The Effects of Ultrasound-Guided Histotripsy on Soft Tissue Sarcoma

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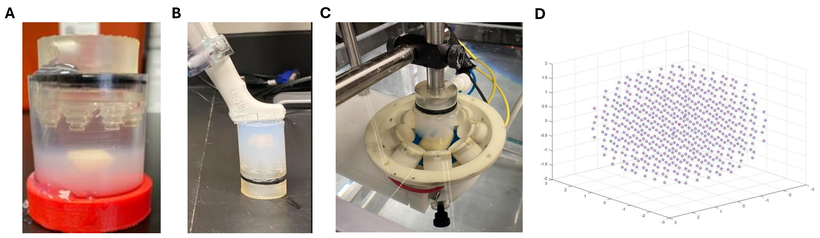
INTRODUCTION

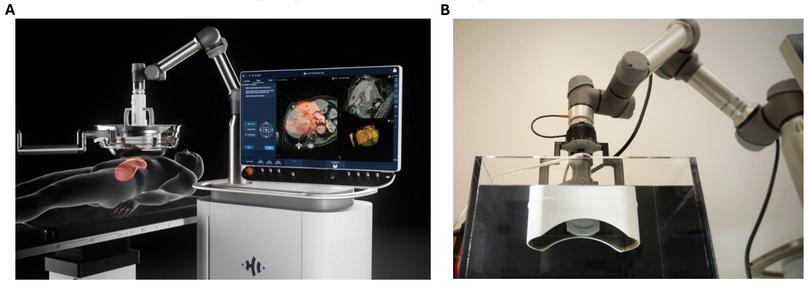
Soft tissue sarcomas [STS] comprise a subset of cancers where novel therapies are desperately needed with a 5-year survival rate [OS] of 65% that drastically declines to 15% when the disease has distantly metastasized. The most effective therapy is surgical resection, however, patients have a high risk of recurrence and limited benefit from current systemic treatments like chemotherapy or immunotherapy highlighting a critical need for novel therapeutics. Additionally, some benign soft tissue tumors pose a challenging management problem when difficult to remove due to size or location to critical structures. Our objective is to determine the pathological effects of ultrasound [US]-guided histotripsy treatment as a potential neoadjuvant therapy for malignant STS and treatment strategy for unresectable benign soft tissue tumors. Histotripsy uses focused ultrasound delivered from outside the body to mechanically destroy tissue through cavitation, rendering the target into acellular debris.

Histotripsy Ex-Vivo Sample Experimental Set Up



Ex-Vivo Histotripsy Experimental Set Up. A) Sample embedded in agarose gel and gel mold. **B)** STS-mimicking phantom embedded in gel while SWE probe sweeps via its positioner. Ultrasound Transducer setup **(C)** in degassed water tank aimed at phantom in gel. The positioner is shown holding the transducer and the ultrasound imaging probe is held beneath the center of the transducer. **D)** Focal point mapping calculated after the boundaries of the treatment volume is established [6x6x4mm]. Each dot represents a focal point, and each focal point is spaced 0.5 mm apart [585 total in the representative image above].

Histotripsy Clinical Implementation



Histotripsy Clinical Integration & Patient Experience. A) HistoSonics® the Edison® Histotripsy System Schematic for patient use. **B)** Actual image of the Edison® Histotripsy System at the University of Michigan Rogel Cancer Center that is currently in use for liver cancer patients after Histotripsy Treatment received FDA approval in late 2023. When used as a local treatment for liver tumors the procedure had a 95% technical success rate in the #HOPE4LIVER single arm, non-randomized prospective clinical trial (*Mendiratta-Lala et al., 2024*).

METHODS

Soft tissue tumors including both benign and malignant histologies were collected from surgical specimens (n=45). Histotripsy was delivered to fresh samples including adipocytic (lipoma, well-differentiated liposarcoma [WDLPS], dedifferentiated liposarcoma [DDLPS]), fibrous (desmoid, dermatofibrosarcoma protuberans, myxofibrosarcoma), and poorly differentiated (undifferentiated pleomorphic sarcoma [UPS]) with a custom 1 MHz 8-element histotripsy US transducer using 1-cycle pulses at 100 Hz pulse-repetition frequency for 50 pulses per focal location and 0.5 mm spacings with peak negative pressure > 30 MPa. Histotripsy treatments were guided by B-mode ultrasound. Shear Wave Elastography [SWE] and B-mode ultrasound imaging were both collected pre-treatment and post-treatment to evaluate the lesion and observe the efficacy of histotripsy treatment. Following treatment, histology was confirmed, and effect of histotripsy was determined by a soft tissue sarcoma pathologist utilizing H&E staining.

