

# Introduction to Histotripsy and Early Experience with Clinical Systems

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# Disclosures

- J. Erik Winterholler, MD
  - None
- Fred T. Lee Jr, MD
  - Inventor, patents, royalties, Covidien (Medtronic) Switching Controller™ (Radiofrequency)
  - Consultant, Ethicon Inc.
  - Board of Directors, Stockholder, Research Support Histosonics, Inc. (Histotripsy)
  - Medical Advisory Board, Canon, Inc.



# History of Histotripsy

- Cavitation is a known phenomenon in ultrasound and is avoided in diagnostic medical imaging
  - Fetal ultrasound keeps "mechanical index" low to prevent tissue damage
- Rather than avoid mechanical effects of ultrasound, scientists at the University of Michigan sought to harness it for targeted therapy

Scan to visit University of Michigan lab site



Varthaliti A, Fasoulakis Z, Lygizos V, Zolota V, Chatziioannou MI, Daskalaki MA, Daskalakis G, Antsaklis P. Safety of Obstetric Ultrasound: Mechanical and Thermal Indexes-A Systematic Review. J Clin Med. 2024 Nov 1;13(21):6588. doi: 10.3390/jcm13216588. PMID: 39518728; PMCID: PMC11545858.



# History of Histotripsy

- New name for technology developed - "Histotripsy"
  - "Histo-" = soft tissue
  - "-tripsy" = crushing/breakdown
- Now, 20+ years of research & 100+ peer reviewed articles support the science of histotripsy
- University of Wisconsin, University of Michigan, and Virginia Tech University working on basic science and clinical translation of histotripsy

Scan to visit Vlaisavljevich lab site (Virginia Tech)



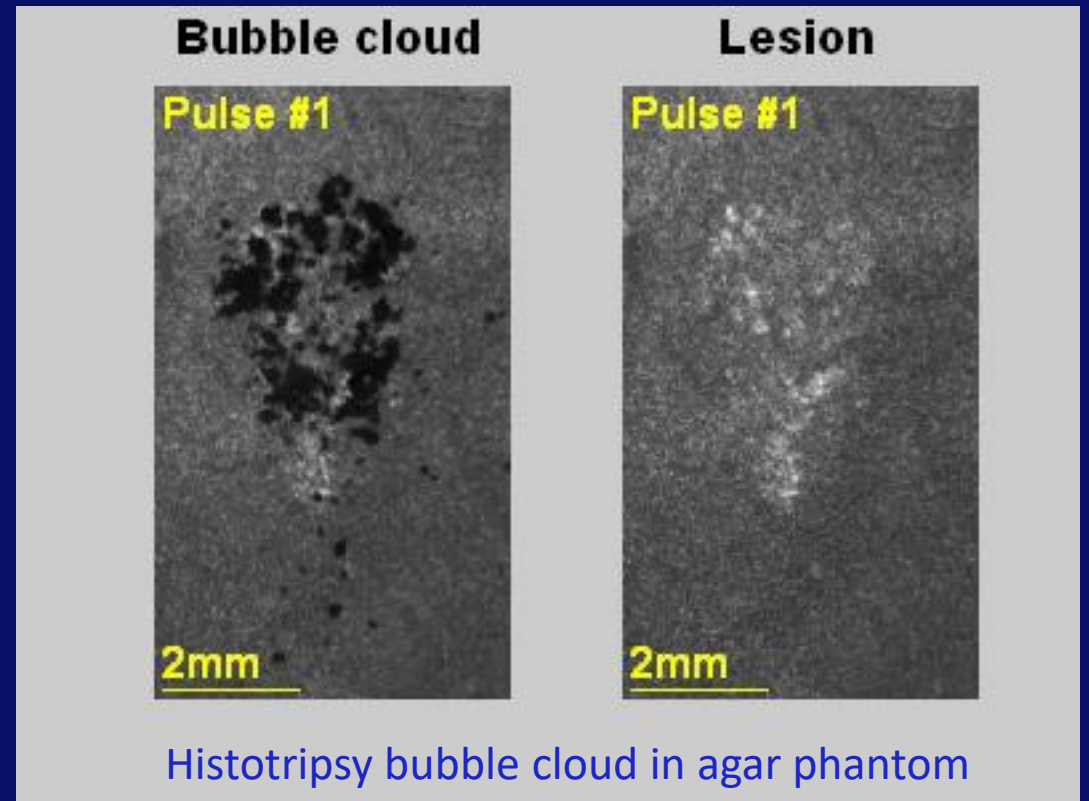
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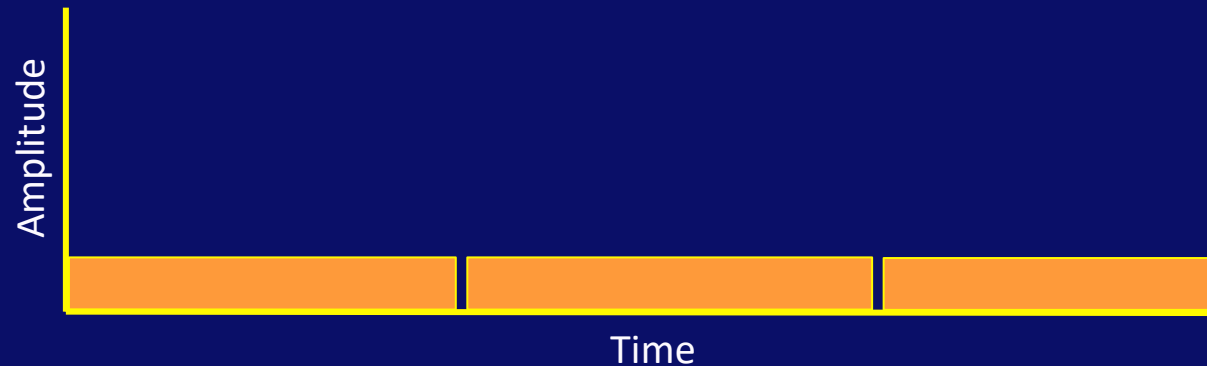
# Basics of Histotripsy

- Treatment consists of high amplitude ultrasound bursts
- High peak negative pressures lead to rapid expansion and collapse of microbubbles in a focal area
- Expansion and collapse of microbubbles shears cells instantly



