Image-guided Histotripsy for Oncological and Vascular Applications

Session: Image-guided Histotripsy for Oncological and Cardiovascular Applications

Speaker 3: Zhen Xu

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University of Michigan, Ann Arbor

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Disclosure

- Zhen Xu is one of the inventors of intellectual property licensed to Histosonics, Inc..
  - Co-inventors: Charles Cain, Tim Hall, Brian Fowlkes, and Will Roberts
- She is a co-founder and holds stock in Histosonics.

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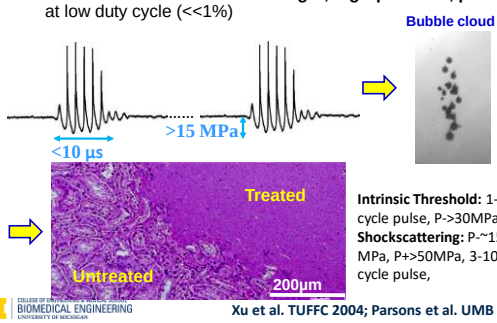
Histotripsy

- Mechanical Tissue liquefaction generated by **inertial cavitation via microsecond-length, high-pressure, pulses** at low duty cycle (<<1%)



Intrinsic Threshold: 1-2 cycle pulse, P->30MPa; **Shockscattering:** P-~15-20 MPa, P+>50MPa, 3-10 cycle pulse,

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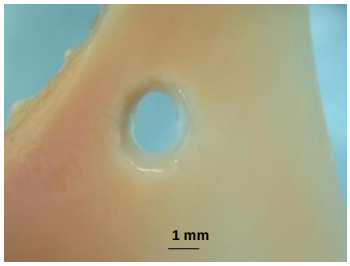
Xu et al. TUFFC 2004; Parsons et al. UMB 2006

In Vitro Histotripsy Treatment

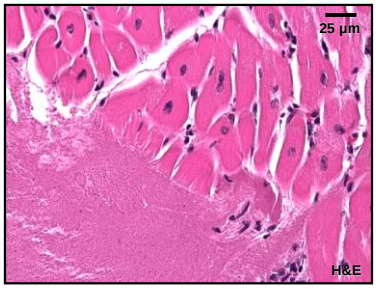
Tissue-Fluid Interfaces: Erosion

Porcine Atrial Wall



Xu et al., IEEE *Trans. Ultrason. Ferroelectr. Freq. Control*. 2004, pp. 726;

Bulk Tissue: Liquefaction



Parsons, Ultrasound in Med & Biol 2006, vol. 32, pp. 115

Bubble-cell Interaction

High strain produced by bubble expansion and collapse mechanically disrupts the cells.

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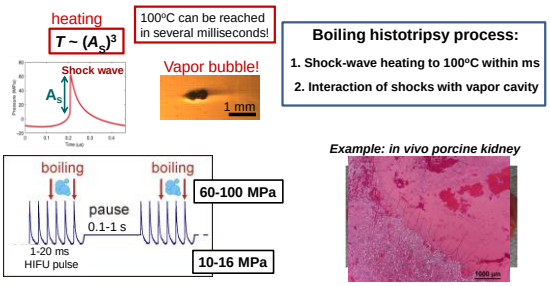
Vlaisavljevich et al. UMB 2016;42(10):2466.

SAM Question

- 1. The mechanism of histotripsy-induced tissue disruption is:
- a. High mechanical strain produced by cavitation
- b. Heating by high energy of ultrasound delivered to the focus
- c. All of above

- Answer: a)

BOILING HISTOTRIPSY



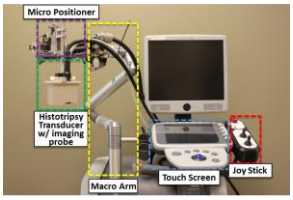
Boiling histotripsy process:

