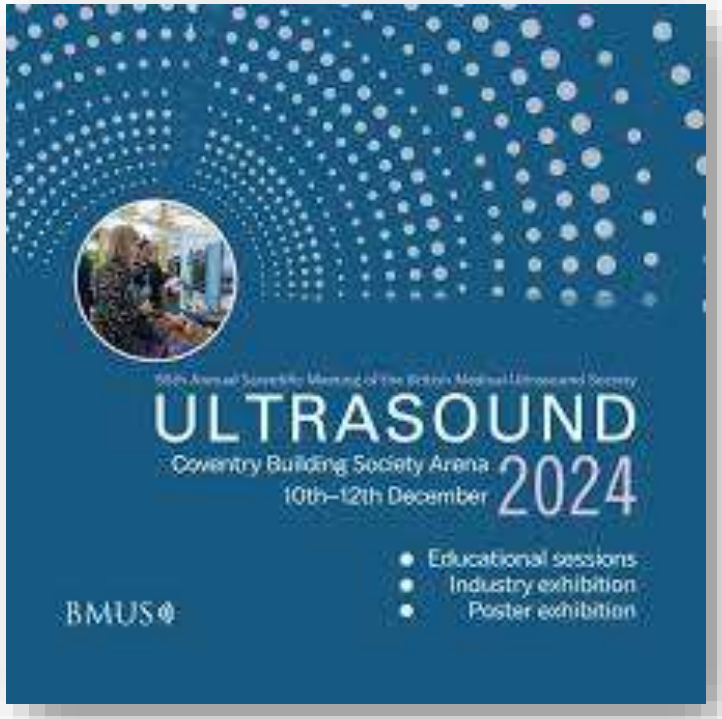
Trial Update: Image Guided Histotripsy of Liver (#Hope4Liver) and Renal (CAIN) Cancers



#HOPE4LIVER

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CAIN

Disclosures

- Boston Scientific Research Grant
- Angiodynamics Education Grant
- HistoSonics Research Grant
- Johnson & Johnson Research Grant

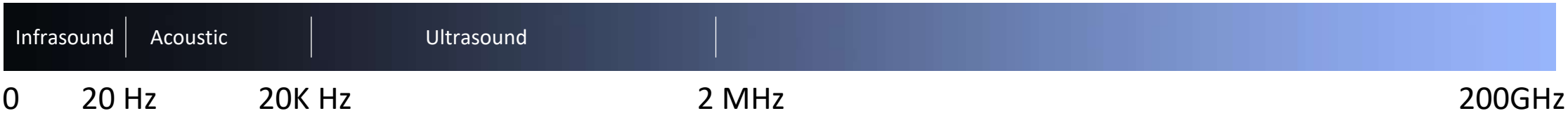
Acknowledgements

- HistoSonics team
- Prof Zhen Xu and research team at Michigan University
- Global research team and trial collaborators
- Interventional Oncology team, R&I and Executive team at Leeds Teaching Hospitals Trust
- Leeds Cancer Centre and Leeds Hospitals Charity

Background

HISTOTRIPSY

Ultrasound Spectrum



Ultrasound

The propagation of mechanical waves into a medium such as gas, liquid, or tissue.

***CUSA= Cavitronic Ultrasonic Surgical Aspirator**
HIFU= High Intensity Focused US

Class	Frequency Range	Power Densities	Examples
High Power Low Frequency	20-60 kHz	10-300 W/cm2	Harmonic Scalpel, CUSA
High Power High Frequency	1-20 MHz	0.5-3.0 W/cm2	HIFU
Low Power High frequency	1-10 mHz	<0.05 W/cm2	Diagnostic Ultrasound

Courtesy of HistoSonics

Bio-effects of Ultrasound Energy

Cavitation Effect

- Mechanical Index - a measure of cavitation threshold in ultrasound imaging

$$MI = \frac{P_{r,3}}{\sqrt{f_c}}$$

or

$$P_{r,3} = \sqrt{f_c} \cdot MI$$

- As frequency decreases the pressure threshold for cavitation becomes lower

Thermal Effect

- Thermal Index - a measure of damage threshold in ultrasound imaging

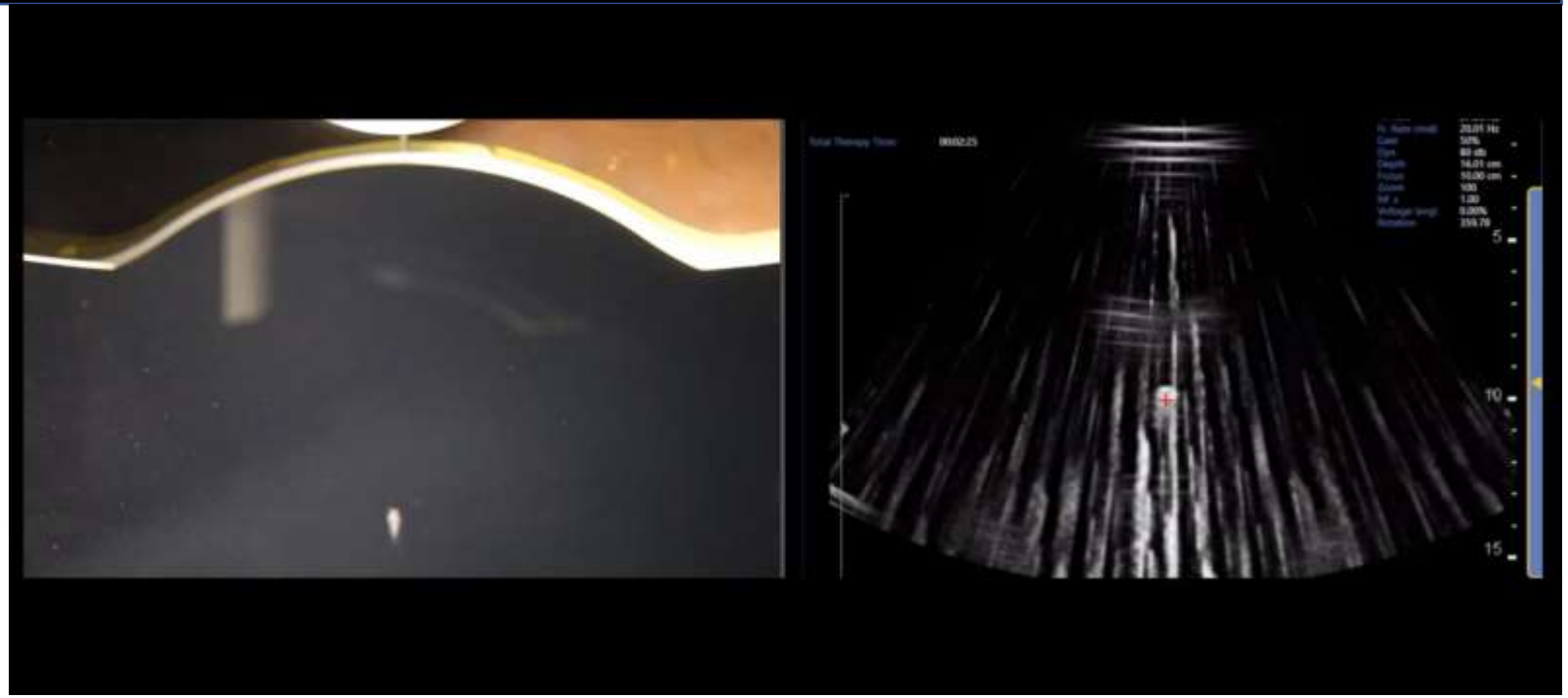
$$TI = \frac{W_O}{W_{\text{deg}}}$$

- W_o = Time averaged power of source
- W_{deg} = Power to raise temperature 1°C
- in specific tissue and thermal models

Courtesy of HistoSonics

Novel Science of Histotripsy

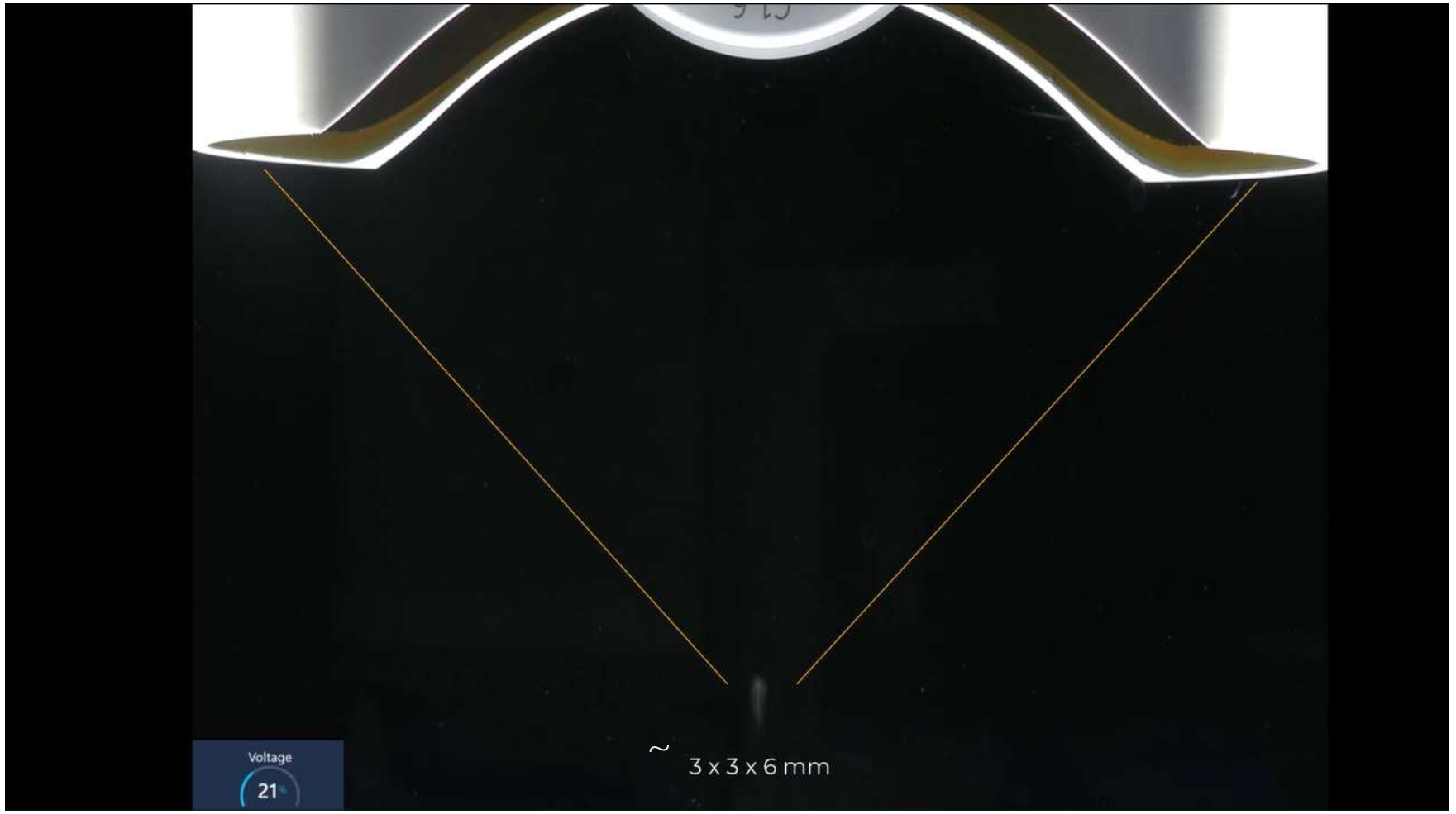
Short, high pressure focused ultrasound pulses (mechanical waves)
Generate cavitation (bubble cloud) at a precise focal point under ultrasound visualization
Destroys & liquifies targeted tissue into acellular debris while tending to spare critical structures