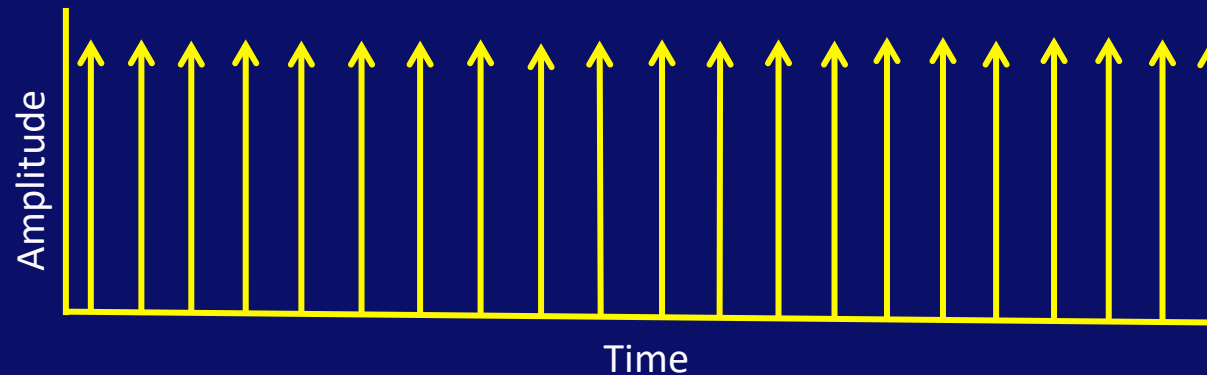
# Comparison: HIFU versus Histotripsy

HIFU



- Long, low amplitude pulses
- Generate heat at the focal point

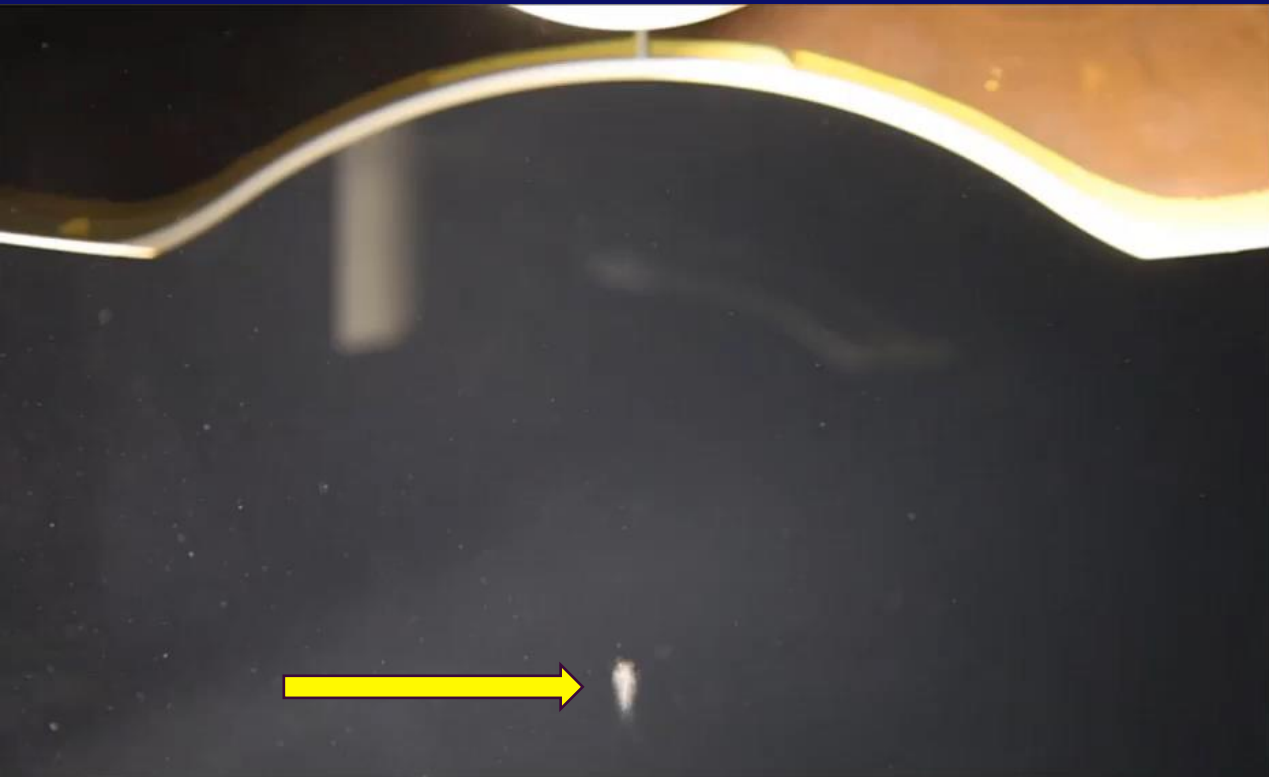
HISTOTRIPSY



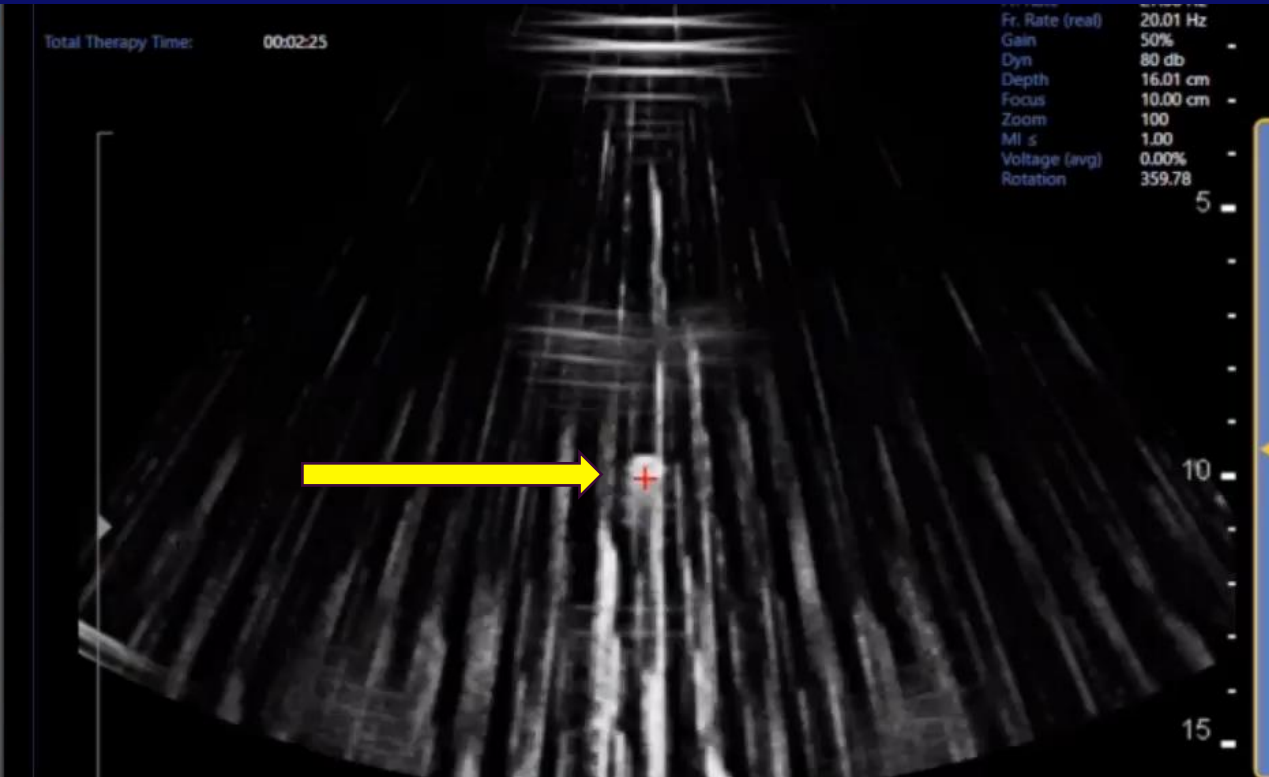
- Short, high amplitude micro-pulses
- Generate cavitation at the focal point

- Bachu VS, Kedda J, Suk I, Green JJ, Tyler B. High-Intensity Focused Ultrasound: A Review of Mechanisms and Clinical Applications. *Ann Biomed Eng.* 2021 Sep;49(9):1975-1991. doi: 10.1007/s10439-021-02833-9. Epub 2021 Aug 10. PMID: 34374945; PMCID: PMC8608284.
- Xu Z, Hall TL, Vlasisavljevich E, Lee FT Jr. Histotripsy: the first noninvasive, non-ionizing, non-thermal ablation technique based on ultrasound. *Int J Hyperthermia.