1. Shock-wave heating to 100ºC within ms
2. Interaction of shocks with vapor cavity

Example: in vivo porcine kidney

Courtesy of Tanya Khokhlova from University of Washington

Ultrasound Image Guided Histotripsy System



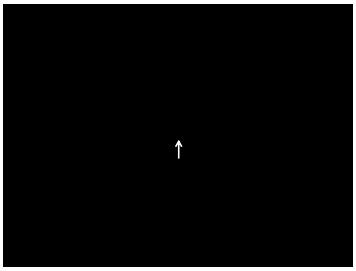
Histotripsy for Cancer Applications

Liver Cancer
Renal Cancer
Prostate Cancer
Pancreatic Cancer
Brain Cancer
Thyroid Cancer

Cavitational Histotripsy in Porcine Liver

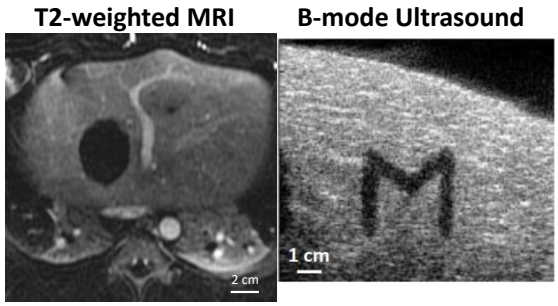
Inside In-vivo Porcine Liver

US

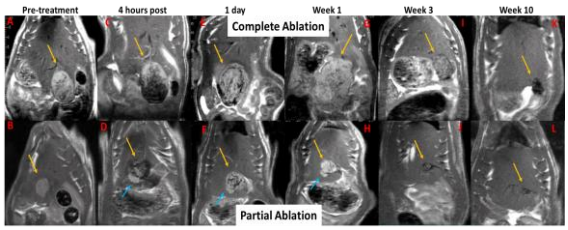


Vlaisavljevich et al. Ultrasound Med. Biol, 2013;39:1398-1409

Cavitational Histotripsy in Porcine Liver



Histotripsy Liver Tumor Ablation
N1-S1 rodent liver tumor model



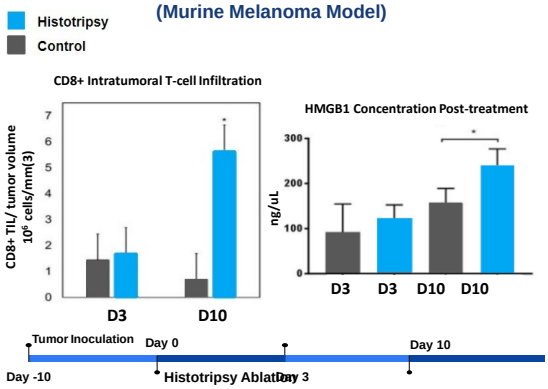
MRI in 14/15 treated tumors (6 partial and 9 complete) demonstrated near complete resorption of the ablated tumor in 7-10 weeks.

SAM Question

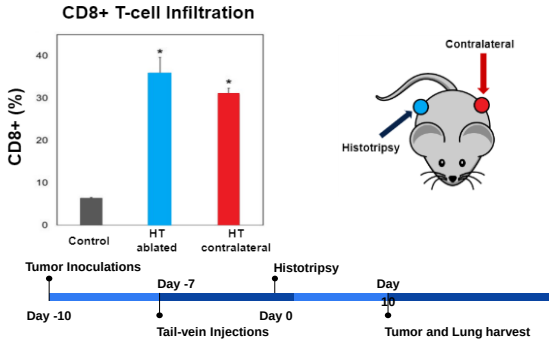
- 2. What happens to the liquefied tissue homogenate after histotripsy ablation in long term?
- a. Remains in situ and forms scar-like tissue in situ
- b. Remains in situ but does not form scar
- c. Goes to blood flow and gets reabsorbed by the body, results in reduction of the targeted tissue volume

- Answer: (c)

Histotripsy Induces Local Immune Response
(Murine Melanoma Model)