NON-INVASIVE **NON-IONIZING** **NON-THERMAL MOA**

The Edison System is not available for sale outside the United States.
CLN2954_rA

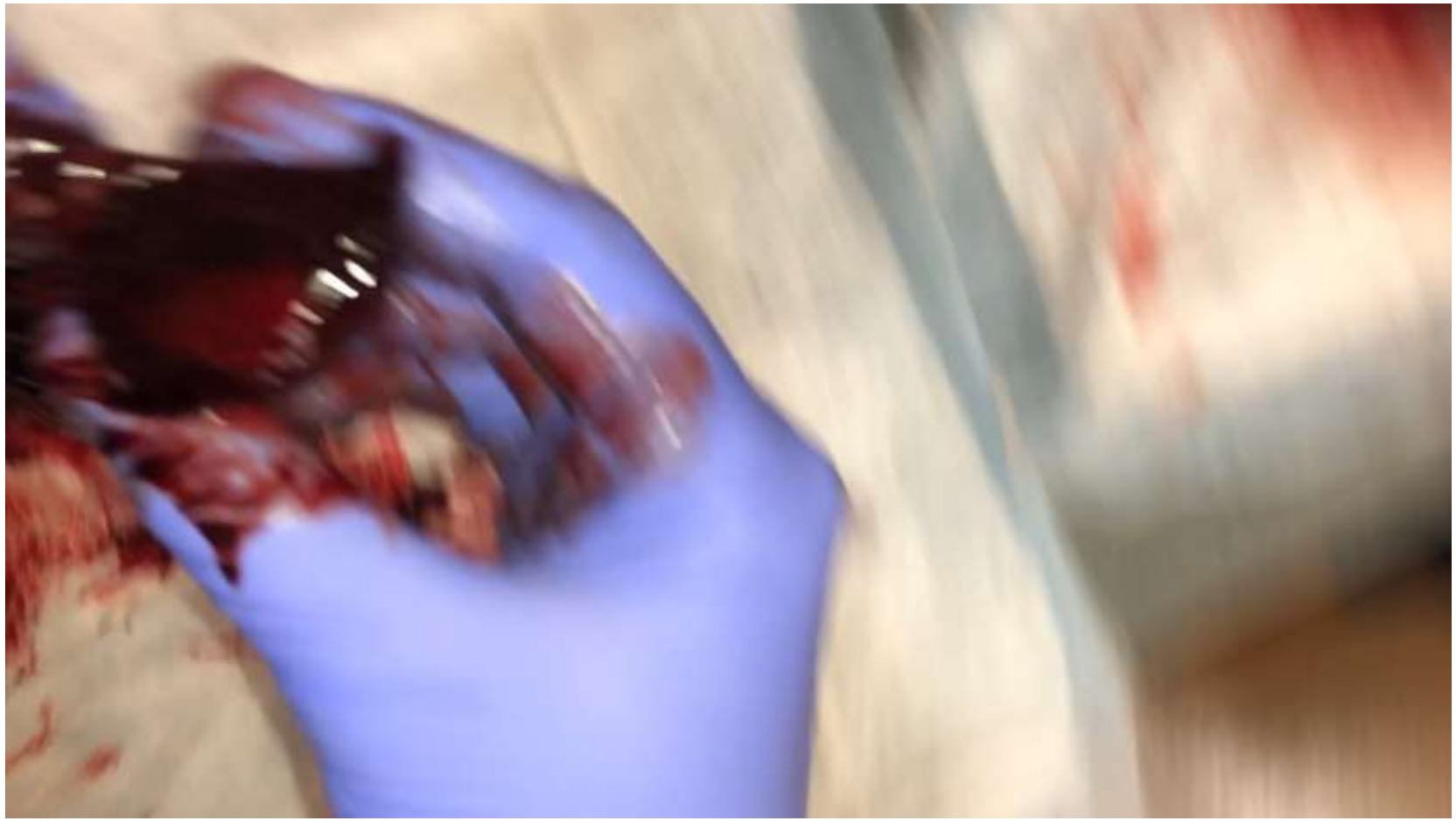
Histotripsy- Threshold Phenomenon



Courtesy of HistoSonics

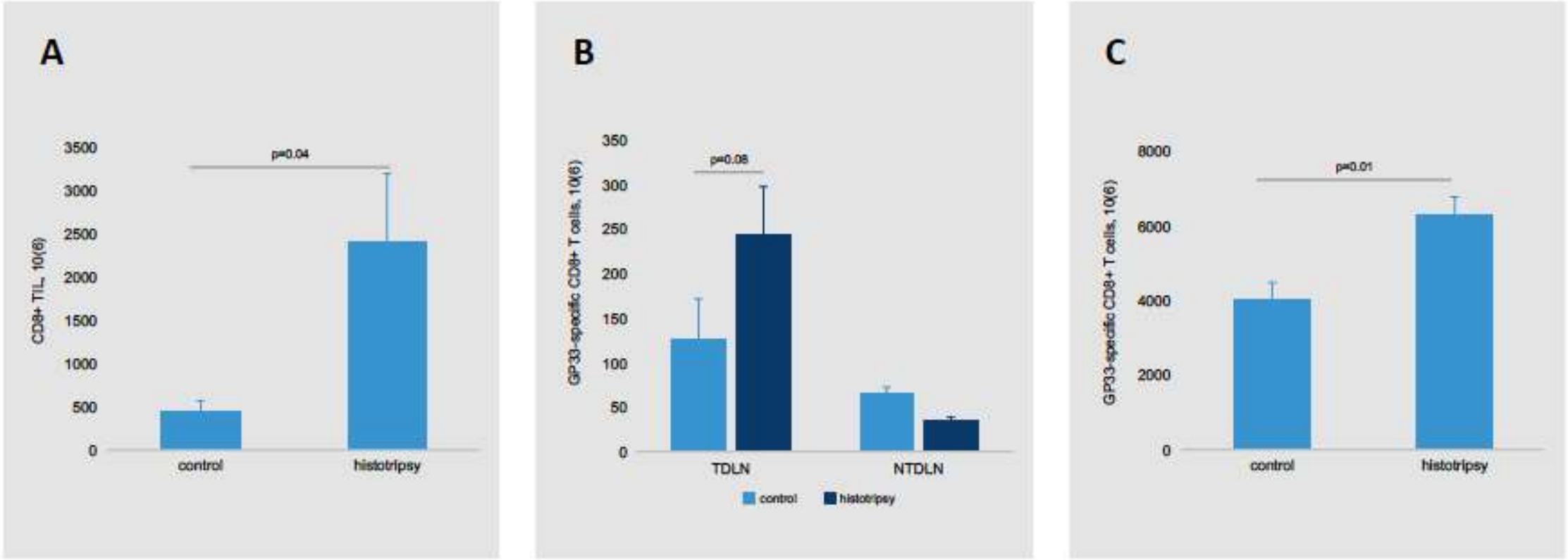
Histotripsy creates soluble acellular slurry

Targeted tissue is mechanically destroyed creating an acellular slurry or lysate in LIVER
Enables rapid treatment absorption and potential antigen preservation



Courtesy of HistoSonics

Preclinical Antigen Recognition Post Histotripsy

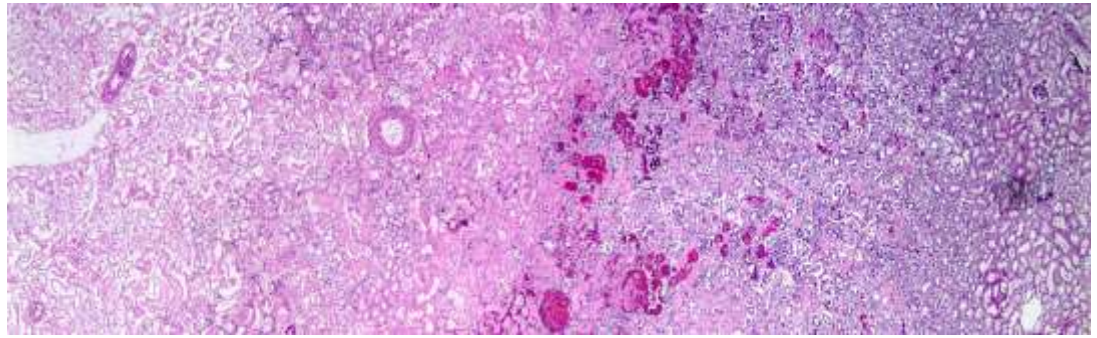


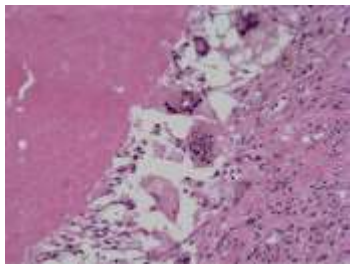
Histotripsy increases CD8+ T cell activation in tumor infiltration (**A**), tumor draining lymph nodes (**B**), and systemic circulation (**C**) in murine models.

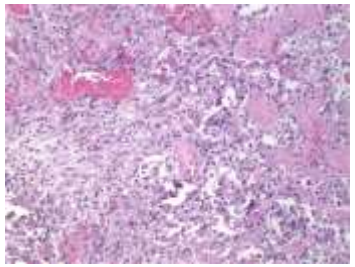
Courtesy of Clifford Cho, University of Michigan

