove et al. (the THERESA feasibility trial published in *International Journal of Hyperthermia*, 2022).[31] Eight patients with either primary or metastatic multi-focal liver tumours have been enrolled and underwent safety and imaging follow-up at eight weeks post-treatment. No major procedural side effects were observed in the patients. Volume reduction was noted in hepatic tumours not subjected to histotripsy in two of eight patients – a first-ever human example of potentially abscopal/immune response – a strong biological justification for moving to pivotal clinical trials.[31,32]

The #HOPE4LIVER Pivotal Trials

The pivotal evidence base for FDA clearance derives from the parallel U.S. and EU/England #HOPE4LIVER trials, which were prospective, multicenter, single-arm investigations at 14 sites across North America and Europe, with consolidated results published in *Radiology* in 2024.[16] Eligible patients had primary or secondary hepatic tumors of up to 3 cm greatest dimension (maximum three lesions) and had been deemed unsuitable for or declined available standard-of-care therapy.

Forty-four participants (mean age 64 years; 41% HCC, 59% non-HCC metastases) with 49 tumors were enrolled and treated. Mean pre-treatment tumour diameter was 1.5 ± 0.6 cm; mean post-treatment ablation zone measured 3.6 ± 1.4 cm, confirming reliable creation of margins beyond the radiologically apparent tumour boundary.(Figure 6) Co-primary endpoints — technical success and freedom from procedure-related major complications within 30

days — were assessed against performance goals of >70% and <25%, respectively. Technical success was achieved in 42 of 44 treated tumors (95.5%; 95% CI: 84–100%), and major complications arose in 3 of 44 participants (6.8%; 95% CI: 2–18%), both results substantially exceeding performance thresholds.[16] These data formed the regulatory basis for the FDA de novo marketing authorization granted to the HistoSonics Edison System in October 2023.

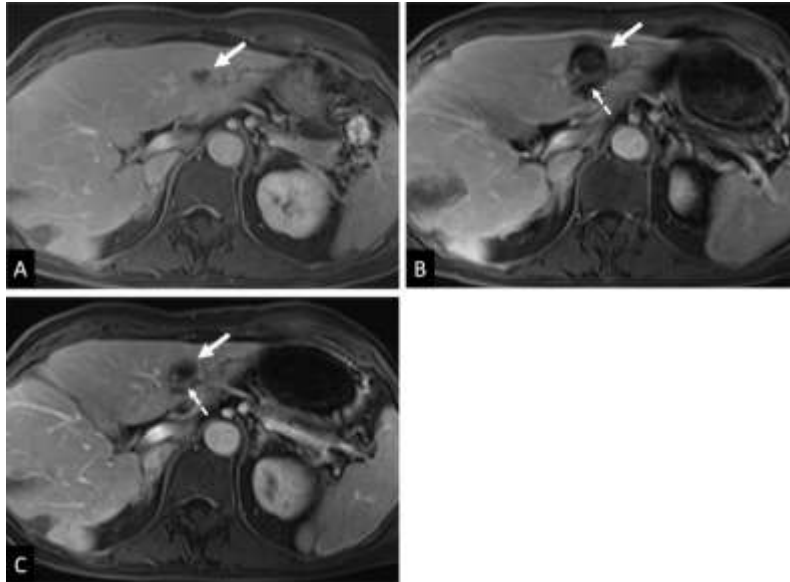


Figure 6: Histotripsy of a colorectal liver metastasis. (A) Preprocedure MRI shows the tumor. (B) MRI <36 hours post-treatment shows the ablation zone with a patent traversing vessel. (C) MRI at 30 days shows zone involution, vessel unchanged.

(Reproduced under CC BY 4.0 license from: Mendiratta-Lala M, Wiggermann P, Pech M, et al. The #HOPE4LIVER Single-Arm Pivotal Trial for Histotripsy of Primary and Metastatic Liver Tumors. *Radiology*. 2024;312(3):e233051.)