Histotripsy (HT) Induces Systemic Immune Response



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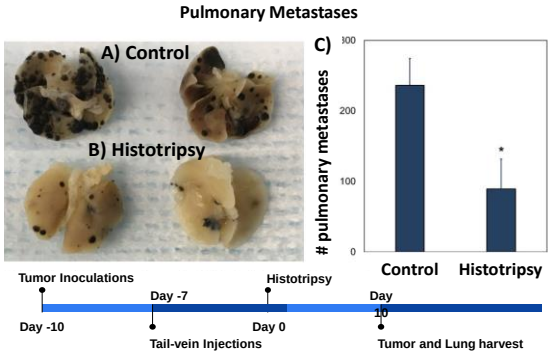
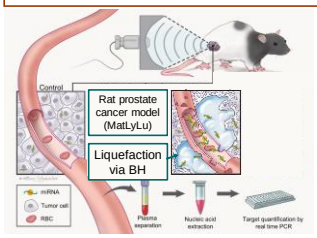


BOILING HISTOTRIPSY NON-INVASIVE LIQUID BIOPSY TOOL

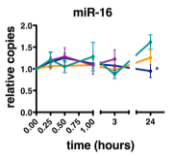
Blood-based cancer biomarker – a cancer-specific molecule secreted by the tumor into the circulation

MicroRNAs – promising class of blood-based biomarkers, but low baseline release levels



Chevillet, Khokhlova et al. Radiology 2016

Broadly expressed control



Courtesy of Tanya Khokhlova from University of Washington

Thrombosis

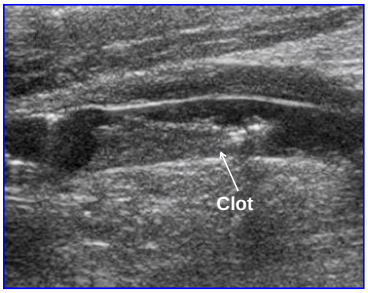
Deep Vein Thrombosis

Large Hematoma Evacuation

Non-invasive Thrombolysis

- **Thrombosis -** blood clot formation, cause of many vascular diseases, such as deep vein thrombosis, stroke, etc.
- **Current techniques have drawbacks:**
  - **Thrombolytic Drugs** – Slow reperfusion, excessive bleeding
  - **Catheters** – Invasiveness, bleeding, and infection

Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model



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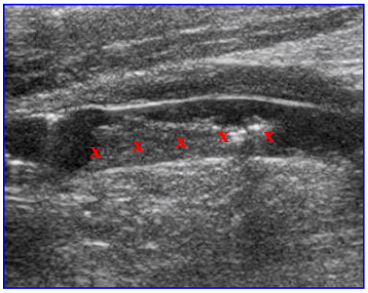
Maxwell et al J Vasc Interv Radiol. 2011; 22: 369-77

Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model



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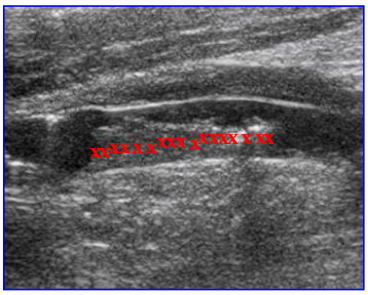
Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model



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Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model

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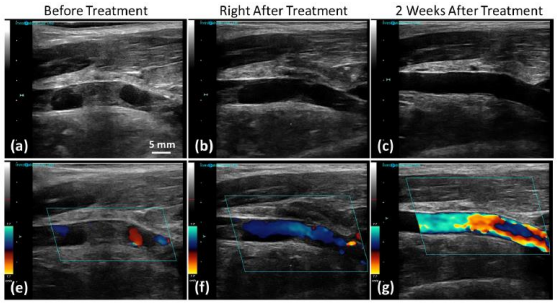
Maxwell et al J Vasc Interv Radiol. 2011; 22: 369-77

Histotripsy Thrombolysis: B-mode and Doppler Post-treatment



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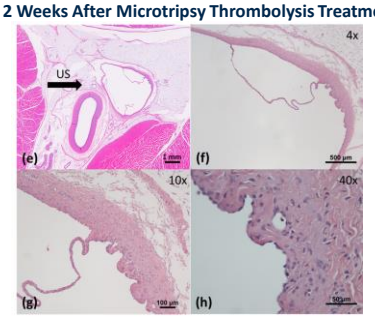
Zhang et al. UMB 2017