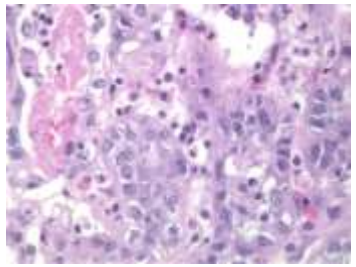
Mechanism of Action- Non Thermal

MICROWAVE







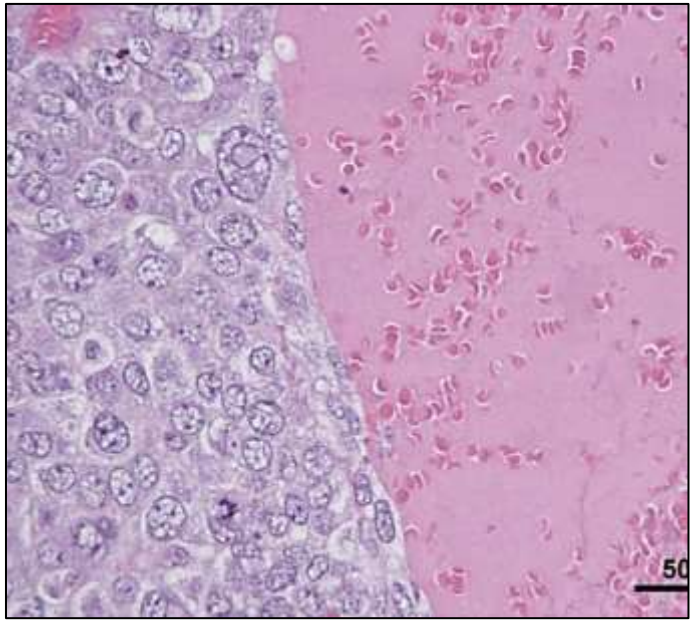


Thermal Fixation — **Resists Healing**

Coagulative Necrosis — **Wound Healing**

Transition Zone — **Regeneration**

HISTOTRIPSY

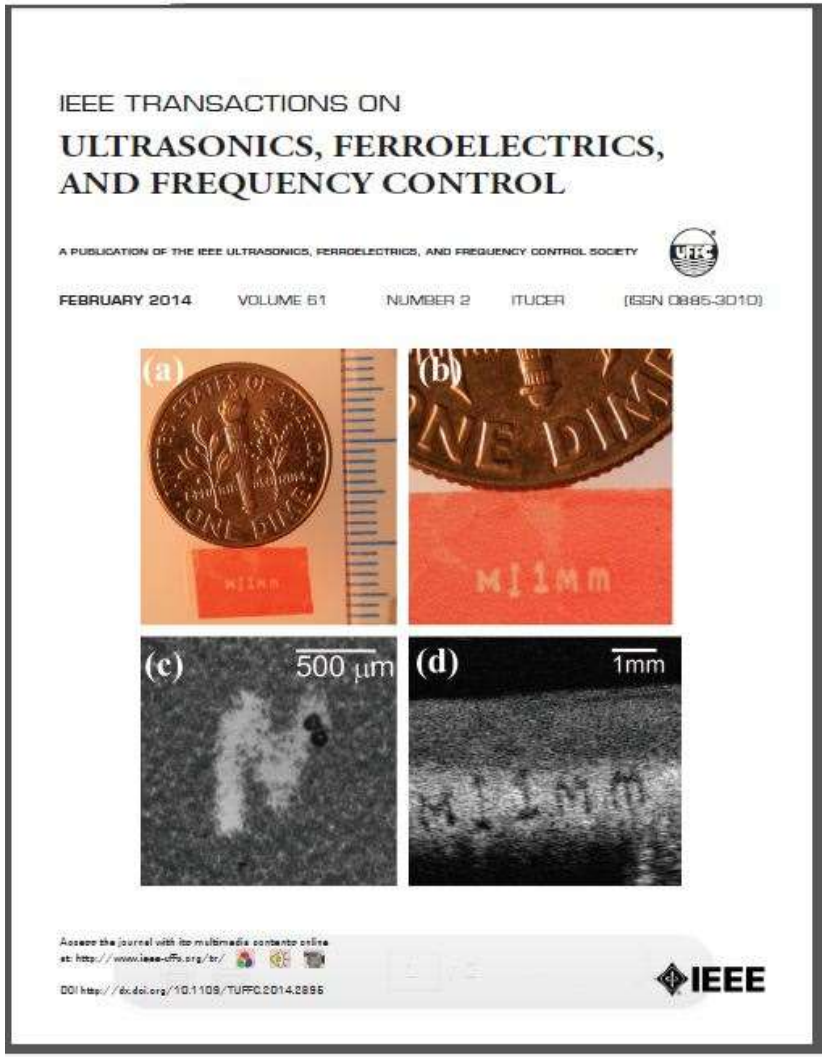


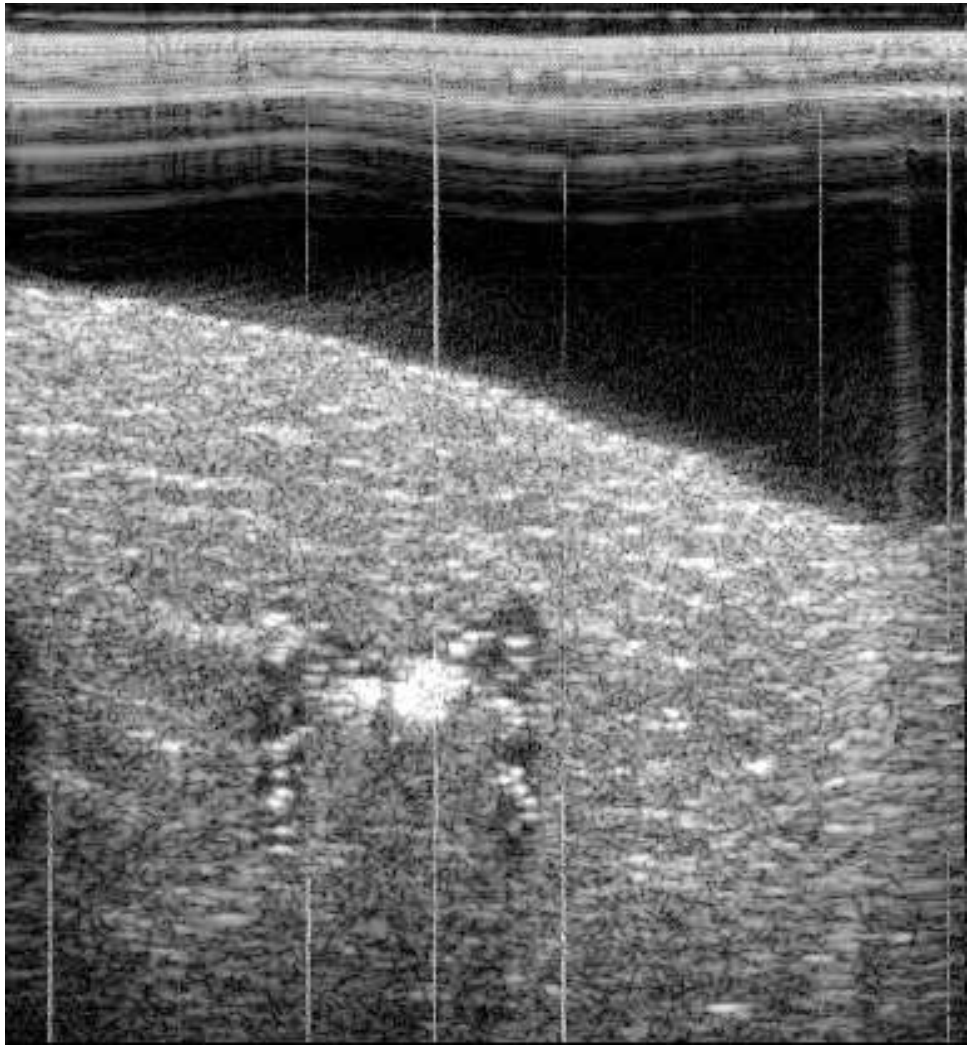
Histotripsy completely fractionated liver tumors into an acellular homogenate *in vivo* – *antigens are preserved*

No Coagulative Necrosis

Courtesy of HistoSonics

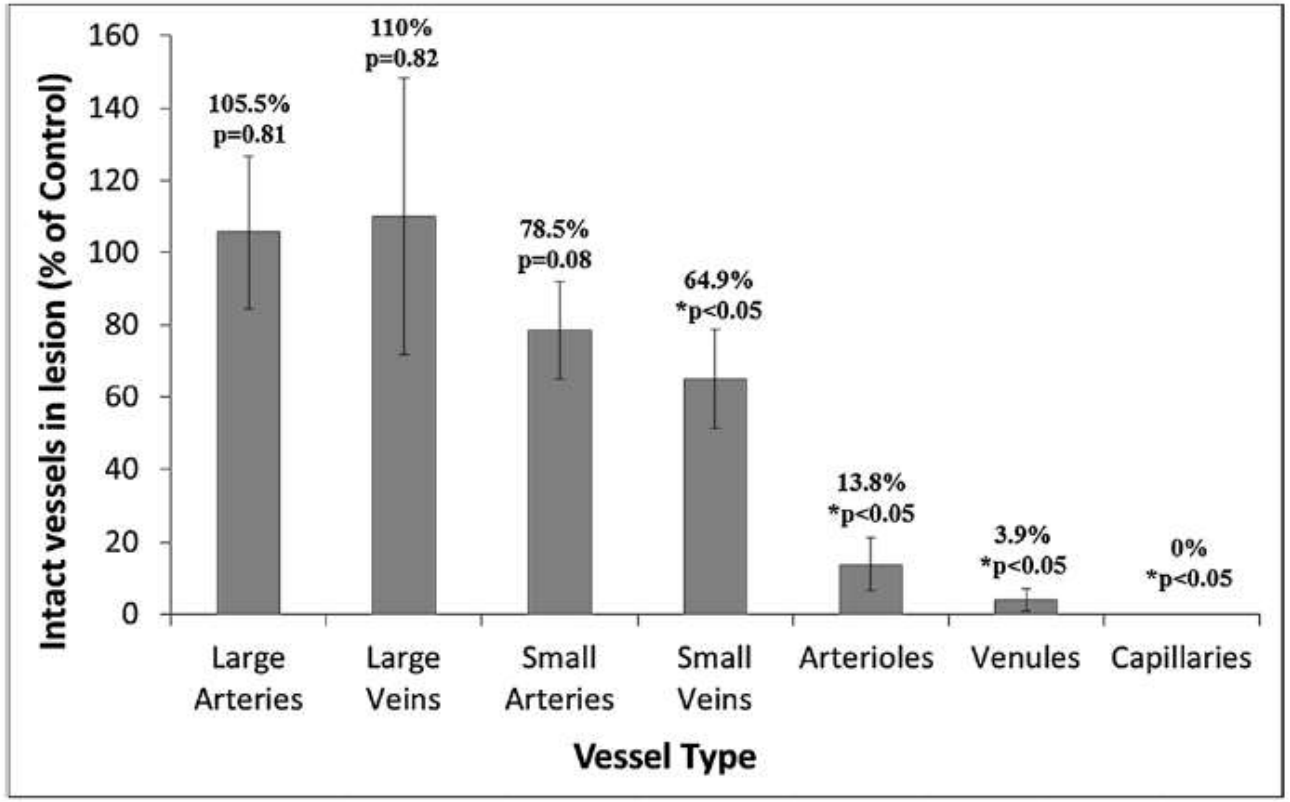
Histotripsy: Precision





Courtesy of HistoSonics

Histotripsy: Sparing Collagen Rich Critical Structures



Vessel Type		Large Arteries	Large Veins	Small Arteries	Small Veins	Arterioles	Venules	Capillaries
Inner Diameter		>1 mm	>1 mm	0.3-1 mm	0.1-1 mm	20-300 μm	20-100 μm	<10 μm
Total Wall Thickness		500-1000 μm	100-500 μm	50-500 μm	10-200 μm	5-50 μm	1-20 μm	0.5 μm
Approximate Layer Thickness	Intima	0.5 μm	0.5 μm	0.5 μm	0.5 μm	0.5 μm	0.5 μm	0.5 μm
	Media	300-600 μm	40-200 μm	30-300 μm	4-80 μm	3-30 μm	0.5-8 μm	0 μm
	Adventitia	200-400 μm	60-300 μm	20-200 μm	6-120 μm	2-20 μm	0.5-12 μm	0 μm

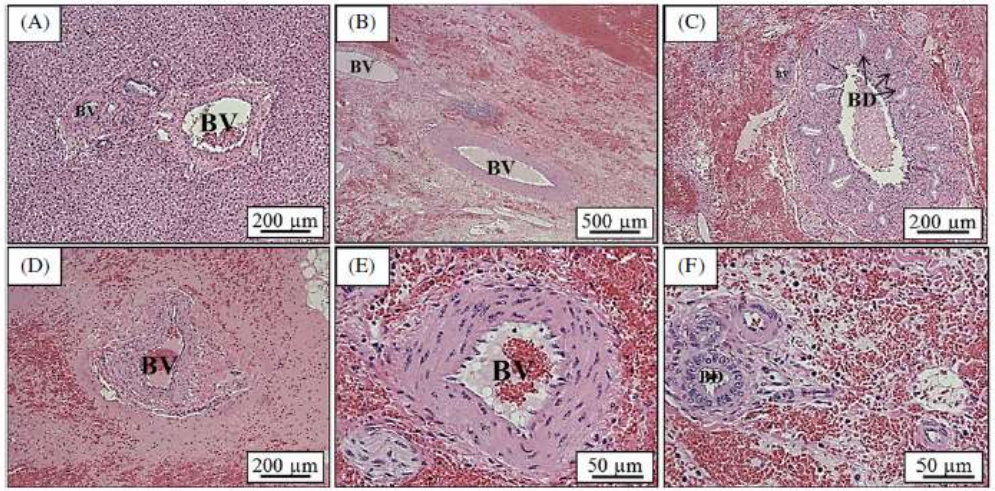


Figure 7. Histotripsy selective ablation results showed hepatic vessels remained intact within fractionated porcine liver *in vivo*. Results show select images of hepatic blood vessels (BV) inside untreated (A) and completely fractionated (B-F) liver tissue. A large number of smaller vessels and bile ducts (BD) were observed in the regions containing connective tissue surrounding hepatic vessels.