* 2021;38(1):561-575. doi: 10.1080/02656736.2021.1905189. PMID: 33827375; PMCID: PMC9404673.

# Histotripsy Bubble Cloud



Visible bubble cloud in water bath



Bubble cloud on real time ultrasound with expected artifact

# Histotripsy Spares Collagen Rich Structures



Porcine liver



Porcine liver  
Skeletonization

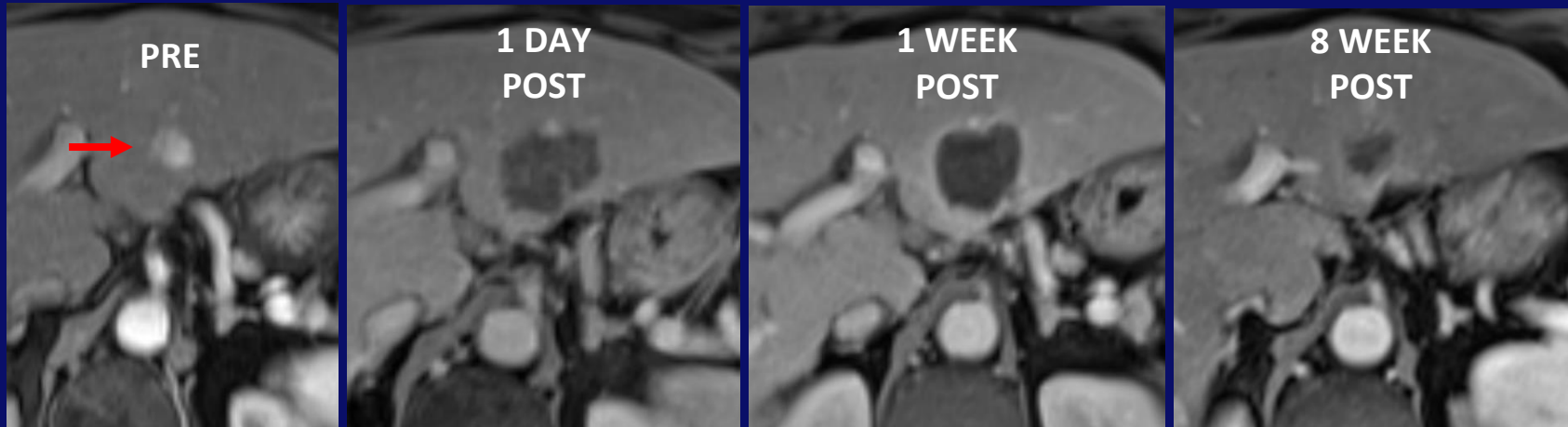


Porcine  
kidney

Bile ducts, large blood vessels and urothelial structures are resistant to damage from histotripsy due to intrinsic mechanical strength



# Treatment Zones Rapidly Involute



THERESA trial images showing the histotripsy treatment zone of an HCC contracting over 8 weeks