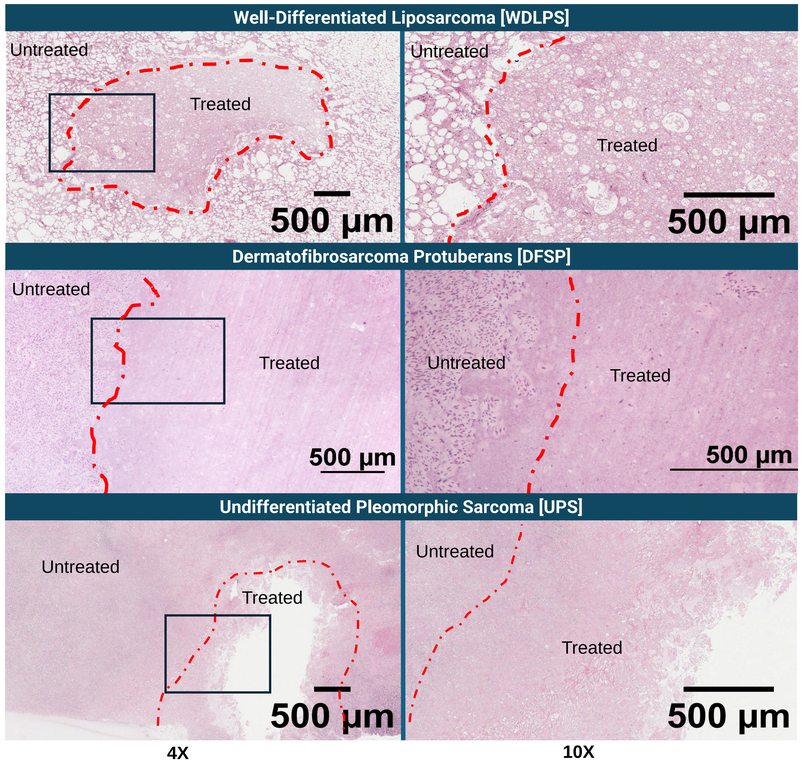
RESULTS

Clinical Pathological Classifications of Patient STS Samples

STS and STT Histotripsy Treatments	
Histotypes/Subtype	**Sample Number**
Adipocytic	**26**
Well-Differentiated Liposarcoma [WDLPS]	13
Lipoma	11
Hibernoma	2
Aggressive Fibrous STS	**9**
Epithelioid Angiomatoid Fibrous Histiocytoma	1
Desmoid	2
Leiomyosarcoma	1
Myxofibrosarcoma	2
Residual Sclerosing Epithelia Fibrosarcoma	1
Dermatofibrosarcoma	2
Poorly Differentiated Tumors	**10**
Dedifferentiated Liposarcoma [DDLPS]	4
Undifferentiated Spindle Cell Sarcoma	2
Undifferentiated Pleomorphic Sarcoma [UPS]	2
Myxoma	2

Table of Human Ex-Vivo STS Samples Treated with Histotripsy. Table of all human ex-vivo samples treated with histotripsy. None of the samples were previously treated with adjuvant radiation or chemotherapy. The majority of the study set was comprised of tumors with lipomatous differentiation [57.8%, 26/45].

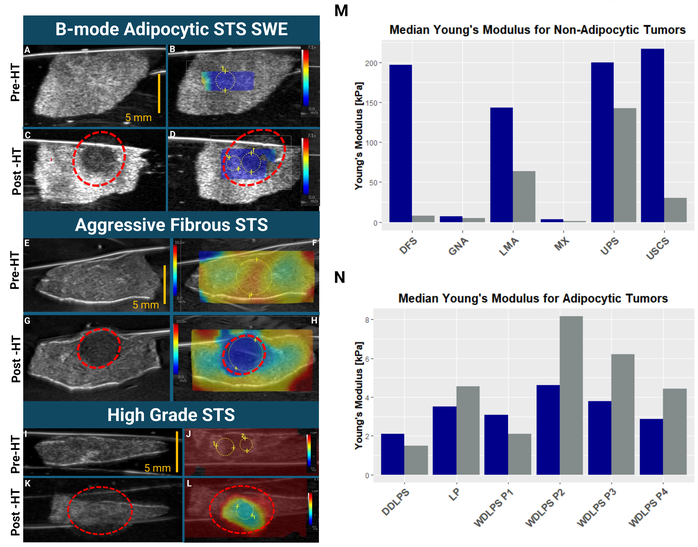
Pathological Treatment Effects of Histotripsy in STS by H&E



Histotripsy Treatment effects can be observed using H&E. Tumor treatment visualized using H&E staining at 4X [left] and 10X [right] with highlighted treatment border, indicated by dashed red line. All tissues exhibit well-defined areas of liquefactive necrosis with complete dissolution of viable cells.

RESULTS

Detectable Structural & Mechanical Changes Post-HT



Structural & Mechanical Differences Post-Histotripsy Treatment. Example B-mode and SWE images pre- and post-histotripsy treatment [HT] from an adipocytic **(A-D)**, a fibrous aggressive **(E-H)**, and a dedifferentiated **(I-L)** case. Median Young's Modulus [kPa] of samples before and after histotripsy treatment for non-adipocytic **(M)** and adipocytic **(N)** tumors.

CONCLUSIONS

- US-guided **histotripsy was efficacious in inducing necrosis within the treatment zone** across multiple different benign and malignant soft tissue tumors
  - Including notoriously difficult to treat tumors such as dedifferentiated liposarcoma and desmoid fibromatosis.
- Based on these preliminary preclinical results, **histotripsy seems to be a viable novel neoadjuvant treatment strategy for STS patients** and a promising potential treatment for symptomatic unresectable benign tumors.
- **Histotripsy is a promising FDA-approved treatment** for tumors of the liver which should be validated for sarcoma in clinical trials.

FUTURE DIRECTIONS

- Validate US-guided histotripsy therapeutic efficacy in a novel immunocompetent genetically engineered mouse model [GEMM] of liposarcoma.
- Probe tumor immune microenvironment [TIME] changes in liposarcoma GEMM.
- Elucidate whether US-guided histotripsy can be combined with immunotherapies to improve therapeutic response.
- Pilot clinical trial of US-guided histotripsy in STS patients at University of Michigan Rogel Cancer Center.

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