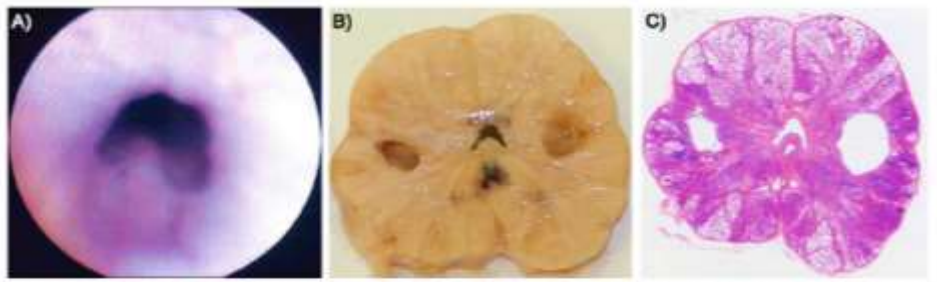


Figure 3. Cystoscopic appearance of intact urethra (**A**) and corresponding gross (**B**) and low-power micrograph (**C**) demonstra ng intact urethral-sparing histotripsy treatment cavities at 8 weeks post-histotripsy. (Color version available online.)

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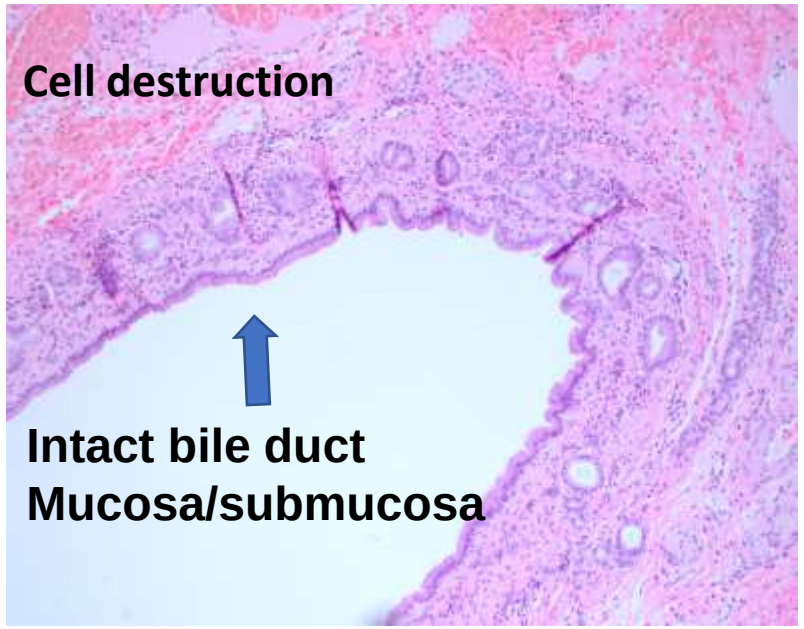
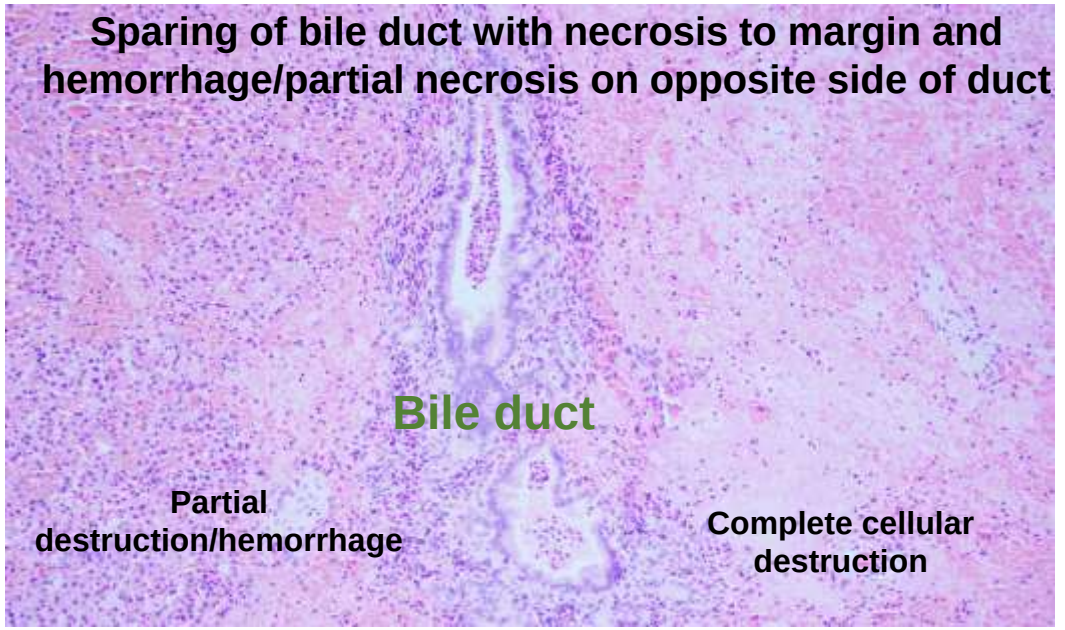
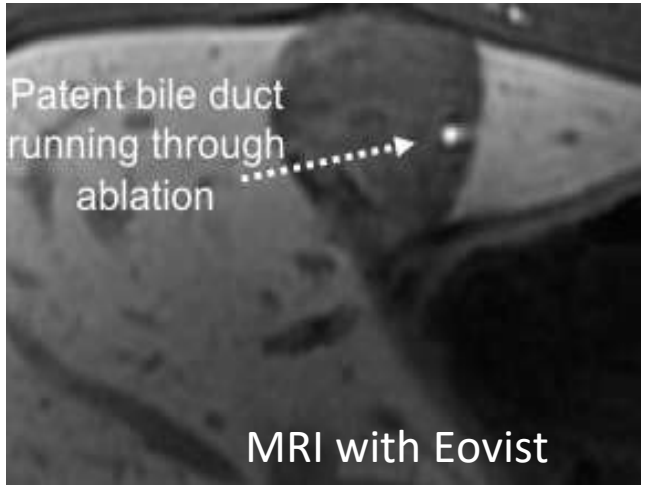
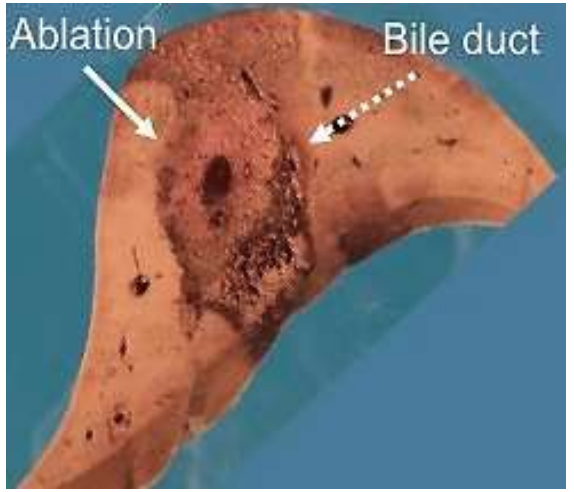
Histotripsy: Sparing Collagen Rich Critical Structures



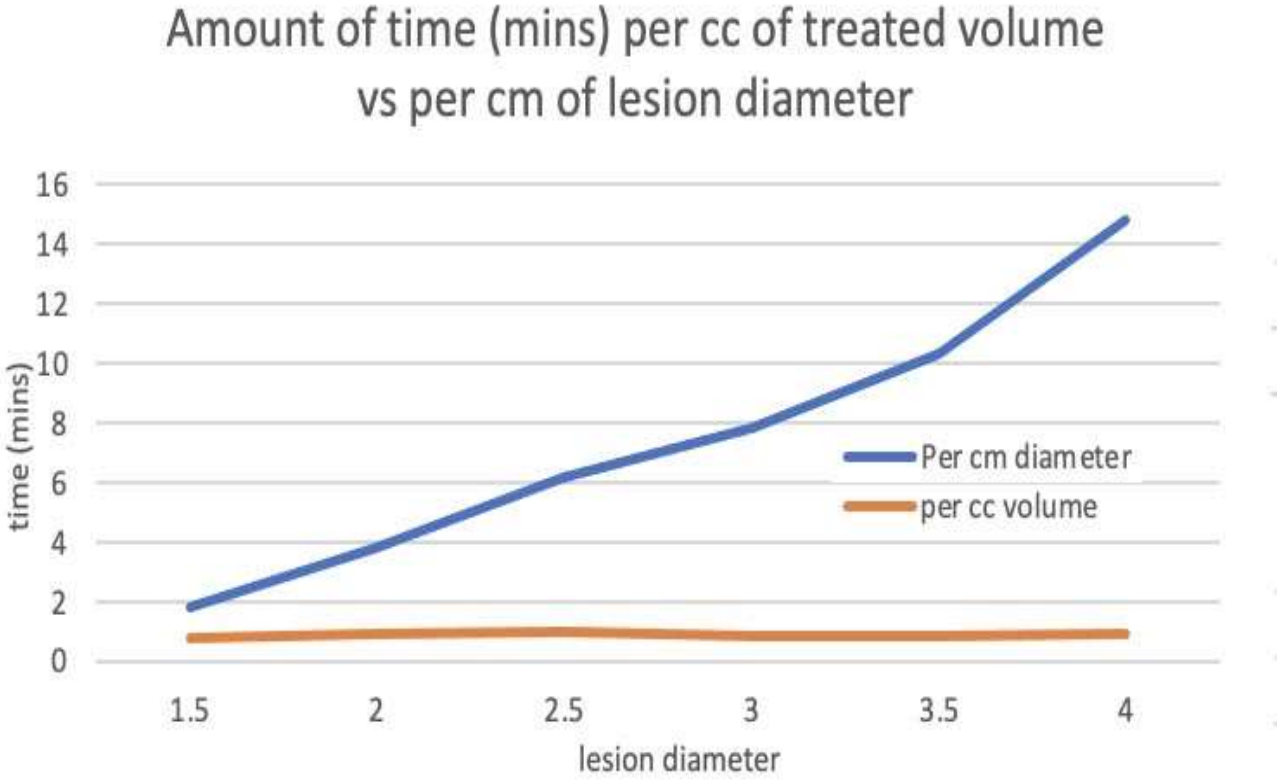






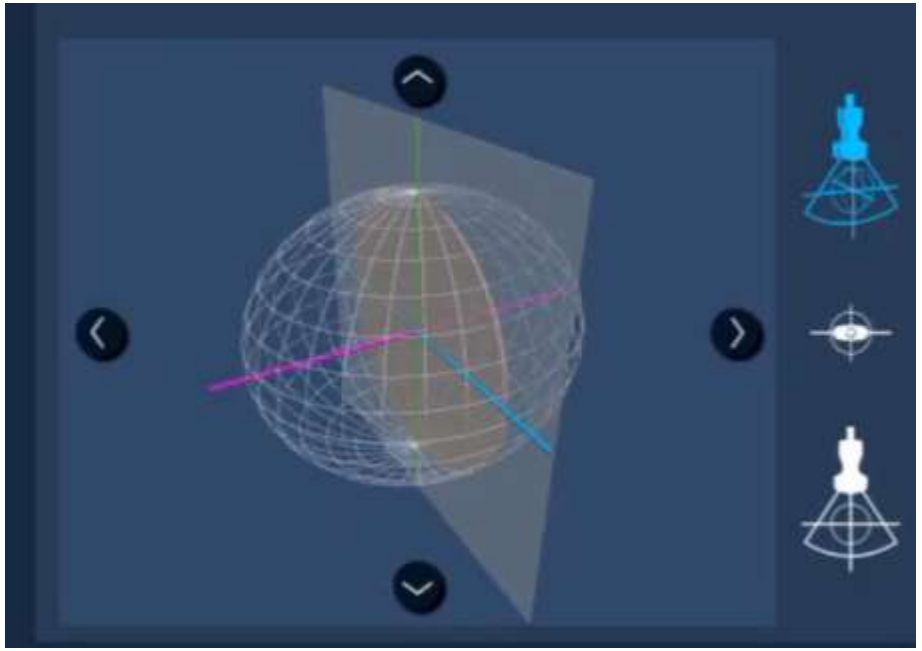
Porcine liver courtesy of University of Wisconsin

