Histotripsy as a Promising Treatment Hepatic Tumors: Insights from the THERESA Trial and Literature Review

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Abstract

Purpose

Histotripsy, an emerging advanced technology, offers a non-invasive approach to tumor removal without heat or ionizing radiation. By utilizing ultrasound, it creates small bubbles that oscillate and collapse through acoustic cavitation, resulting in cell fragmentation. This technique effectively liquefies bulk tissue, including tumors, into an acellular homogenate. The body naturally absorbs the debris within 1-2 months, leaving only minor scars. Post-treatment evaluation can be accomplished using MRI. Histotripsy shows promising potential as a novel treatment for primary and secondary hepatic tumors. This abstract aims to review the application and potential advantages of histotripsy in this context.

Materials/Methods

A systematic literature review was performed using the PubMed database with the search term "hepatic histotripsy" to assess the safety and outcomes of histotripsy as a treatment for hepatic tumors.

Results

The THERESA trial, using the HistoSonics System, investigated histotripsy as a treatment for primary and secondary hepatic malignancies. The trial included eight patients with tumors ranging from 0.5-2.1 cm, including hepatocellular carcinoma (HCC) and metastatic liver cancer. The primary endpoint of achieving tissue destruction within the planned volume was successfully met for all procedures, confirmed by MRI evaluation. No significant adverse events occurred, except for a mistargeted tumor. Tumors exhibited regression and decline in tumor markers, with shrinkage of non-target tumors observed. The HistoSonics System was also successful in treating HCC and liver metastases at an academic institution, with confirmed ablation and no adverse events reported.

Introduction

Hepatic tumors are classified as primary or secondary in origin. Of 2.4 million patients diagnosed with cancer in SEER, 5.14% were diagnosed with liver metastasis at primary cancer detection (4). While secondary liver cancers are more common than primary liver cancers, incidence rates of primary liver cancer in the US have tripled since the 1980's, with death rates doubling since then (5). By 2040, similar trends are expected to hold true, as the global burden of primary liver cancer are expected to increase by 55%, with mortality rates expected to increase by 56.4% (6).

With the dramatic projected increases in both liver cancer incidence and mortality, much medical research has become dedicated to improving current standards of treatments as well as discovering novel technologies. While surgical resection and heat/radiation ablation have dominated the treatment of liver cancer recently, histotripsy has gained traction as a viable alternative.

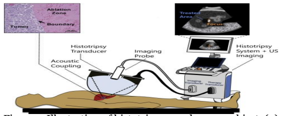


Figure 1. Illustration of histotripsy on a human subject. (9)

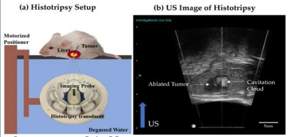
Introduction (cont.)

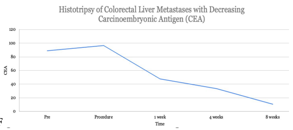
Histotripsy works by using short ultrasound waves to noninvasively generate, oscillate, and collapse microbubbles within the target tissue, with the body absorbing any debris within two months of therapy (3). This study aims to review literature surrounding histotripsy as an up-and-coming treatment for liver cancer.

Methods

This literature review was conducted using the PubMed database, with search terms that included a combination of "histotripsy", "liver cancer", and "hepatic histotripsy". Articles that met these terms were then sorted to distinguish animal models to human ones, in order to evaluate and assess the safety and viability of histotripsy as an alternative to current standards of treatment of hepatic tumors.

Of the studies included in our review, two included human subjects, with the three others including mammal models. Within the animal models, two were rodent models with the third being a porcine model. Though there were other studies of histotripsy being used in other forms of cancers, including bone cancers, they were ultimately excluded from our study. Within the two rodent studies, one focused on the precision and peripheral damage that histotripsy causes on liver tissue while the other focused on the treatment aspects of histotripsy on implanted hepatic tumors. The porcine model focused on the efficacy of histotripsy on anticoagulated subjects.





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histotripsy tumor (10)

patient's Histotripsy of Colorectal Liver Metastases(1).

Results (cont.)

In the THERESA trial, eight patients were identified with unresectable hepatic tumor of varying metastatic and primary origins. After treatment, all patients were found to have acute technical success, confirmed using MRI. Moreover, no patient had experienced device-related adverse effects (1). In this trial, one patient with colorectal cancer was also found to have involution of their non-treated tumors, with declining CEA levels as shown in Figure 3. This was further corroborated by researchers at the University of Chicago, where they had achieved similar complete ablation of the hepatic tumor in one patient (2).

Similar results were found in the animal studies. Precision of pressure-modulated shockwave histotripsy (PSH) was demonstrated in a rodent model. As compared no pressure modulation, PSH treatment resulted in a lesion that was 58% shorter in length ($p = 0.027$) and 26% smaller in width ($p = 0.1295$) (7). Another rodent study found of the 11 treated with histotripsy, 9 were found to have complete tumor ablation, and no recurrence or metastasis was observed in any subject for twelve weeks. Safety was further investigated in the porcine model, with non-tumor-bearing, anticoagulated subjects. While mild hematuria was found in about 20% of the subjects, there were no signs of intraparenchymal, peritoneal, or retroperitoneal hemorrhage that resulted from the histotripsy (8).

Conclusions

Histotripsy is an innovative treatment for hepatic tumors, offering various advantages such as real-time ultrasound feedback to optimize energy deposition, improve leukocytic infiltration within the tissue, and minimize unintended effects. It avoids thermal energy deposition, reducing harm to surrounding structures, while also having beneficial effects on untreated tumors . The THERESA trial demonstrated histotripsy's potential for inducing an abscopal effect in humans, with implications for future cancer therapies. Prospective clinical trials are currently evaluating the efficacy of the HistoSonics System for liver lesions.

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