One-Year Outcomes: #HOPE4LIVER Update

Follow-up data after one year from enrolment in the trial for 47 patients (19 HCC, 28 metastatic patients; 52 tumors treated) from 14 different institutions were published in the *Annals of Surgery* in 2025.[17] Overall survival and freedom from local tumor recurrence were analyzed using Kaplan-Meier curves. Importantly, 89.5% of HCC patients and 96.4% of metastatic patients presented with multifocal hepatic involvement at the time of treatment, indicative of a heavily pre-treated and refractory study cohort. One-year local tumor control was 63.4% by the trial's primary core-laboratory assessment and 90% by a post hoc reassessment performed to account for a learning curve in interpreting post-treatment imaging appearances; one-year overall survival was 73.3% for HCC and 48.6% for metastatic disease.[17] These data support histotripsy as an appropriate locoregional therapy for patients who exhausted or declined other options, but they underline the necessity of calibrating post-treatment imaging according to institutional experience, and show that the often-quoted 90% local-control figure depends on which assessment method is used.[17]

First International Real-World Safety Study

The largest published safety database on histotripsy included 295 patients who received treatment for 510 liver tumors in 18 different international centers between FDA approval (December 2023) and July 2024.[33] Histologic types of tumors included colorectal metastases (n=140), neuroendocrine deposits (n=46), HCC (n=31), pancreatic metastases (n=30), and breast cancer metastases (n=26) (Fig 8) and involved all eight hepatic segments.(Figure 7) Of 230 patients with full safety data, 12 (5.2%) had any grade adverse event, none of which required intervention for complications related to histotripsy.[33]

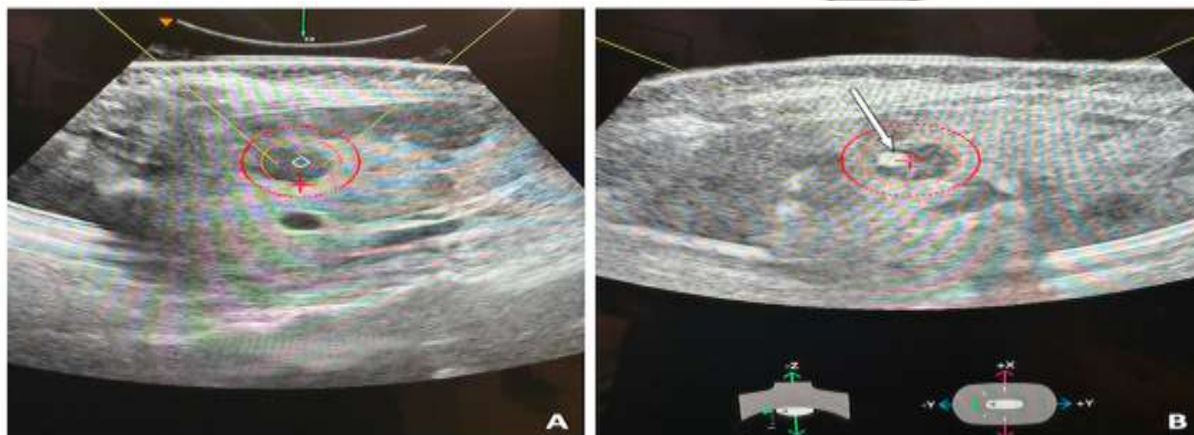


Figure 7: Histotripsy planning and treatment of a breast cancer liver metastasis. (A) Planning ultrasound shows the hypoechoic lesion with ablation zone and 5-mm margin marked. (B) Intraprocedural ultrasound shows the cavitation bubble cloud targeting the lesion.

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Post-Clearance Efficacy Data

The first retrospective multicenter study performed nationwide, including all cases of histotripsy at four academic institutions from December 2023 to December 2024, presented the initial dataset of post-clearance efficacy in routine clinical settings.[48] Tumor viability was assessed using RECIST and modified RECIST criteria on contrast-enhanced images on post-procedure days 1, 30, and 90.(Figure 8) The 90-day local tumor control rate reached 90%, confirming pivotal trial standards in an unselected clinical cohort. A systematic review and meta-analysis performed by Wehrle et al. included ten clinical studies eligible for inclusion, both prospective and retrospective, demonstrating consistently high levels of technical feasibility, local tumour control, and a low burden of serious adverse events.[49] The authors highlighted heterogeneity between the studies caused by different outcome criteria, imaging assessment methods, and varying follow-up periods, stating that their results are restricted by the number of studies included and that larger prospective studies with standardized reporting are required.[49] Further single-centre studies include 26-patient series by Mabud et al. reporting 97% technical success among 56 patients with hepatic metastases and a minor adverse event rate of 5.2% (Fig 9),[50] and a prospective substudy of 30 patients on immunology assessing systemic cytokines and a cytokine composite predictive score for clinical outcomes.[51]

