Review Article

Histotripsy –AReviewArticle

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Abstract

Histotripsy is an innovative, non-invasive therapeutic ultrasound technique that uses mechanical(non-thermal)energyto disrupt and liquefytargettissues. Unliketraditionalhigh- intensity focused ultrasound (HIFU), which relies on heat for tissue ablation, histotripsy depends on the generation of cavitation bubble clouds to mechanically fractionate cellular structures. This review summarizes the history, mechanism, technological principles, clinical applications, advantages, limitations, and future perspectives of histotripsy as a novel therapeutic tool in medicine. [2025, 6(1): 32-36]

Keywords: Cavitation, Focused Ultrasound, Histotripsy, Liver Tumor, Non-Thermal Ablation.

Introduction

Histotripsy represents a new frontier in non-invasive therapeutic ultrasound, offering precise and controlled mechanical tissue destruction without incisions, radiation, or heat. The term *"histotripsy"* originates from the Greek words *"histo" (tissue)* and *"tripsy" (to crush)* (1). It has emerged as a promising alternative to conventional ablative techniques such as radiofrequency ablation (RFA), microwaveablation (MWA), and thermal HIFU. By inducing controlled cavitation within target tissues, histotripsy achieves tissue disintegration with submillimeter precision (2).

Initially developed at the University of Michigan in the early 2000s, histotripsy has progressed from preclinical research to early-phase clinical trials, particularly in treating liver, prostate, and kidney tumors (3). In 2023, it received FDA approval in the United States for liver tumor ablation, marking a significant milestone in its translation to clinical use (4).

Historical Background

The concept of using focused ultrasound for tissue destruction dates back to the 1940s, but the mechanical (non-thermal) mechanism of histotripsy emerged only recently. Early studies in the 2000s by Xu, Hall, and colleagues introduced "cavitation cloud histotripsy"—a technique where microbubbles generated by high-pressure ultrasound pulses mechanically disrupts tissue (5).

Subsequent development led to two distinct histotripsy modalities:
Cavitation Cloud Histotripsy: Relies on short, high-amplitude ultrasound pulses.

Boiling Histotripsy: Uses longer pulses that form vapour bubbles through localized boiling (6).

These advances made histotripsy a controllable, image-guided, and non-thermal ablation technique that is now actively being studied in multiple clinical disciplines.

Mechanism of Action
Basic Principles:

Histotripsy employs focused ultrasound pulses with extremely high peak negative pressures (>10–25 MPa) and very short duty cycles (<1%) (2). The mechanical energy induces cavitation—a phenomenon where negative acoustic pressures generate microbubbles within the tissue.

These microbubbles expand, oscillate, and collapse violently, generating intense mechanical stress that disrupts cellular and subcellular structures. The process results in a localized homogenate of acellular debris, which is later cleared by the body's immune and lymphatic systems (7). The mechanism of histotripsy is based on the rapid formation and subsequent collapse of cavitation bubbles generated by focused ultrasound waves. The violent collapse of these bubbles produces intense, localized mechanical forces that disrupt targeted tissues, leading to precise cellular destruction (Fig 1) (8).

Cavitation Cloud Histotripsy:

This modality relies on generating a bubble cloud at the ultrasound focus. Each bubble oscillation cycle causes strain and shear forces that fragment tissue without significant thermal effect (1).

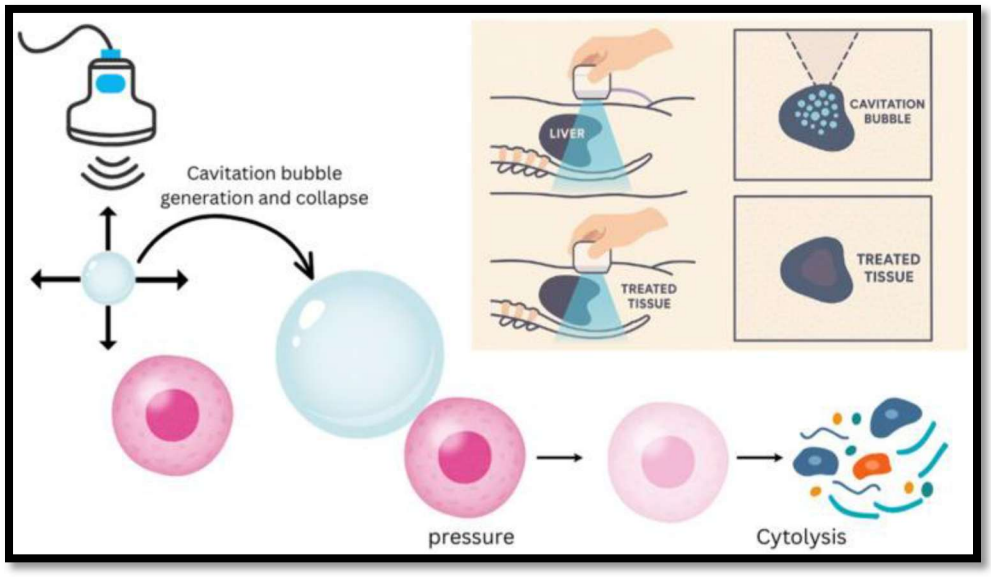

Fig 1: Mechanism of Action of Histotripsy

Boiling Histotripsy:

In this variation, longer ultrasound pulses (milliseconds) cause rapid localized heating and vapour bubble formation. However, mechanical effects rather than thermal necrosis remain the dominant mechanism of tissue disruption (6).

Imaging and Guidance

Real-time ultrasound or magnetic resonance imaging (MRI) is used to guide histotripsy procedures. Ultrasound imaging provides immediate feedback on cavitation activity, while MRI offers high-resolution visualization of treatment zones. Integrated feedback mechanisms help ensure precise targeting and minimize off-target effects (9).

Clinical Applications

Liver Tumors

The most advanced application of histotripsy is for liver tumor ablation. It offers an alternative to surgical resection and thermal ablation for patients with inoperable hepatocellular carcinoma or liver metastases. Clinical trials have demonstrated effective tumor ablation with minimal adverse effects (Fig 2) (4). In 2023, the FDA approved the HistoSonics® Edison system for liver tumor treatment.

Prostate Disease

Histotripsy has been explored as a non-invasive approach for benign prostatic hyperplasia (BPH) and prostate cancer. Animal studies show precise removal of prostatic tissue with rapid healing and minimal urinary complications (7).

Kidney and Pancreatic lesions

Preclinical studies have shown histotripsy's ability to ablate renal masses and pancreatic tumors effectively. It avoids damage to surrounding vasculature due to its non-thermal nature (9).

Neurological Disorders

Focused histotripsy is being investigated for treating intracerebral haemorrhage and targeted brain lessening. It allows selective tissue fractionation while sparing neuronal structures (1).

Thrombosis and Vascular applications

Microtripsy, a specialized form of histotripsy, can non-invasively recanalize occluded vessels and dissolve thrombi, showing potential in deep vein thrombosis management (7).

The role of histotripsy in immunomodulation

When cancer metastasizes beyond its primary site, localized debulking of individual tumors is unlikely to achieve a curative outcome. Hence, an optimal debulking therapy should not only shrink or eradicate targeted tumors but also activate the immune system to recognize and eliminate metastatic lesions throughout the body. This systemic anti-tumor response is known as the **abscopal effect** (Fig 3) (7).

Advantages of Histotripsy

- Non-invasive and bloodless procedure–No incision or probe insertion required.
- Non-thermal mechanism–Avoids heat-sink effects near major vessels.
- High precision– Binary nature of cavitation allows sharp lesion boundaries.
- Rapid tissue clearance –Debris reabsorbed naturally without necrosis.
- Preservation of surrounding structures– Minimal collateral damage.
- Potential immune activation – Tissue breakdown products may stimulate anti-tumor immune responses (3).

Limitations and Challenges

Despite its promise, several challenges remain:

Acoustic access limitations–Ultrasound cannot easily

penetrate bone or gas-containing tissues, limiting use in lungs or bowel (1).

Equipment complexity– Requires high-power transducers and precise imaging integration. Limited clinical data – Long-term safety and recurrence rates remain under study.
Potential side effects– Rare complications include haemorrhage or incomplete ablation (9).

Ongoing Research and Future Directions

Expanding Indications: Efforts are underway to extend histotripsy applications beyond hepatic lesions to other solid organs such as the pancreas, kidneys, and cardiac tissues, exploring both therapeutic and diagnostic potential.

Real-Time Imaging Integration: The development of MRI-guided and ultrasound- guided histotripsy systems aims to provide enhanced precision, enabling accurate targeting and monitoring of tissue cavitation dynamics during treatment.

Combination Therapies: Researchers are exploring the synergistic use of histotripsy with immunotherapy and chemotherapy, seeking to improve tumor response rates through immune modulation and increased drug delivery efficiency.

Device Miniaturization: Technological innovations are directed toward portable, adaptive histotripsy systems, which can broaden accessibility and usability across diverse clinical environments, including minimally invasive and outpatient settings.

Clinical Trials: Multiple multi-centre, randomized controlled trials are ongoing to evaluate the efficacy, safety, and long-term outcomes of histotripsy across various disease models, establishing its role in mainstream clinical practice (3).

