Histotripsy - Harnessing the Power of Acoustic Cavitation for Medicine

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Histotripsy ≠ HIFU

Histotripsy
- Very high intensity
- Pulsed energy
- Mechanical effect
- Cellular fractionation

HIFU
- High intensity
- "Continuous" energy
- Thermal effect
- Coagulation necrosis

Histotripsy
Definition: Non-invasive, non-thermal, mechanical (cavitational) tissue ablation

histo- tissue [G. histos]
-tripsy to crush [G. tripsis]

What is Cavitation?

- Rapid formation and collapse of vapor/gas bubbles in a liquid.

Disclosures
Histosonics – Founder and Scientific Advisor with financial interest.

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  - The Hartwell Foundation
Histotripsy: Bulk Tissue Scan Pattern

B-mode Image After Treatment

38 locations, 10-μs pulses, PRF = 50 Hz, P- > 20 MPa, 2000 pulses at each location

Ultrasound on Steroids!

Before and After

Precision of Mechanical Tissue Ablation

2 mm

Before and After

Urothelialization

Treated (28 days post treatment)

Pressure Waveforms

Lithotripsy

Histotripsy

Time (μs)

Normalized Pressure

Pressure Waveforms

Lithotripsy

Histotripsy

Time (μs)

Normalized Pressure

p- = 14 MPa

p+ = 76 MPa

p- = 22 MPa

p+ = 74 MPa
Initiation of Histotripsy

- Cavitation-cloud
  - Shock Scattering
  - Intrinsic Threshold
- Boiling
  - Boiling
  - And?

High Speed Imaging


Bubble Cloud Evolution


Conceptually Speaking

NOTE: Ultrasound propagating from the LEFT.


What about short pulses?

Intrinsic Threshold for Bubble Clouds


Vessel Sparing


Differential Ablation Threshold


Differential Ablation Threshold


Differential Ablation Threshold

Monopolar Pulsing

Different mechanisms – similar result – exciting field

Rapid heating of tissue mimicking gel due to absorption at the shocks

Characteristic intensity levels of therapeutic ultrasound and corresponding bioeffects

Shock wave heating in excised liver

Tissue fractionation

Protocol:
• 10 ms pulse
• 1 Hz PRF
• 1% duty cycle
• 50 seconds

Tissue damage observed included repeatable “holes” in tissue filled with disintegrated tissue
**Mechanism of Tissue Disruption by BH**

**Proposed Mechanism**
Acoustic fountain in bubble causes tissue fractionation

**Boiling Histotripsy for Tissue Engineering**
Tissue selective ablation for decellularization?

**Histotripsy Applications**
- Renal Stones
- Prostate Cancer
- BPH
- Liver Masses
- Fetal Intervention
- Vasectomy
- Cardiac Ablation
- Liposculpting
- Vascular Interventions
- Drug Delivery
3D Imaging 2 Days After Treatment

Treatment Outcome – Occlusive Thrombus
Before Histotripsy After Histotripsy – 500 s

Brain Applications
Supported by R01 NS108042
NIH R01EB 028309
Focused Ultrasound Foundation
American Heart Association

Transcranial Histotripsy for Brain Applications
250/500kHz
256E
hemispherical array
30 cm diameter
15 cm focal distance
Transcranial clot liquefaction rate: 16 mL/min

Gerhardson et al. Neurosurgery 2019

Sukovich et al. TUFFC 2016; Gerhardson et al., TUFFC; 2017

Courtesy of Zhen Xu, University of Michigan
Transcranial Histotripsy

**Capability to**
- ablate a volume
- ablate near skull surface
- Without overheating skull

Gerhardson et al., UMB, 43(10):2302-17

Acoustic Cavitation Emission (ACE): Transcranial focal pressure measurement

<table>
<thead>
<tr>
<th>Aberration Correction Method</th>
<th>Pressure Est'd Peak (MPa)</th>
<th>% Increase Over None</th>
<th>-3dB Width (x x y x z) (mm)</th>
<th>Estimated Steered Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>55</td>
<td>N/A</td>
<td>1.21 x 1.77 x 3.54</td>
<td>16</td>
</tr>
<tr>
<td>Hydrophone</td>
<td>70</td>
<td>100%</td>
<td>1.17 x 1.36 x 2.75</td>
<td>42</td>
</tr>
<tr>
<td>ACE</td>
<td>58</td>
<td>68%</td>
<td>1.26 x 1.58 x 3.66</td>
<td>30</td>
</tr>
</tbody>
</table>

Aberration correction through excised human skull improves the focal pressure >60%

Courtesy of Zhen Xu, University of Michigan

Liver Cancer

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American Cancer Society (RSG-13-101-01-CCE)
Forbes Institute
Focused Ultrasound Foundation

Histotripsy Induces Systemic Immune Response

Qu et al. Journal for ImmunoTherapy of Cancer 2020;8:e000200.
Histotripsy Initial Human Trial

**Purpose:** To evaluate the safety and short-term efficacy of histotripsy for hepatic ablation in patients with primary or metastatic liver cancer

Joan Vidal Jove, Surgery, Barcelona University Hospital
Fred Lee, Tim Ziemlewicz, Radiology, University of Wisconsin
Jon Cannata, Ryan Miller, Alex Duryea, HistoSonics

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**Patient Population**

- **8 patients**
  - 5 Female/3 Male (mean 64 yrs, range 46-87)
- **11 tumors**
  - 6 patients - 1 tumor
  - 1 patient - 2 tumors
  - 1 patient - 3 tumors
- **Mean tumor size 1.3 cm (0.5-2.3 cm)**

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**Results**

**Secondary Endpoints**

- Local tumor regression
  - 90 % (9/10)
- Liver function
  - Transient 2-3x elevation of AST/ALT which normalized 1 week after histotripsy in all patients
- Analgesic requirements
  - No analgesic requests
  - No reported pain
- Abscopal effect
  - In 1 patient, overall tumor burden reduced in 2 months

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**Conclusions**

- Controlling acoustic cavitation and its associated effects is possible using ultrasound fields.
- Histotripsy provides a means for tissue disruption using a non-thermal mechanism.
- A wide variety of applications are envisioned histotripsy therapies.

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Thanks for your attention!!!!!