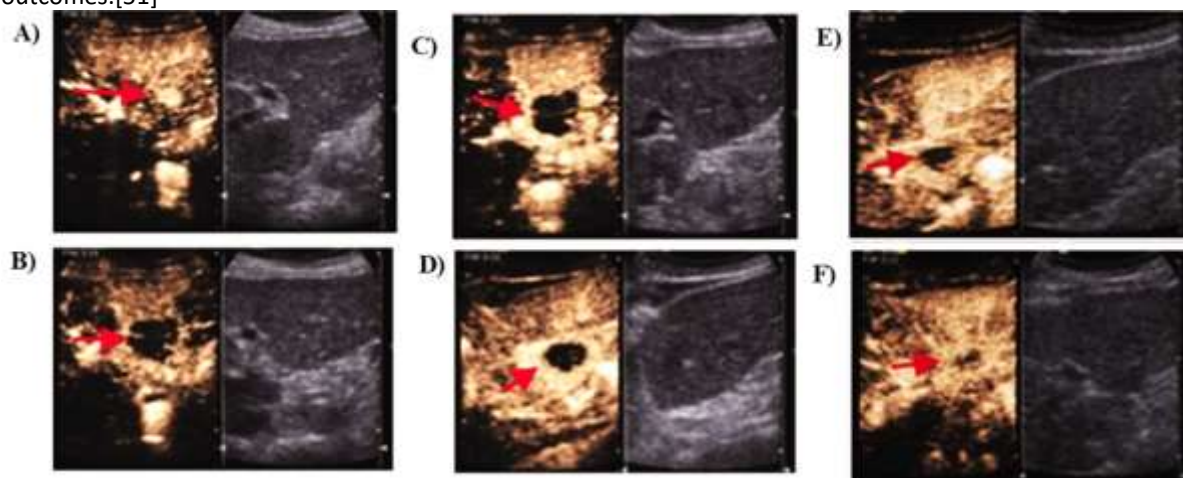


Figure 8: Contrast-enhanced ultrasound (left) and B-mode ultrasound (right) demonstrating serial imaging changes following histotripsy of a liver tumor. (A) Baseline tumor. (B) Treatment site with no residual tumor at 1 day. (C) Treatment site involuting at 1 week. (D) Approximately 70% reduction in treatment site volume at 4 weeks. (E) Approximately 90% volume reduction at 8 weeks. (F) Near-complete healing with no evidence of residual tumor at 12 weeks. (Reproduced from Vidal-Jove J, et al. First-in-man histotripsy of hepatic tumors: the THERESA trial. *Int J Hyperthermia*. 2022;39(1):1115–1123. Published under CC BY 4.0)

Translational and Scoping Reviews

Worlikar et al. (*Radiology: Imaging Cancer*, 2025) reviewed the entire process of translation, ranging from preclinical feasibility to clinical validation of histotripsy in the liver.[38] Queen et al. (2025) conducted a focused scoping review on the evolving use of histotripsy in HCC management.[52] These reviews provide context for the available evidence within the larger realm of hepatic oncology.

6. Discussion

Despite the genuine scientific and clinical interest generated by early histotripsy data, an objective appraisal of the literature reveals evidentiary gaps that materially limit how, when, and on whom the technique can be recommended. The most fundamental of these is the absence of long-term oncologic outcome data: #HOPE4LIVER's co-primary endpoints were assessed at 30 days and, at most, one year, leaving two- and five-year recurrence, progression-free survival, and overall survival entirely uncharacterized [16,17]. This is a critical omission given that intrahepatic recurrence after locoregional HCC treatment exceeds 50% within two years even in well-selected patients [53,54], and that resection and thermal ablation of colorectal liver metastases are benchmarked against five-year survival of 25–35% [55]. Without comparable follow-up, histotripsy's true oncologic effectiveness cannot yet be established.