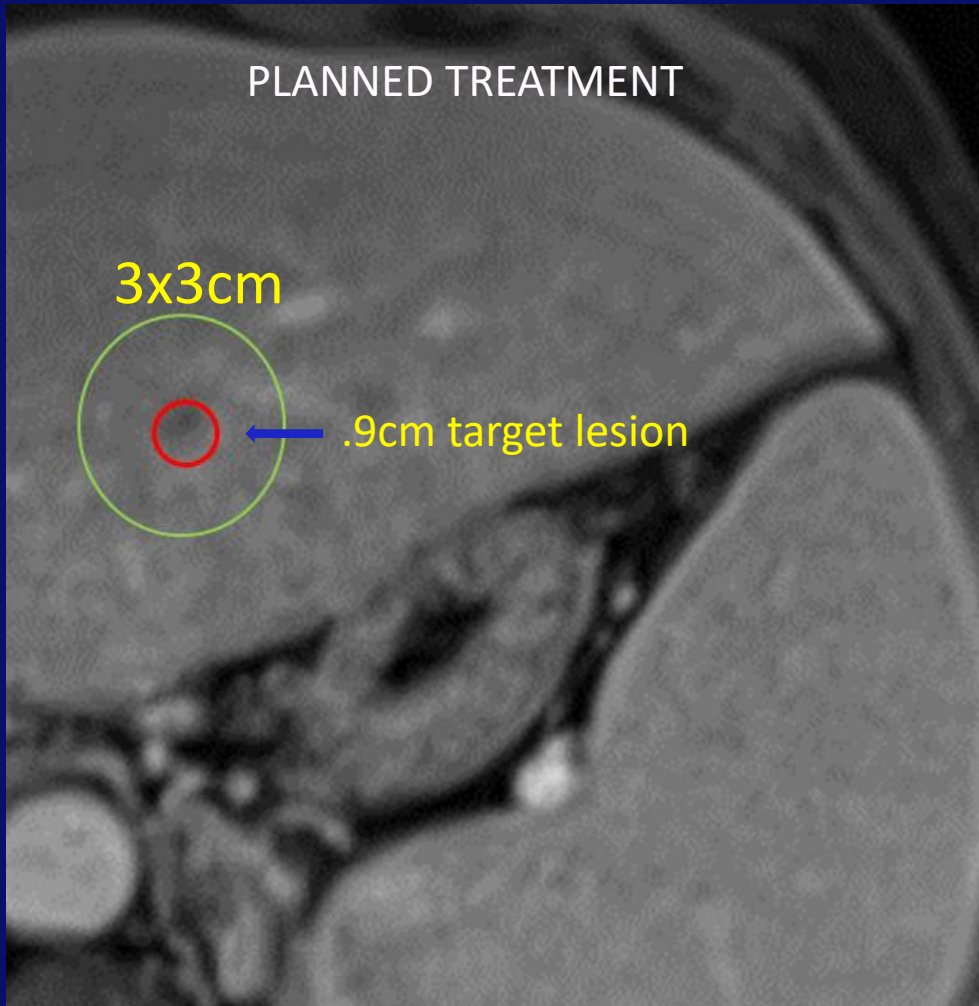


Near complete resolution of a porcine kidney histotripsy treatment zone over 1 month with residual scar

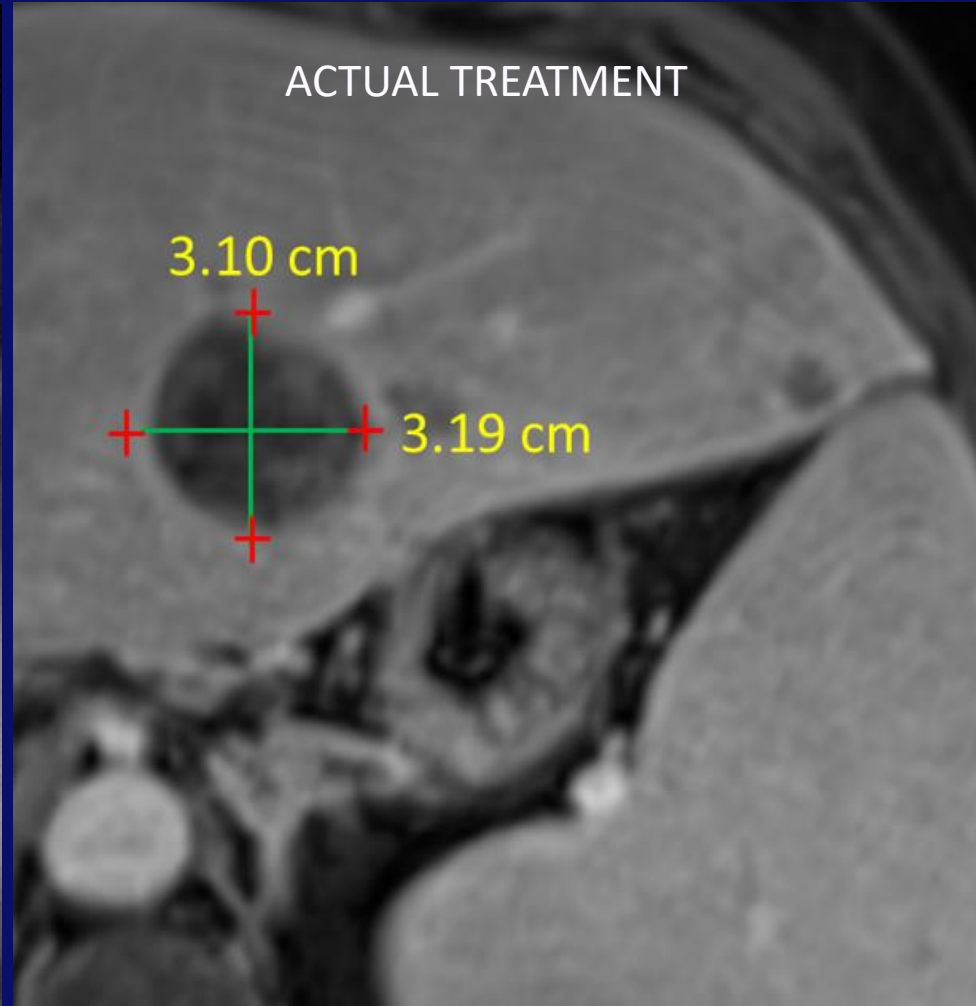
Vidal-Jove J, Serres X, Vlaisavljevich E, Cannata J, Duryea A, Miller R, Merino X, Velat M, Kam Y, Bolduan R, Amaral J, Hall T, Xu Z, Lee FT Jr, Zierniewicz TJ. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. *Int J Hyperthermia*. 2022;39(1):1115-1123. doi: 10.1080/02656736.2022.2112309. PMID: 36002243.