Histotripsy:
Treatment Time is d/o Volume of Tumour



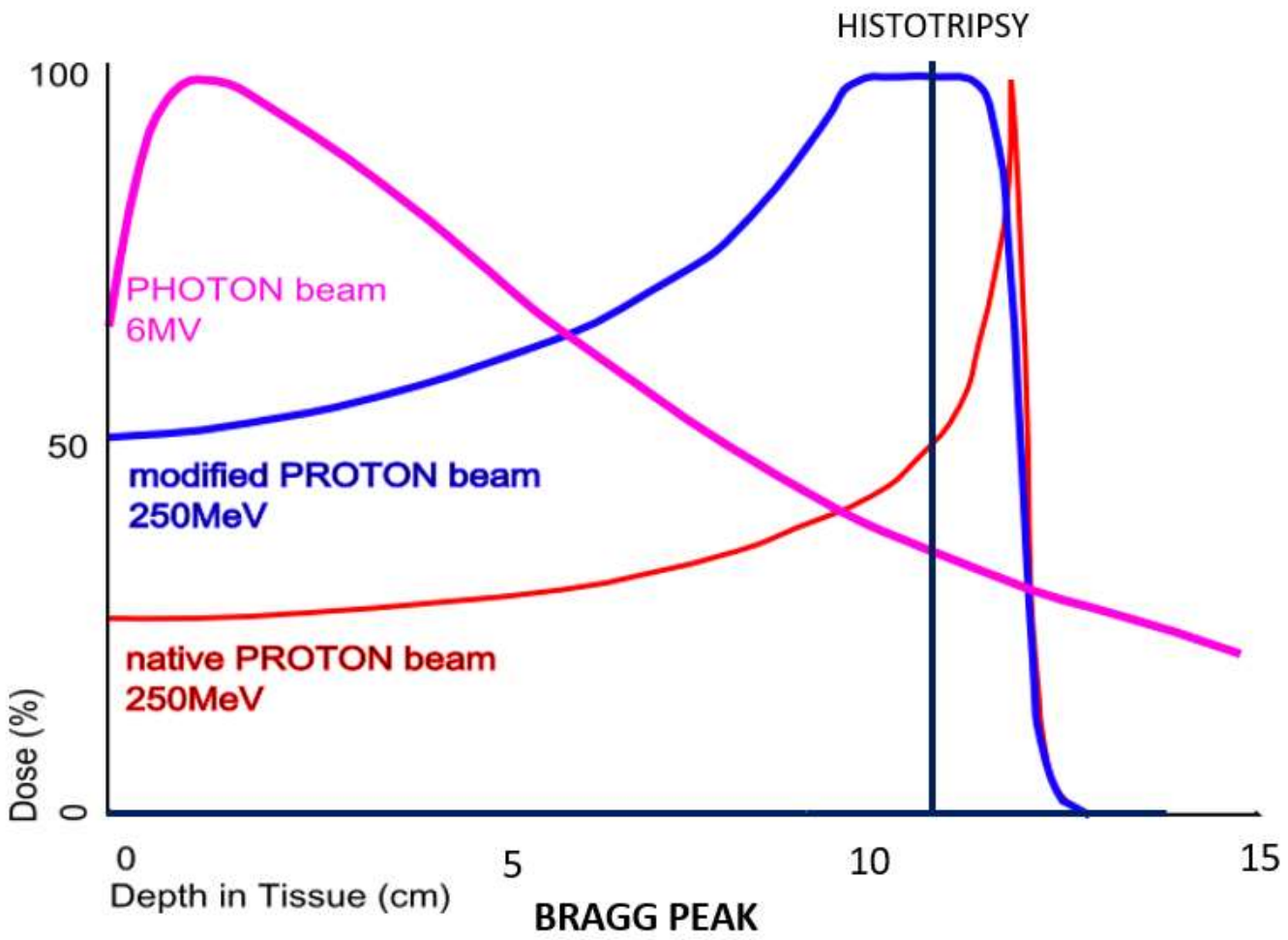
$$V = \frac{4}{3}\pi r^3$$

No thermal damage
No thermal "chaos"
No thermal gradient

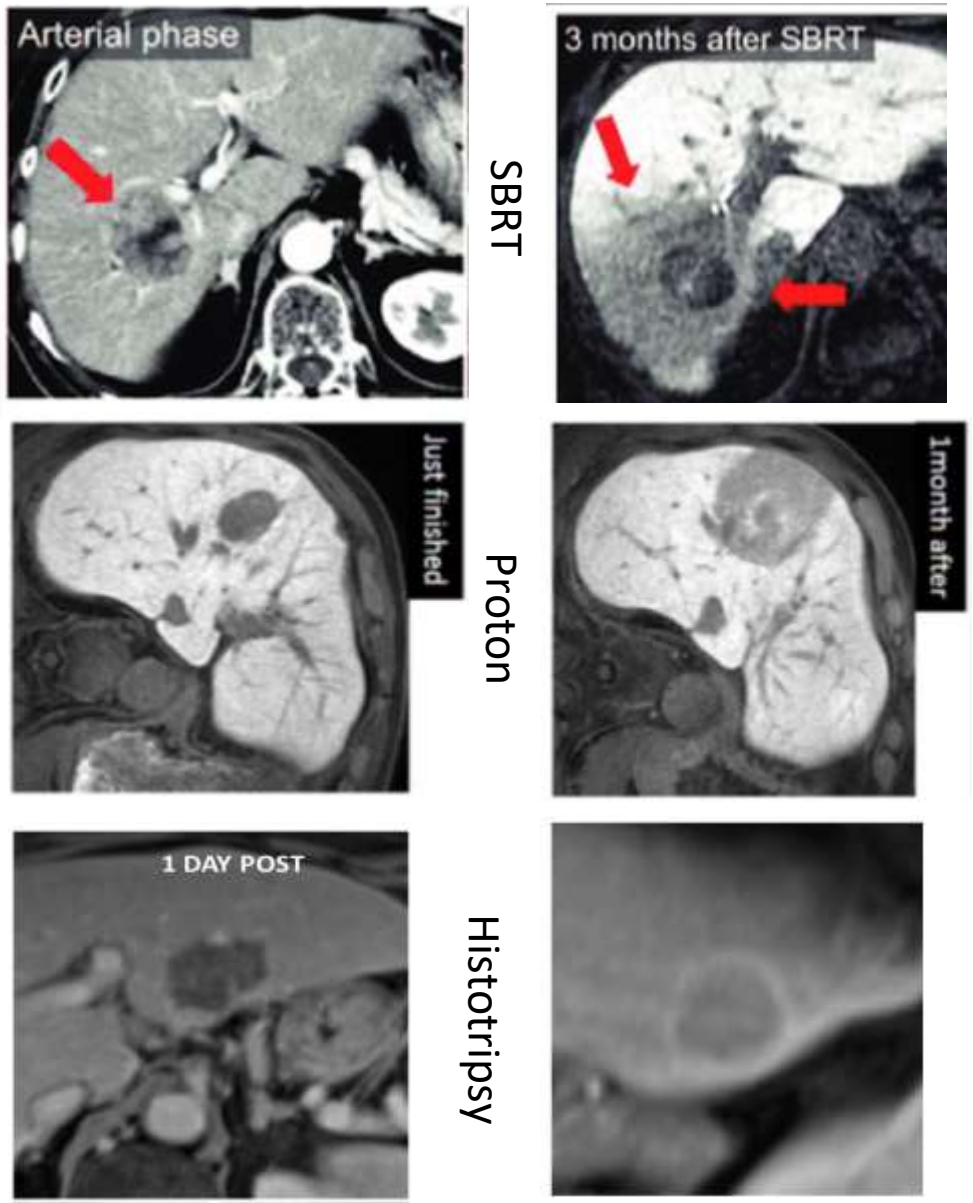


Courtesy of HistoSonics

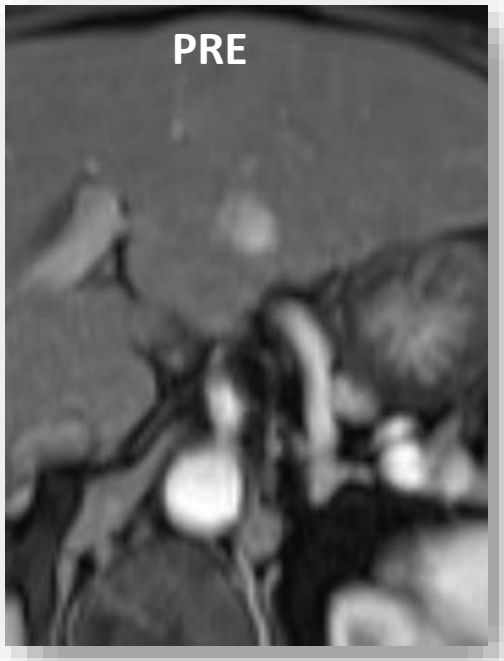
Histotripsy: Non-Ionizing

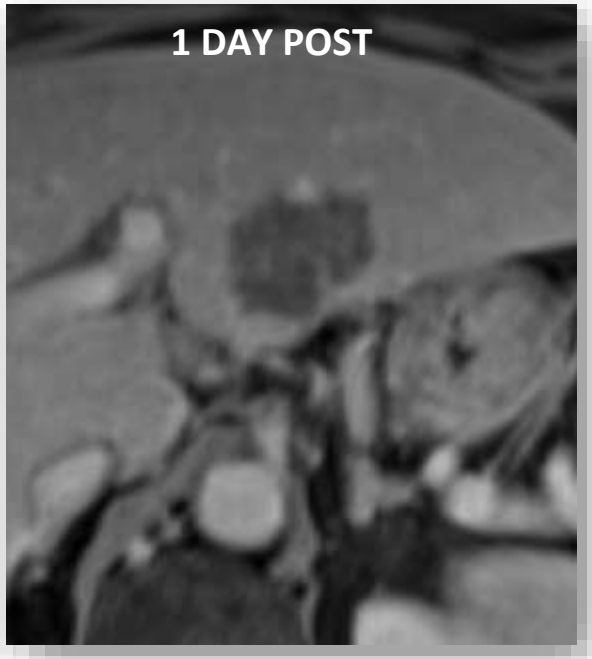


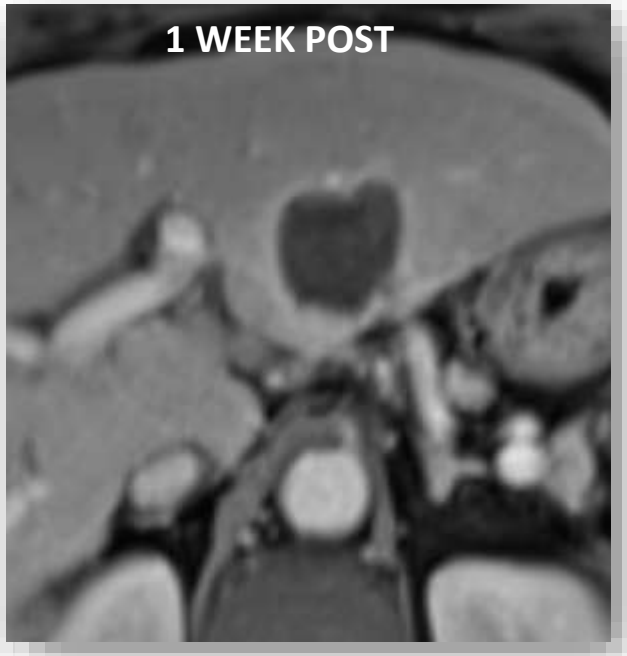
Courtesy of HistoSonics

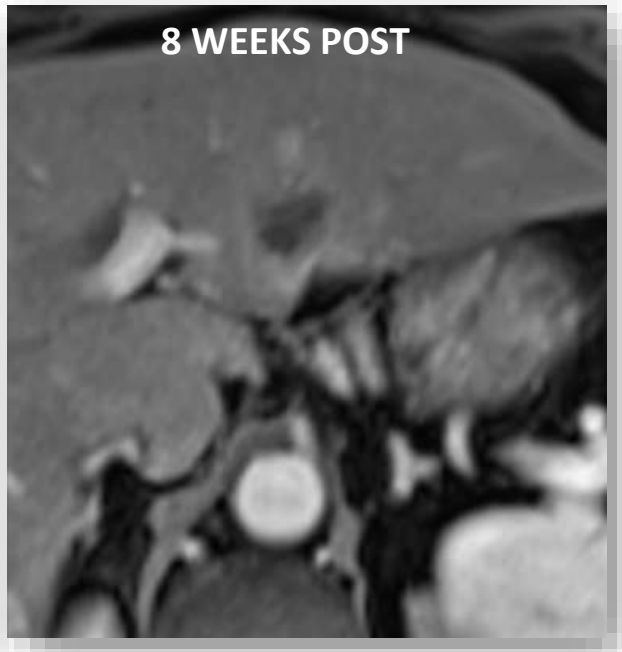


Histotripsy: Rapid Involution Post Treatment









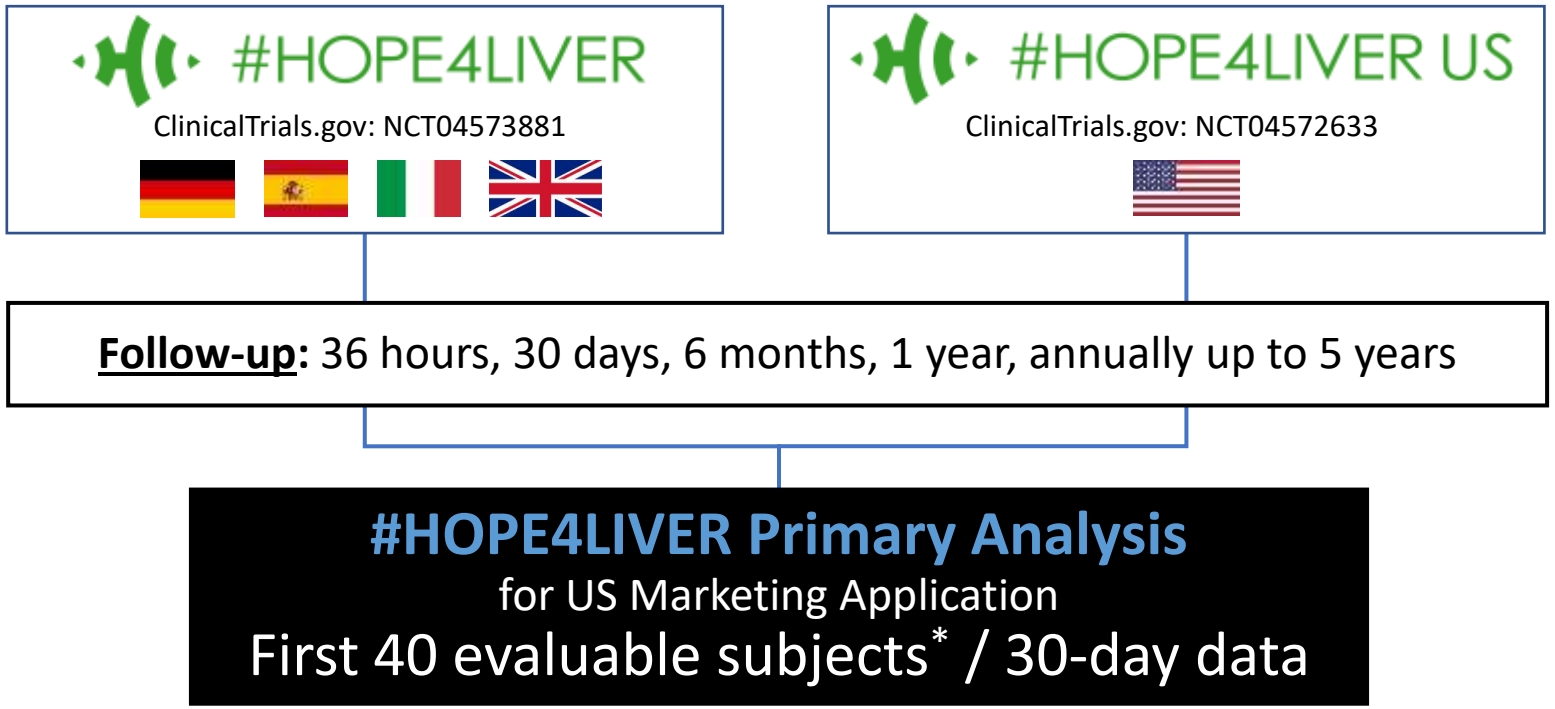
Courtesy of HistoSonics

Theresa Study image

TRIAL DESIGN

Prospective, multicenter, single-arm, IDE trials

Objective: Evaluate efficacy & safety of HistoSonics System for treatment of primary or metastatic tumors located in the liver



*Evaluable subjects are those with sufficient data that the primary endpoint of Technical Success can be evaluated
Flag images from Countryflags.com
CLN2954_rA

Key General and Imaging Eligible Criteria

Key Inclusion Criteria

- Subject diagnosed with HCC or liver metastases.
- Tumour(s) must be ≤3 cm in longest diameter.
- Maximum of 3 tumours allowed for treatment regardless of number present.
- Subject has not responded to and/or has relapsed and/or is intolerant of other available therapies including locoregional therapies, chemotherapy, immunotherapy and targeted therapies.