Compounding this, no randomized, matched, or propensity-adjusted study has directly compared histotripsy with RFA, MWA, TACE, SBRT, or resection [16]. This stands in sharp contrast to the mature comparative literature underpinning established modalities, including randomized RFA-versus-MWA trials, resection-versus-ablation studies, and the COLLISION trial for colorectal metastases [56–58]. A clinician choosing between histotripsy and RFA for a small perivascular HCC currently has no comparative evidence to draw on, making rigorously designed comparative trials an unambiguous priority.

Efficacy also remains uncharacterized beyond the 3 cm threshold to which current eligibility criteria are restricted; the mean tumor diameter in #HOPE4LIVER was only 1.5 ± 0.6 cm [16], a size range where established thermal ablation already performs well. Because histotripsy's theoretical advantage over thermal modalities is most relevant for larger perivascular lesions — precisely the population excluded from existing trials — whether this structural selectivity translates into clinically meaningful ablation in larger human tumors remains unknown [6].

A related methodological weakness is the lack of standardized, modality-specific imaging response criteria. Post-histotripsy ablation zones appear distinct from thermal ablation zones on CT, MRI, and contrast-enhanced ultrasound [59], yet published series have applied a mix of RECIST, modified RECIST, and institutional criteria, undermining cross-study comparability. Even the #HOPE4LIVER investigators acknowledged needing retrospective recalibration of imaging assessments as their understanding of post-treatment appearances matured [17,49].

Histotripsy's immunostimulatory potential — among its most scientifically distinctive features — likewise remains only rudimentarily characterized in humans. The most rigorous available dataset, a single-center, 30-patient cytokine profiling study, did not include immunophenotyping, tumor-infiltrating lymphocyte quantification, or circulating tumor DNA kinetics [51], and abscopal effects have been documented only anecdotally [31]. Notably, no trial has yet combined histotripsy with checkpoint inhibitor therapy despite compelling preclinical rationale and its status as first-line systemic treatment for unresectable HCC [8,60].

Treatment dosimetry is similarly undefined. Unlike thermal ablation, which is guided by decades of parameter–outcome correlation, no prospective study has linked histotripsy's acoustic parameters — transducer frequency, focal pressure, pulse density, and duration — to clinical outcomes, nor validated an appropriate ablation margin analogous to the 5 mm standard used in thermal ablation [23,61–63].

Populations studied to date are also narrow: published series are skewed toward Child-Pugh A patients with preserved hepatic reserve, while those with decompensated cirrhosis, portal hypertension, coagulopathy, or

significant comorbidity — arguably the patients most likely to benefit from a non-invasive approach — remain underrepresented [16,17].

The operator learning curve is another open question. No study has quantified the procedure volume required for proficiency or how outcomes evolve with experience, even though the #HOPE4LIVER investigators themselves noted a period of institutional recalibration [17]. As adoption spreads beyond specialist centers, this gap carries direct implications for training and credentialing.

Finally, no formal cost-effectiveness or health economic analysis has compared histotripsy with established alternatives, despite its substantially higher capital cost and its current requirement for general anesthesia. Until such data exist, payers and institutions have no rational basis for weighing its acquisition cost against potential benefits such as reduced hospitalization and avoidance of surgical risk.

Collectively, these gaps — spanning long-term outcomes, comparative effectiveness, large-tumor efficacy, imaging standardization, immunological characterization, dosimetry, high-risk population safety, learning curve, and health economics — are not peripheral concerns but fundamental deficiencies that will determine histotripsy's eventual place in the liver oncology treatment algorithm. Addressing them will require randomized controlled trials with extended follow-up, prospective immunological studies, validated imaging criteria, standardized protocols, and inclusive patient populations reflective of real-world practice.

Any comparison between histotripsy and established locoregional therapies must be read with an important caveat: no head-to-head trial has yet enrolled patients to histotripsy against an established alternative. Table 1 juxtaposes the strongest available histotripsy evidence against representative data for RFA versus MWA and thermal ablation versus resection, but these datasets differ in study design, tumor histology, and patient population, and are not directly interchangeable (Table 1).