# Histotripsy is Targeted with Ultrasound

PLANNED TREATMENT



ACTUAL TREATMENT

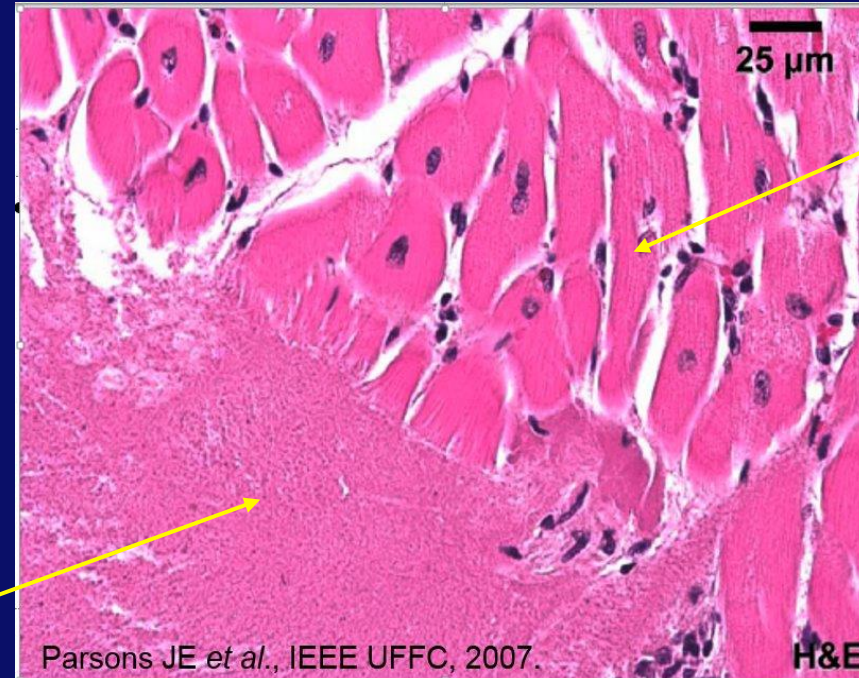


Prescribed treatment (left) and actual treatment (right) for a histotripsy case treating a 0.9 cm liver metastasis



# Histotripsy Treatment Margin is Razor Thin

- Treatment margin in static tissue can be less than the width of a cell
- Cellular lysis is tissue-dependent and varies with collagen content and tissue stiffness
- Cirrhotic livers (higher stiffness) respond differently than healthy livers



Normal untreated porcine cardiac myocytes

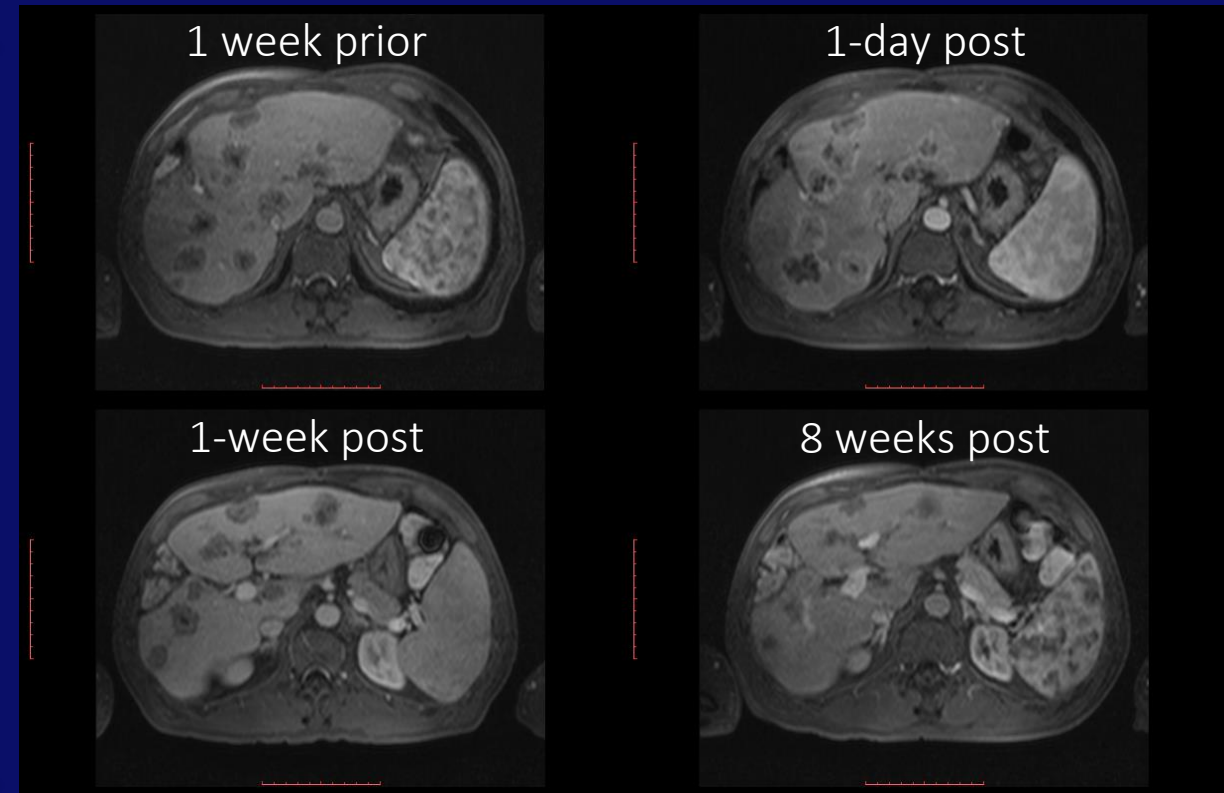
Treated, anuclear cellular lysate

Parsons JE, Cain CA, Fowlkes JB. Spatial variability in acoustic backscatter as an indicator of tissue homogenate production in pulsed cavitation ultrasound therapy. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2007 Mar;54(3):576-90. doi: 10.1109/tuffc.2007.280. PMID: 17375826.

# Clinical Response and the Abscopal Effect

- Some cases show response in non-targeted lesions, suggesting immune response to histotripsy treatment