Key Exclusion Criteria

- Subject is eligible for surgical resection.
- Subject has planned cancer treatment prior to 30-day follow-up visit.
- The Planned Treatment Volume includes or encompasses any portion of the main portal vein, common hepatic duct, common bile duct, gallbladder or stomach/bowel.

Co-Primary Endpoints

Primary Efficacy Endpoint: Technical Success at ≤ 36 hours

- Treatment volume ≥ targeted tumour volume and complete tumor coverage (CT/MRI)
- Adjudicated by imaging core lab
- Tumor success performance goal >70%

Primary Safety Endpoint: Major Complications up to 30 days post-procedure

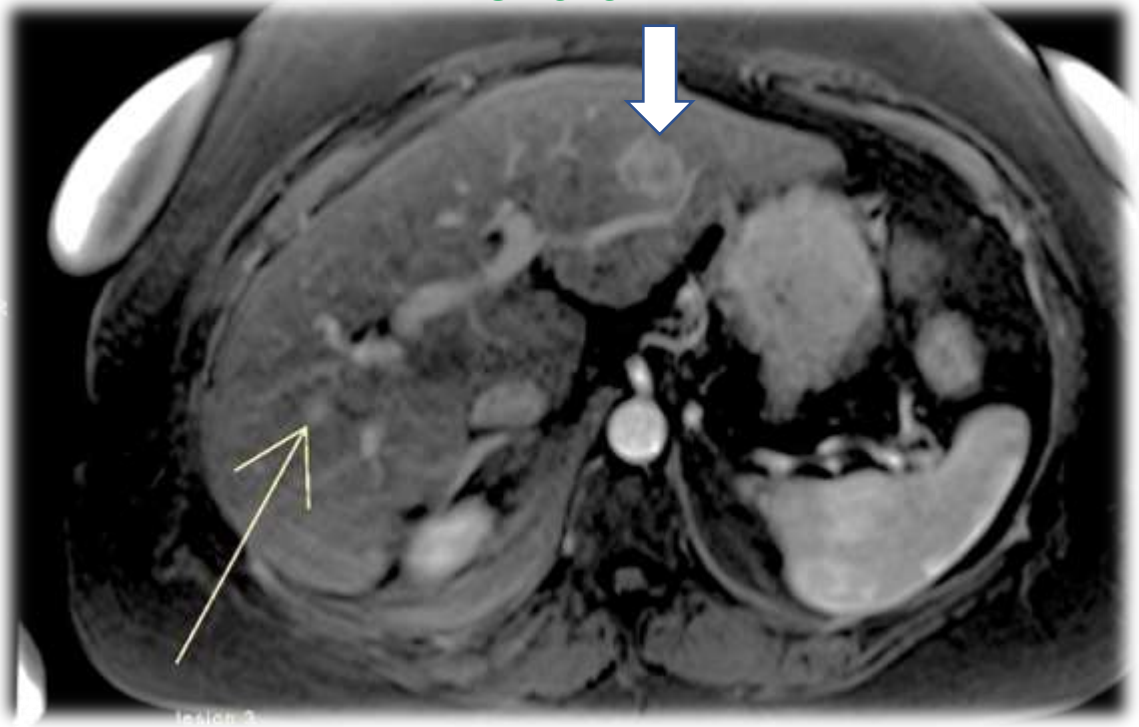
- Index-procedure related adverse events defined as Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher
- Adjudicated by Clinical Events Committee (CEC)
- Patient success performance goal <25%

Results must be positive for both co-primary endpoints for the trial to be considered successful

LIVER CANCER MDT

Case SR- 68 years old
Two HCCs-. 2.5cm LR5 HCC segment 2 and 1.5cm LR5 HCC segment 8

Alcoholic liver disease - child pugh A, DM, hypertension, urticarial vasculitis, prev septic arthritis, cholecystectomy, smoker.

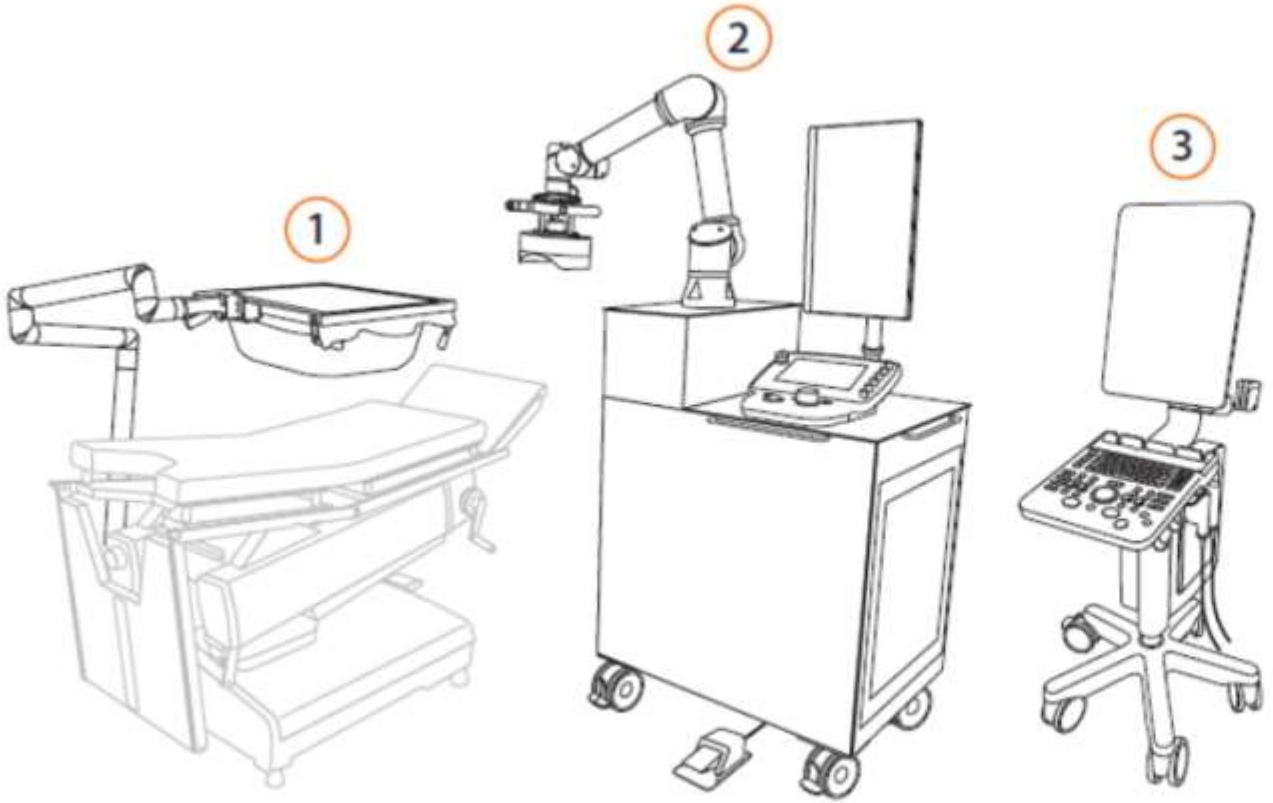


- Non- surgical candidate; options- thermal ablation & #H4L
- Patient opted for –