Histotripsy Thrombolysis: Vessel Damage (2 weeks)

2 Weeks After Microtripsy Thrombolysis Treatment



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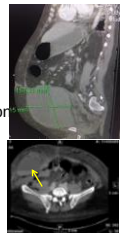
Boiling Histotripsy For Liquefaction And Aspiration Of Large Hematomas

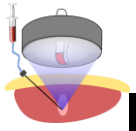
Large (up to 1-2 L) hematomas often caused by trauma or post-surgical bleeds

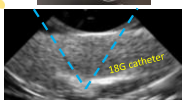
Health effects:
- pain
- compartment syndrome
- organ failure
- risk of infection

Clinical management:
- Surgery
- Indwelling drain (ineffective)



Approach: fast liquefaction with boiling histotripsy, simultaneously drain with fine needle





Highest liquefaction rate achieved to date: **16 mL/min**

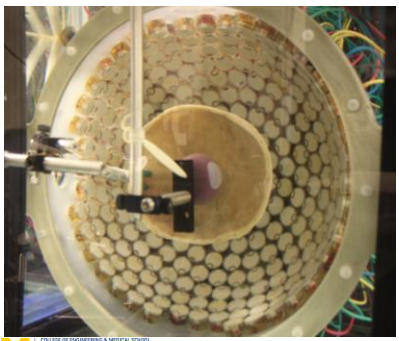
Courtesy of Tanya Khokhlova from University of Washington

Histotripsy for Brain Applications

Brain Tumor

Hemorrhagic Stroke

Transcranial (Cavitational) Histotripsy



250/500kHz 256E hemispherical array

30 cm diameter
15 cm focal distance

Can ablate brain tumor or liquefy clot through human skull in deep and shallow locations in the brain

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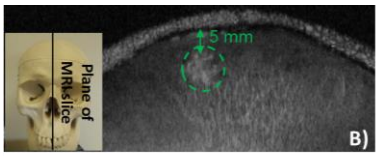
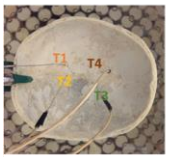
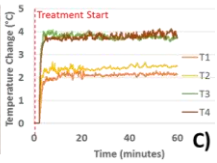
Sukovich et al. TUFFC 2016; Gerhardson et al., TUFFC; 2017

Transcranial Histotripsy
In vitro bovine brain ablation through human skull

Capability to
- ablate a volume
- ablate near skull surface (5mm)
- Skull heating (<4°C)







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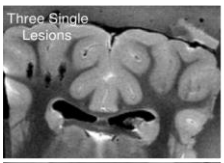
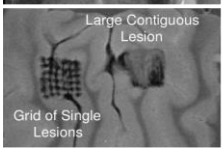
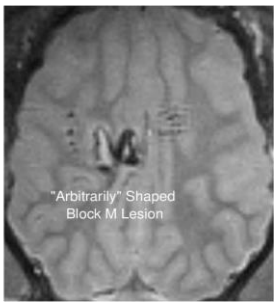
Gerhardson et al., UMB, 43(10):2302-17

Histotripsy in the In Vivo Porcine Brain







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Sukovich et al., J. Neurosurgery, 2018

Acknowledgement

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  - William Roberts (Urology)
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  - American Heart Association

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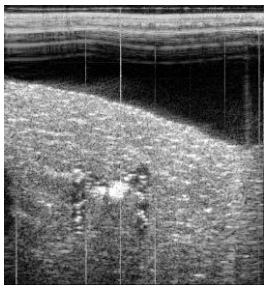
The End

Thank you!
Questions?



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Brain Diseases and Treatment Options

- Brain Tumor Treatment
  - Craniotomy surgery - invasive
  - Chemotherapy – blood brain barrier
  - Radiation therapy – normal brain structure susceptible to radiation damage
- Hemorrhagic stroke treatment
  - Medical management – no active clot reduction
  - Craniopuncture (tPA + catheter drainage) – Slow
- MR guided Focused Ultrasound (MRgFUS)
  - Essential Tremor
  - Can only treat a small volume in the central region of the brain