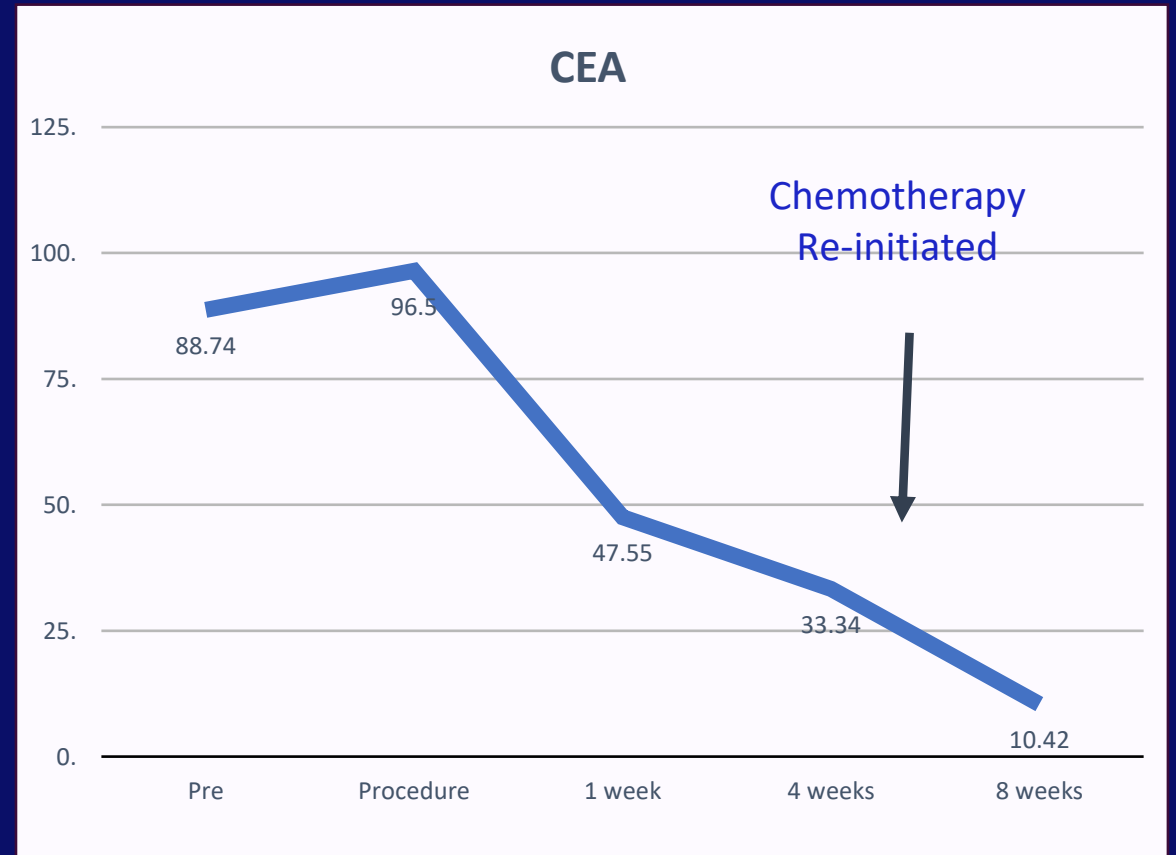
Multifocal colorectal cancer (CRC) liver metastasis before, 1 day post, 1 week post, and 8 weeks following histotripsy treatment with response of all lesions to treatment, including non-targeted metastases



Vidal-Jove J, Serres X, Vlaisavljevich E, Cannata J, Duryea A, Miller R, Merino X, Velat M, Kam Y, Bolduan R, Amaral J, Hall T, Xu Z, Lee FT Jr, Ziemlewicz TJ. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. *Int J Hyperthermia*. 2022;39(1):1115-1123. doi: 10.1080/02656736.2022.2112309. PMID: 36002243.

# Clinical Response and the Abscopal Effect, continued

- Carcinoembryonic antigen (CEA) response of the previously detailed case of metastatic CRC
- Details biochemical response to histotripsy treatment at follow up without chemotherapy



Vidal-Jove J, Serres X, Vlaisavljevich E, Cannata J, Duryea A, Miller R, Merino X, Velat M, Kam Y, Bolduan R, Amaral J, Hall T, Xu Z, Lee FT Jr, Ziemlewicz TJ. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. *Int J Hyperthermia*. 2022;39(1):1115-1123. doi: 10.1080/02656736.2022.2112309. PMID: 36002243.

# Past Clinical Trials

- Theresa Trial (Liver, Spain) n=8 patients, 11 tumors
  - Phase 1, first in human trial

Mendiratta-Lala M, Wiggermann P, Pech M, Serres-Créixams X, White SB, Davis C, Ahmed O, Parikh ND, Planert M, Thormann M, Xu Z, Collins Z, Narayanan G, Torzilli G, Cho C, Littler P, Wah TM, Solbiati L, Ziemlewicz TJ. The #HOPE4LIVER Single-Arm Pivotal Trial for Histotripsy of Primary and Metastatic Liver Tumors. *Radiology*. 2024 Sep;312(3):e233051. doi: 10.1148/radiol.233051. PMID: 39225612; PMCID: PMC11427859.

- HOPE4LIVER (US, Europe) n=44 patients
  - Endpoints for technical success, safety, and efficacy met

Mendiratta-Lala M, Wiggermann P, Pech M, Serres-Créixams X, White SB, Davis C, Ahmed O, Parikh ND, Planert M, Thormann M, Xu Z, Collins Z, Narayanan G, Torzilli G, Cho C, Littler P, Wah TM, Solbiati L, Ziemlewicz TJ. The #HOPE4LIVER Single-Arm Pivotal Trial for Histotripsy of Primary and Metastatic Liver Tumors. *Radiology*. 2024 Sep;312(3):e233051. doi: 10.1148/radiol.233051. PMID: 39225612; PMCID: PMC11427859.