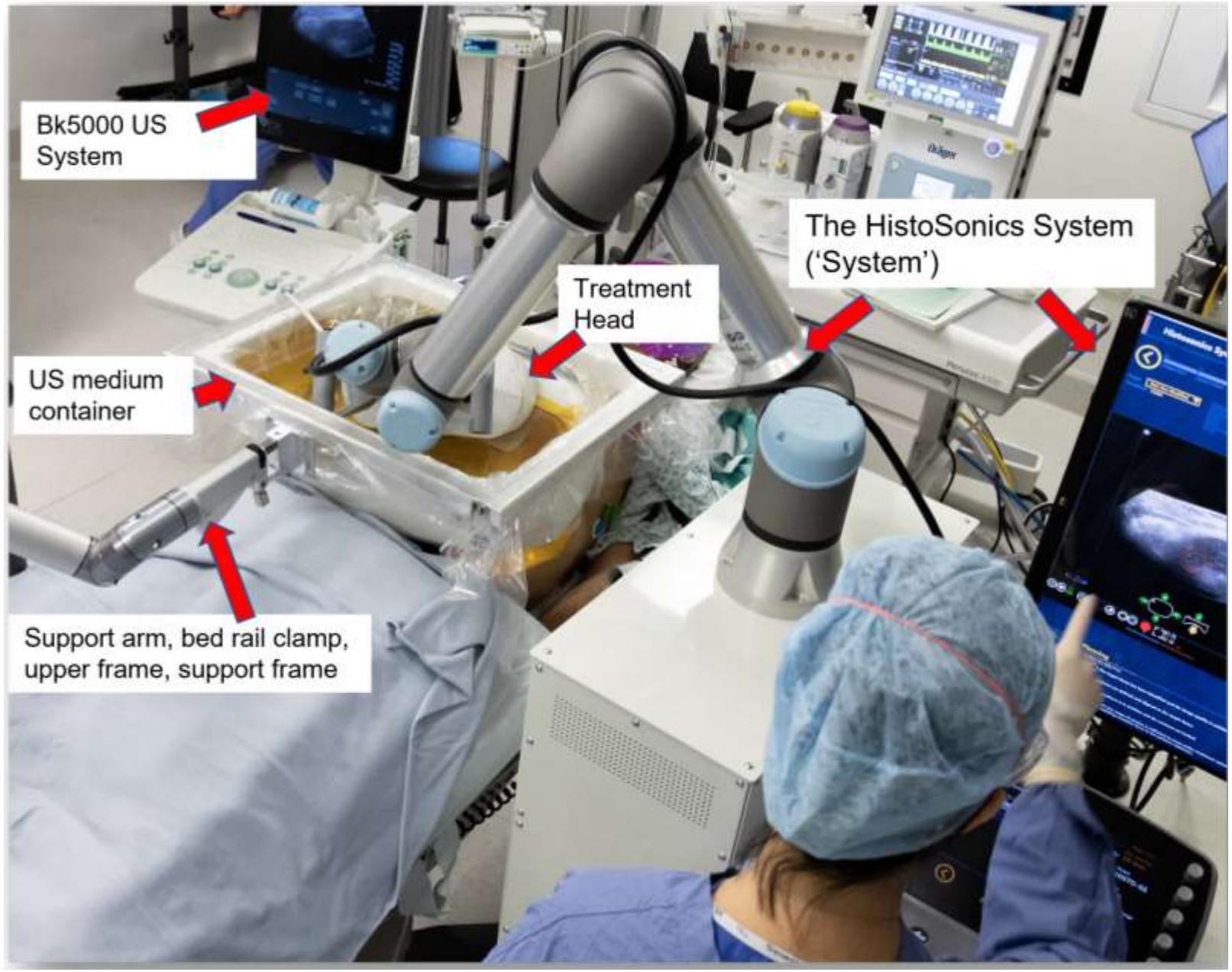
❑ Image guided ablation –segment 8

❑ #Hope4Liver Trial- segment 2

‘Cloud Breaker’-
Histotripsy System for Treatment

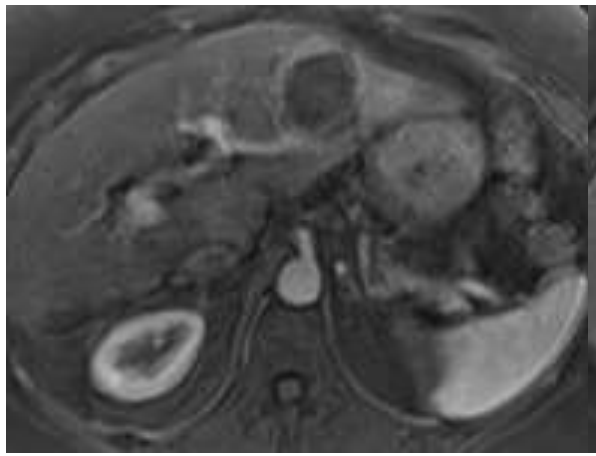


1. HistoSonics System – Ultrasound Medium Container Assembly
2. HistoSonics System – Treatment Cart
3. BK Medical™* bk5000 Ultrasound System

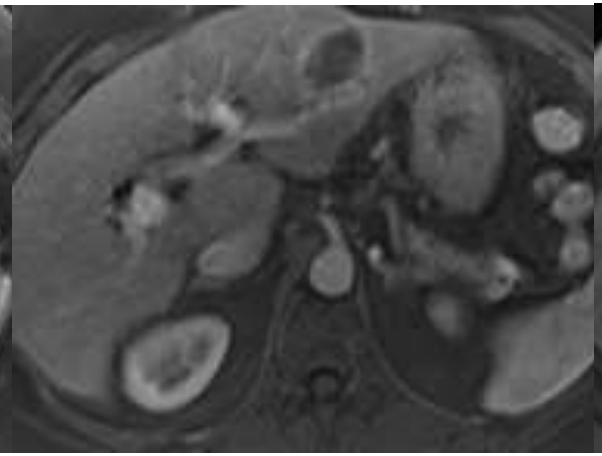

Bk5000 US System
Treatment Head
The HistoSonics System ('System')
US medium container
Support arm, bed rail clamp, upper frame, support frame