Table 1. Comparative evidence maturity across liver ablation modalities

Modality	Study design	Technical success / ablation completeness	Major complications	Local tumor control	Head-to-head comparative data?
Histotripsy[16,17]	Single-arm, prospective, n=44	95.5% (42/44 tumors; 95% CI 84–100%)	6.8% at 30 days (3/44; 95% CI 2–18%)	63.4% (primary assessment) / 90% (post hoc assessment) at 1 year	None
RFA vs MWA (HCC)[57]	Meta-analysis, 6 RCTs, n=826	Complete ablation: RFA 455 vs MWA 485 events (OR 0.91, p=0.81)	MWA 20 vs RFA 15 events (OR 0.81, p=0.52)	LTP: MWA vs RFA OR 0.70, p=0.27	Yes — direct RCTs
Thermal ablation vs resection (CRLM)[58]	Single RCT, n=300	—	Serious AEs: 7% (ablation) vs 20% (resection); any-grade AEs: 19% vs 46%, p<0.001	Per-tumor: HR 0.09, p=0.024 (favors ablation)	Yes — direct RCT

RFA/MWA figures are drawn from an HCC population; ablation-versus-resection figures are drawn from a colorectal liver metastasis population — different tumor biology and patient populations from each other and from the #HOPE4LIVER cohort. This table illustrates the maturity gap in evidence design (single-arm vs. randomized), not a direct outcome-by-outcome comparison across tumor types.

Note: AE, adverse event; CI, confidence interval; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; HR, hazard ratio; LTP, local tumor progression; MWA, microwave ablation; OR, odds ratio; RCT, randomized controlled trial; RFA, radiofrequency ablation.

Histotripsy's reported outcomes — 95.5% technical success, and one-year local tumor control of 63.4% by primary assessment or 90% by post hoc reassessment — derive from a single-arm, uncontrolled pivotal trial of only 44–47 patients. By contrast, the RFA-versus-MWA comparison is drawn from a meta-analysis of six randomized trials totaling 826 patients, and the thermal-ablation-versus-resection comparison from a single randomized trial of 300 patients. This asymmetry in evidentiary maturity, rather than any single outcome figure, is the central limitation of the current comparative landscape: histotripsy cannot yet be benchmarked against RFA, MWA, TACE, or Y90 within a common trial framework, so apparent similarities or differences in technical success or complication rates should not be read as evidence of relative superiority or inferiority.

This gap carries direct clinical implications. RFA and MWA remain first-line ablative options for HCC within Milan criteria, supported by decades of dosimetry data, randomized comparisons, and incorporation into AASLD, EASL, and BCLC guidelines, while TACE and Y90 radioembolization occupy established roles for intermediate-stage and unresectable disease. Until histotripsy is tested against these modalities in prospective, ideally randomized, trials with matched tumor and patient populations, its positioning in the treatment algorithm — as an alternative, an adjunct, or a modality reserved for anatomically unfavorable lesions unsuitable for thermal ablation — cannot be determined on evidentiary grounds alone.

Conclusion

Histotripsy represents a genuine and scientifically grounded paradigm shift in liver tumor ablation. Its non-thermal, non-invasive, acoustically guided mechanism directly addresses key limitations of established thermal techniques — the heat-sink effect near large vessels, the absence of real-time tissue homogenization feedback, the risk of thermal injury to adjacent structures, and the inability to exploit the immunogenic potential of mechanical tumor destruction. Early clinical evidence anchored by the #HOPE4LIVER pivotal trials, and reinforced by emerging real-world safety and multicenter efficacy data, consistently demonstrates high technical success, acceptable short-term safety, and encouraging preliminary local tumor control, supporting continued clinical development.

However, by any objective evidentiary standard, the current evidence base remains early-stage and methodologically limited — insufficient to support the confident, guideline-level recommendations that an established modality would merit. The gaps identified here are not peripheral concerns but fundamental deficiencies that will determine histotripsy's appropriate scope and positioning within the liver oncology treatment algorithm. Future research must prioritize rigorously designed randomized controlled trials with a minimum three-to-five-year follow-up, prospective immunological biomarker studies, validated imaging response criteria, standardized treatment protocols, and inclusive patient populations reflecting the full clinical complexity of liver cancer practice. Only through this systematic, evidence-based investigative program can histotripsy fulfill its considerable and legitimate promise as a transformative non-invasive tool in the management of primary and metastatic liver cancer.

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Conflict of Interest

Conflict of Interest: none declared.

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