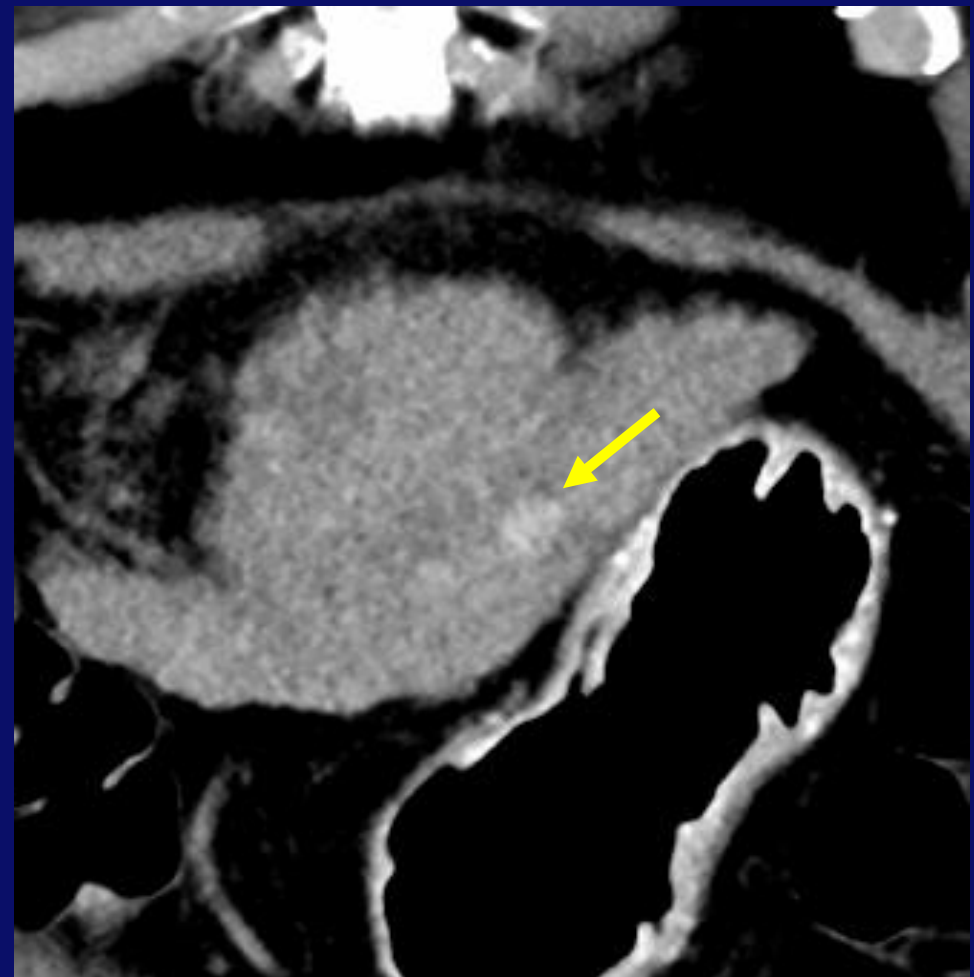
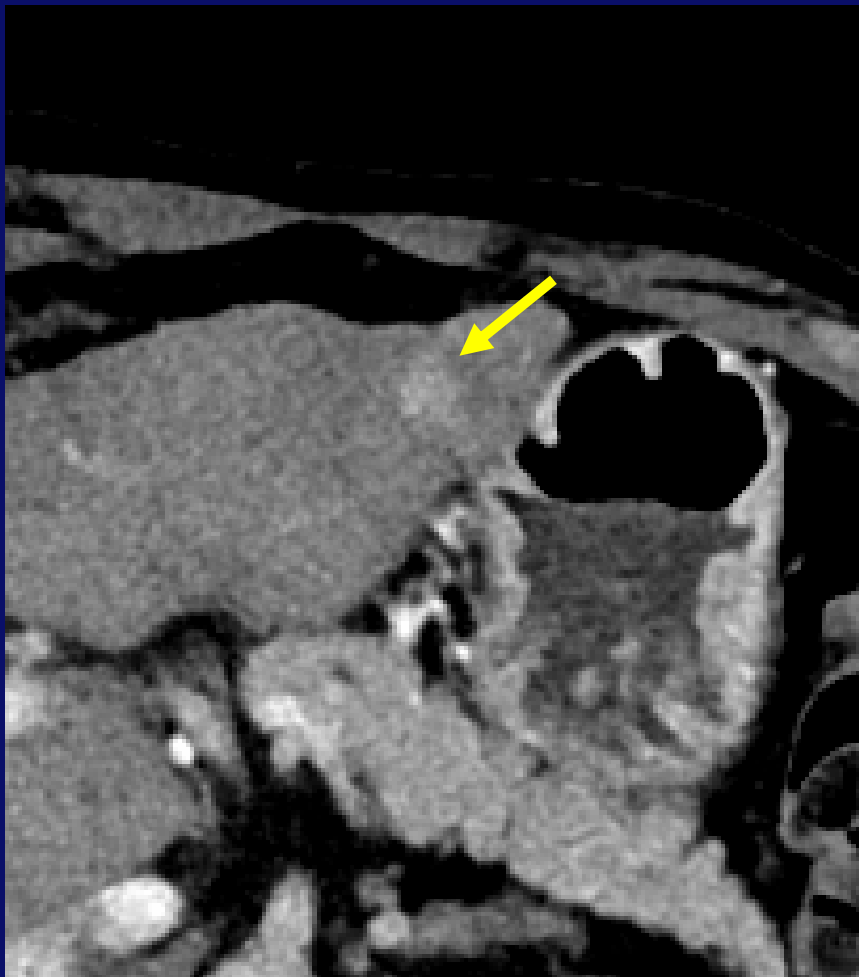
# FDA Approval

- FDA approval for histotripsy treatment of liver tumors took place October 2023
- Approximately 20 cases of in human histotripsy treatment of liver tumors have taken place at the University of Wisconsin



Dr. Laeseke, Dr. Ziemlewiecz, Dr. Knavel-Koepsel, and Dr. Swietlik (left to right) after completing the first liver histotripsy case for hepatocellular carcinoma at the University of Wisconsin