Conclusion

Histotripsy represents a paradigm shift in non-invasive therapeutic technologies. Its mechanical, non-thermal mechanism enables precise, scar-free ablation of soft tissues while preserving surrounding structures. With recent clinical validation and regulatory approvals, histotripsy is poised to become a mainstream modality in oncology, urology, and vascular medicine. Continued innovation in ultrasound engineering and clinical trials will define its ultimate role in modern medical practice.

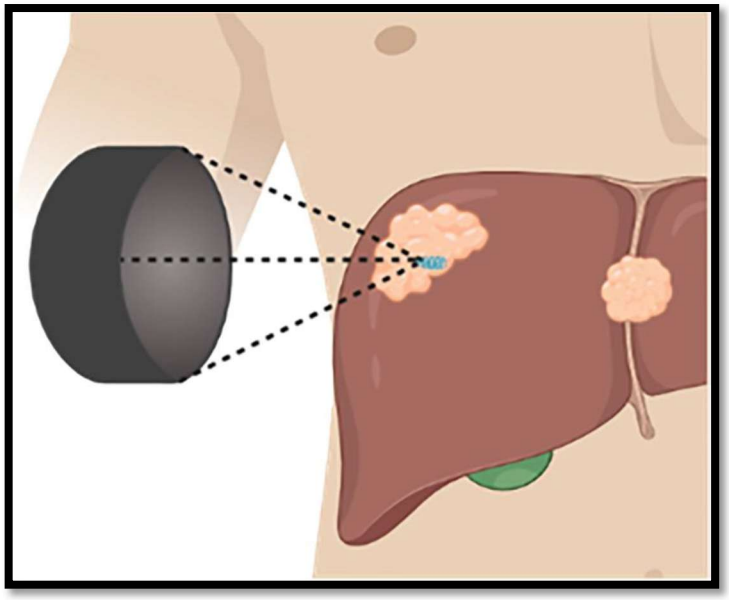

Fig 2: Therapeutic ultrasound transducer positioned outside of the body, focuses ultrasound waves within a targeted tissue generating a cavitation bubble cloud.

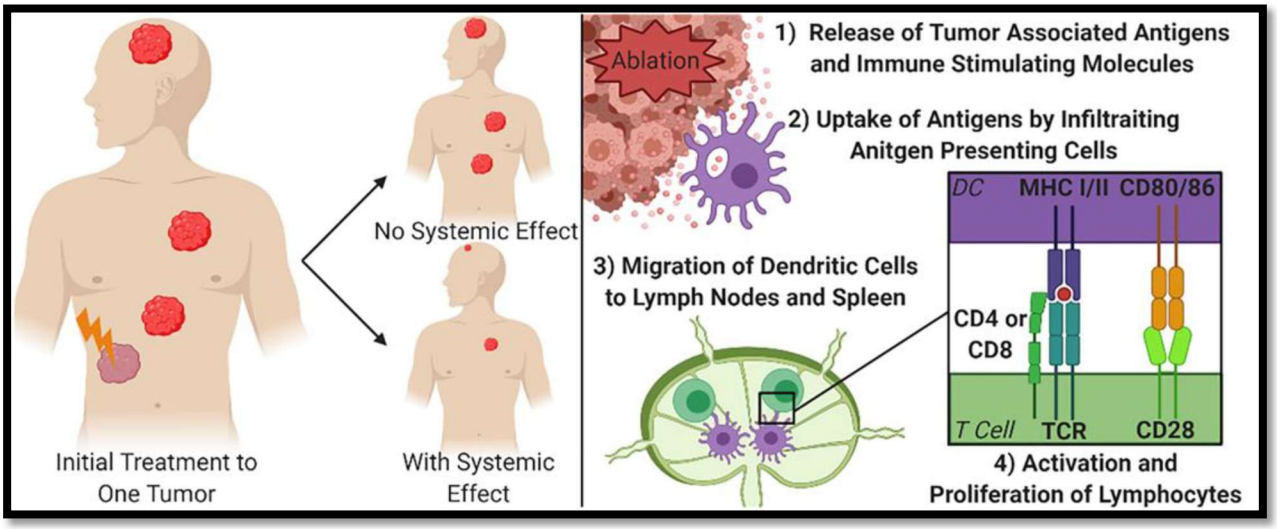

Fig 3: Focal Treatment of Targeted Tumor and Mechanism for Systemic Tumor Control.

The right diagram demonstrates the principal of the abscopal effect, where the treatment of one tumor can cause other tumors in the body to shrink or be eliminated to varying degrees due to immune system engagement. The left diagram depicts the simplified mechanism for achieving a systemic effect from focal therapies.

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