# First University of Wisconsin Liver Histotripsy Case



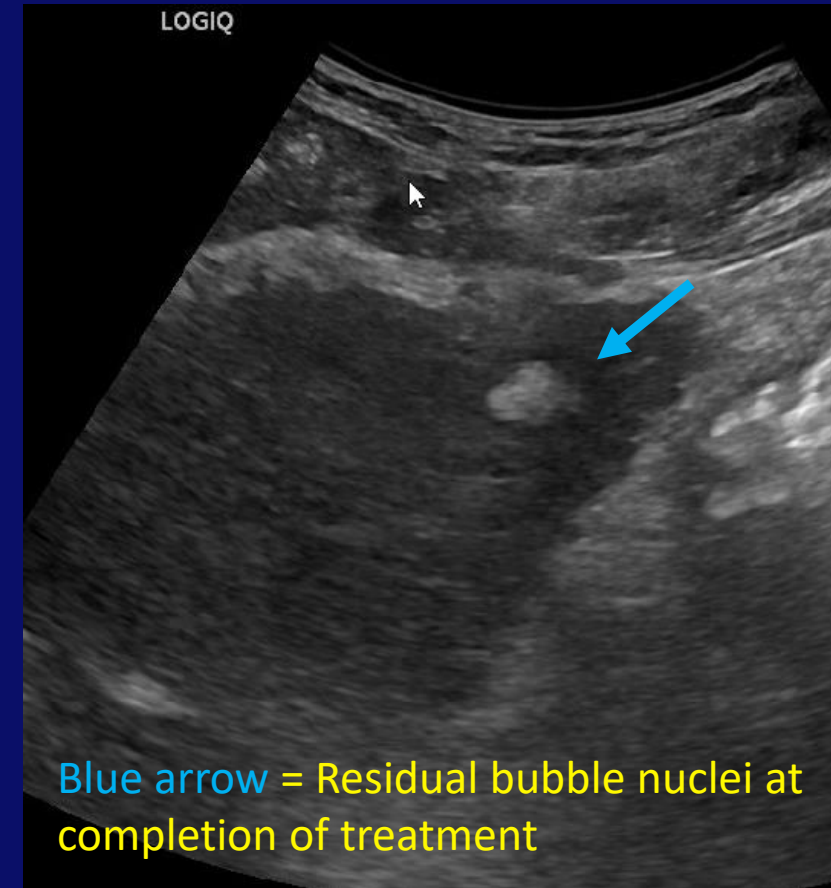
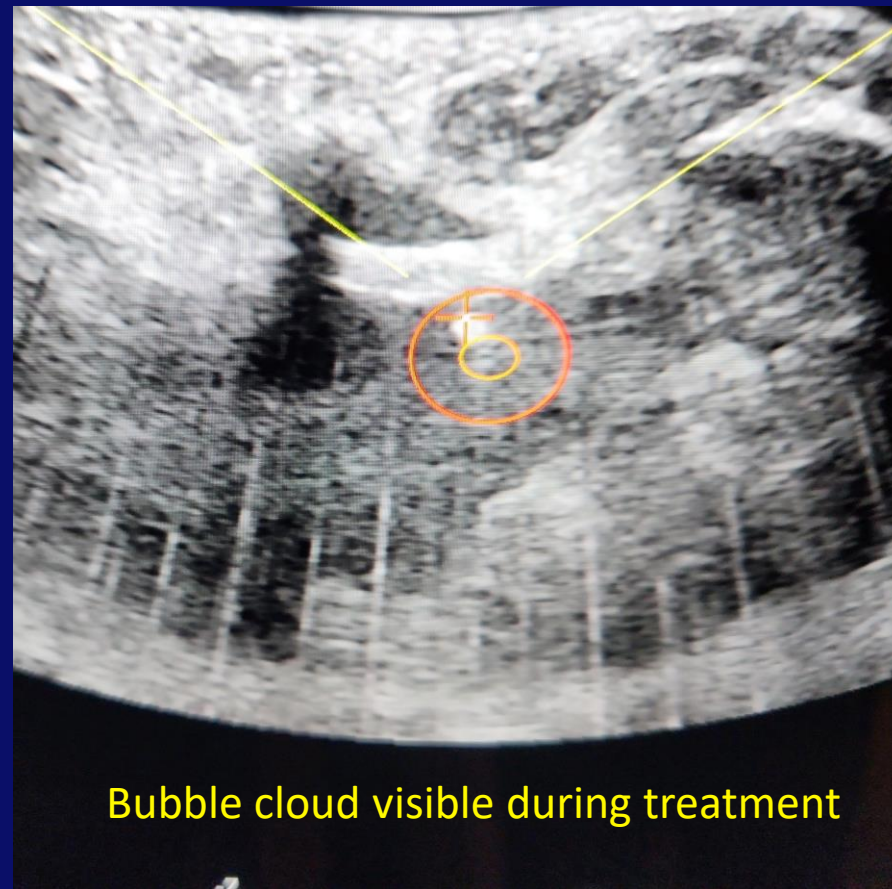
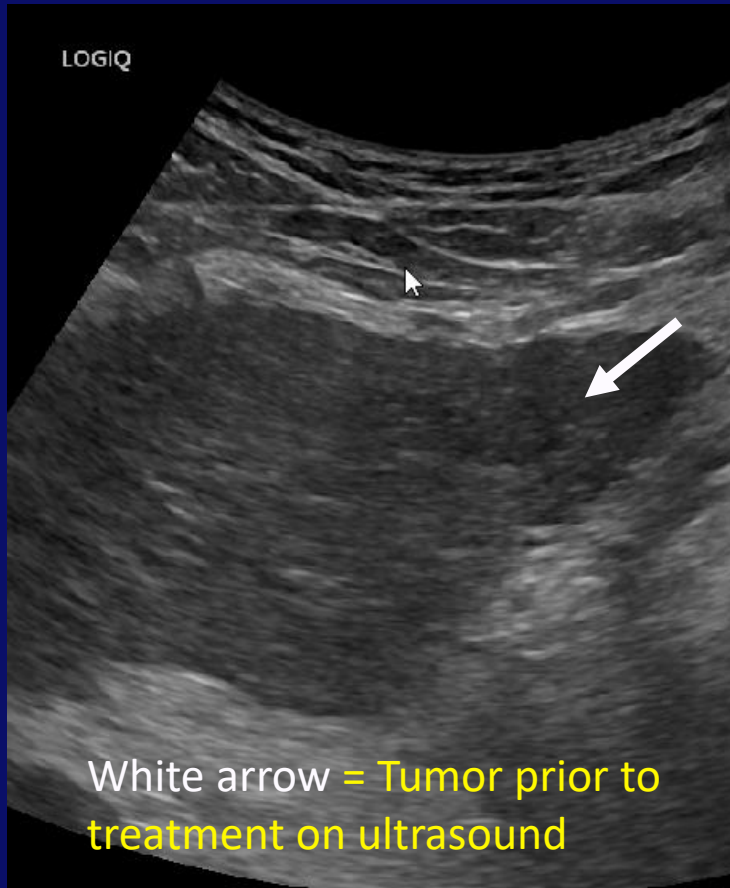
Contrast enhanced CT showing the target lesion - a ~1 cm hepatocellular carcinoma in hepatic segment 3 (yellow arrows)



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# First University of Wisconsin Liver Histotripsy Case



# Ongoing and Upcoming Research

- CAIN trial: clinical trial for histotripsy treatment of solid kidney tumors based in the United Kingdom
  - March 2023-present
- HOPE4KIDNEY: multi-center trial for histotripsy treatment of solid renal tumors based in the United States
  - January 2024-present
- GANNON trial: safety/feasibility trial for histotripsy treatment of pancreatic tumors
  - December 2024-present



Questions?

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