Follow up MRI Post Histotripsy of HCC

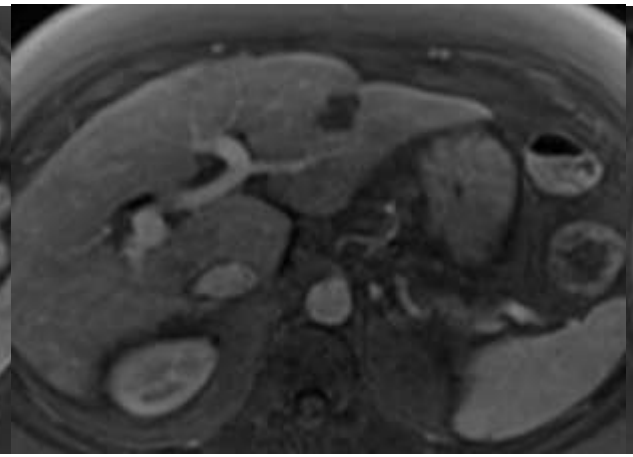
1-day



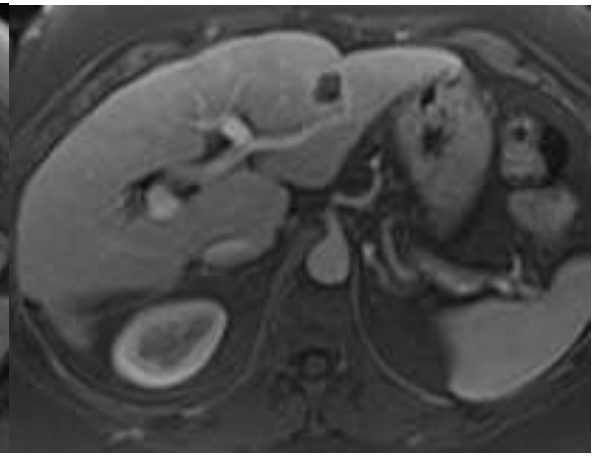
1-month



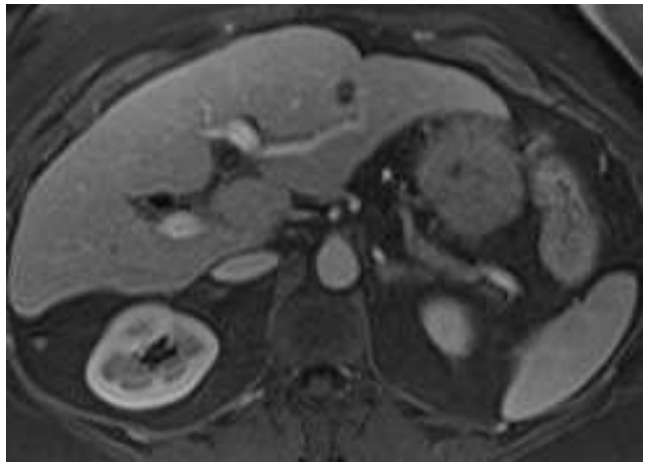
3-months



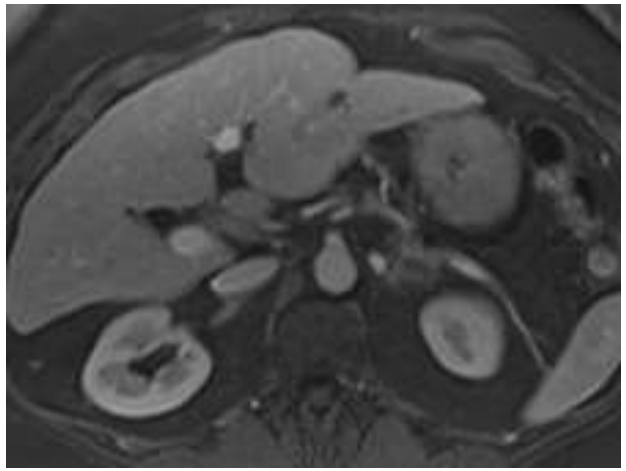
6-months



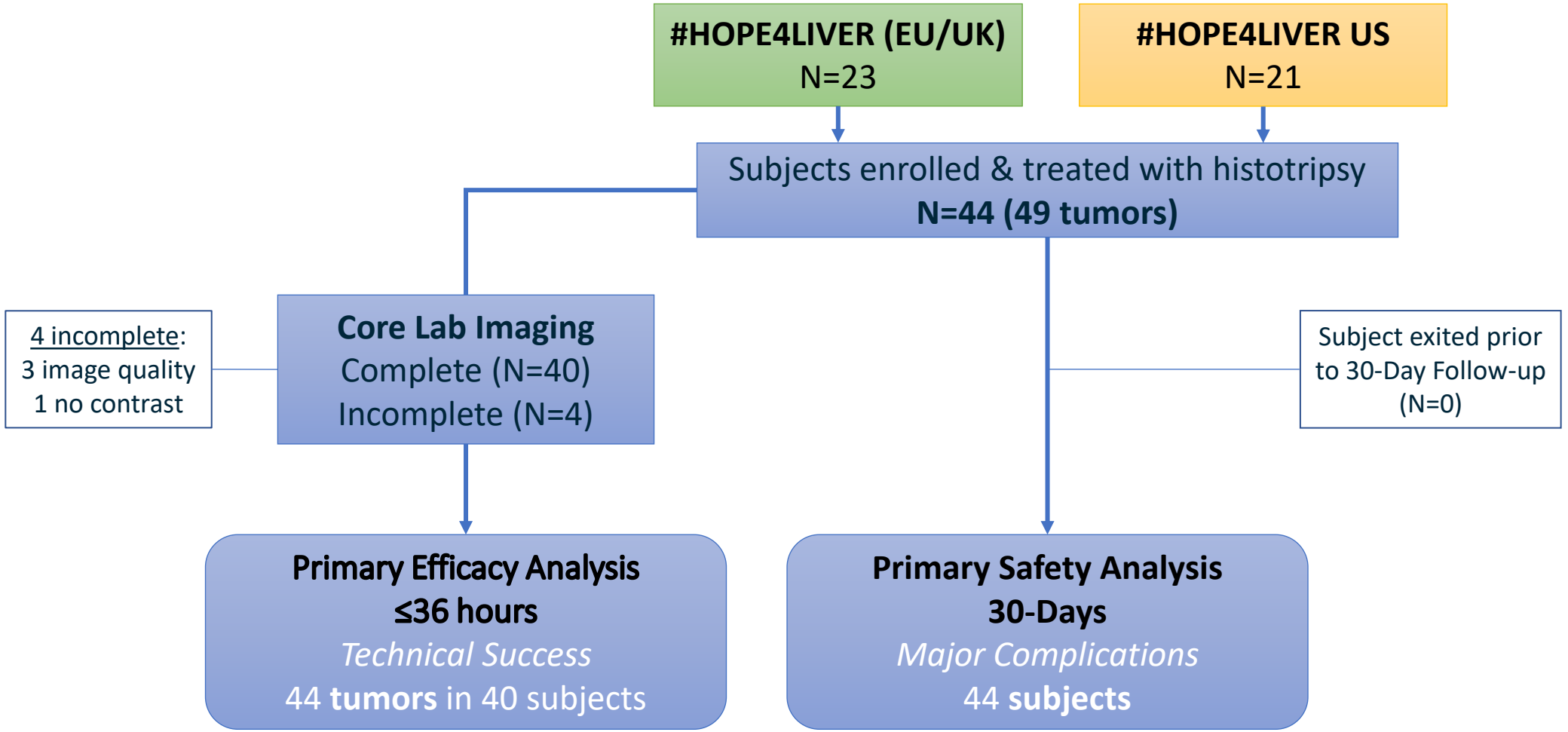
1-year



2-years



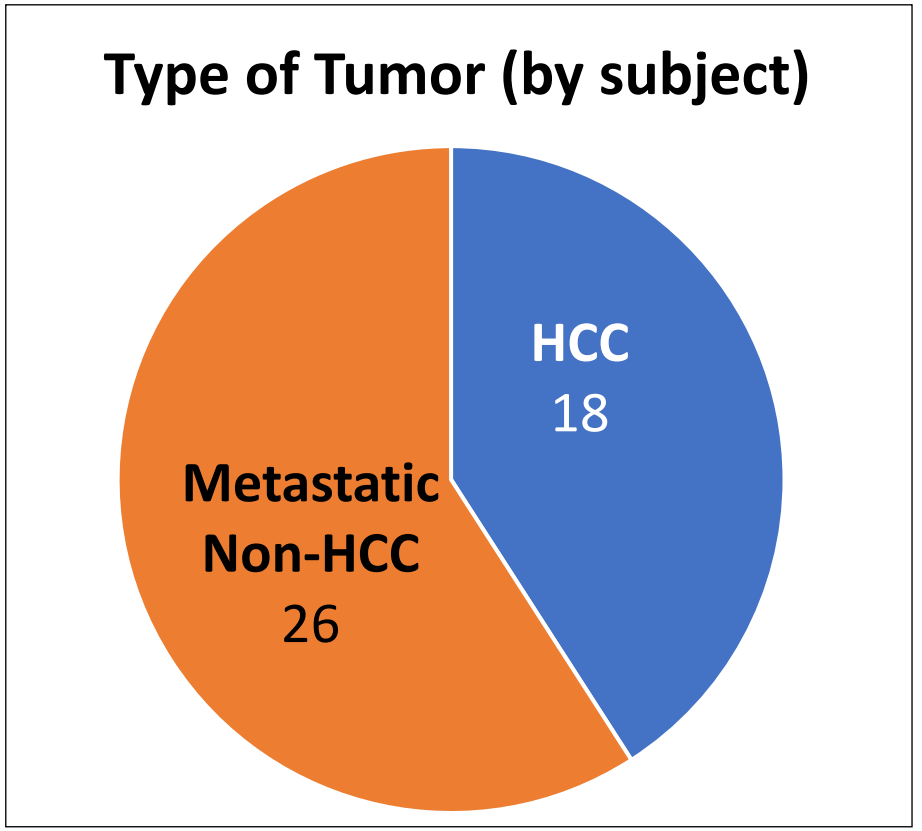
Subject Flow Through 30 days



HistoSonics Data on File (CSR2472 Rev. A)
CLN2954_rA

Demographics & Baseline Characteristics

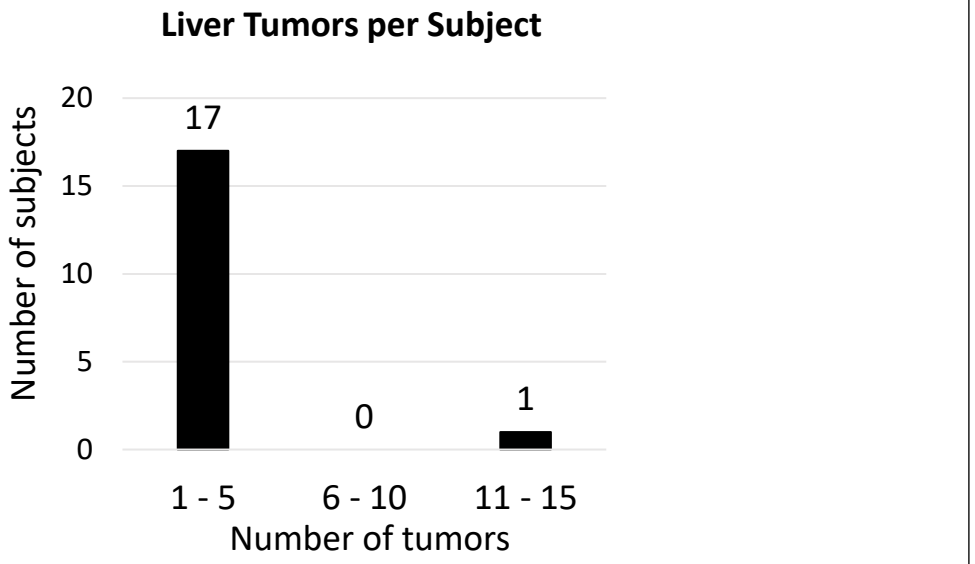
Category	N=44
Age (years)	63.9 ± 12.3
Female	22 (50.0%)
Child-Pugh Class	
A	37 (84.1%)
B	6 (13.6%)
C	0



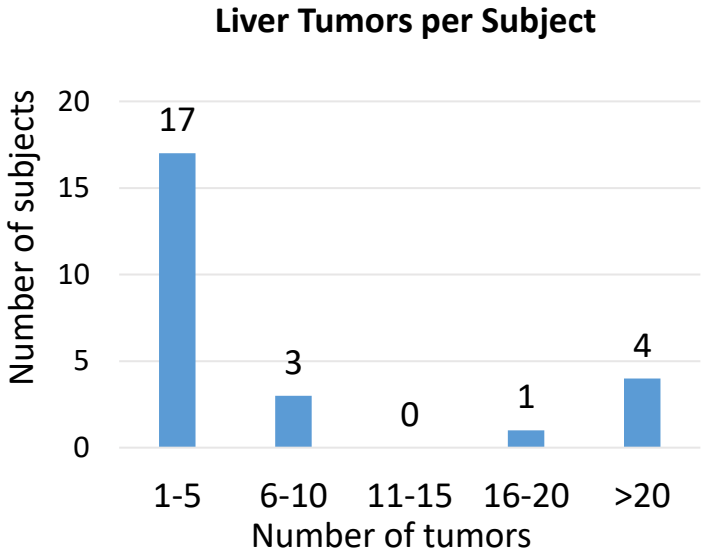
Values presented as mean ± standard deviation or n/N (%) as appropriate
Child-Pugh Class at baseline was missing for 1 subject
HistoSonics Data on File (CSR2472 Rev. A)

Baseline Tumour Information

HCC Subjects (N=18)



Metastatic Non-HCC Subjects (N=26)



Primary tumor location	N=26
Colon	5 (19.2%)
Rectum	5 (19.2%)
Breast	4 (15.4%)
Pancreas	5 (19.2%)
Other*	7 (26.9%)

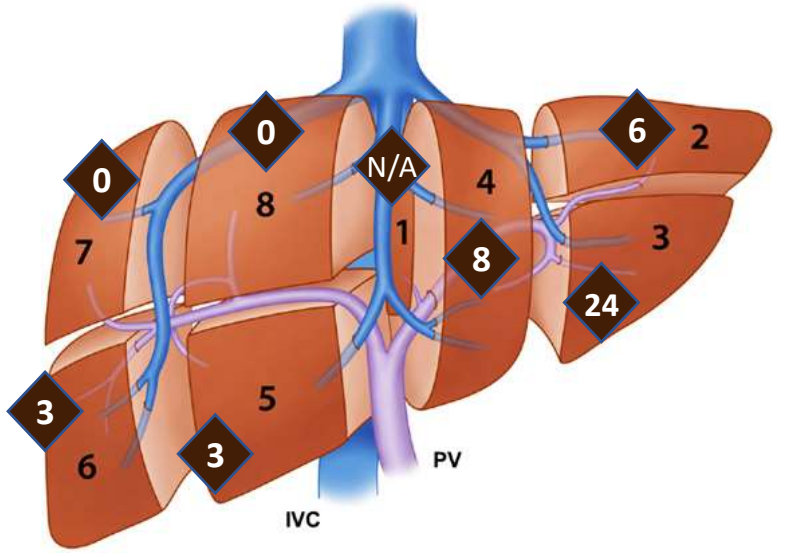
*Other primary tumor locations: brain (N=1), liver neuroendocrine tumor (N=1), ovary (N=1), uveal melanoma (N=2), bronchial carcinoma (N=1), large cell neuroendocrine lung (N=1)

Values presented as n/N (%)
Number of liver tumors was missing for 1 metastatic non-HCC subject
HistoSonics Data on File (CSR2472 Rev. A)
CLN2954_rA

Core Lab Assessed Imaging Data

Category (Core Lab Reported)	Evaluable Tumors N=44
Targeted tumor longest diameter, cm	1.48 ± 0.58
Treatment zone longest diameter, cm	3.55 ± 1.45
Treatment zone volume ≥ targeted tumor volume	43 (97.7%)
Full tumor coverage	42 (95.5%)
Evidence of procedural off-target damage	6 (13.6%)
Perfusion changes contiguous to treatment area	5 (83.3%)
Treatment area lateral to targeted tumor	1 (16.7%)

Segments Treated



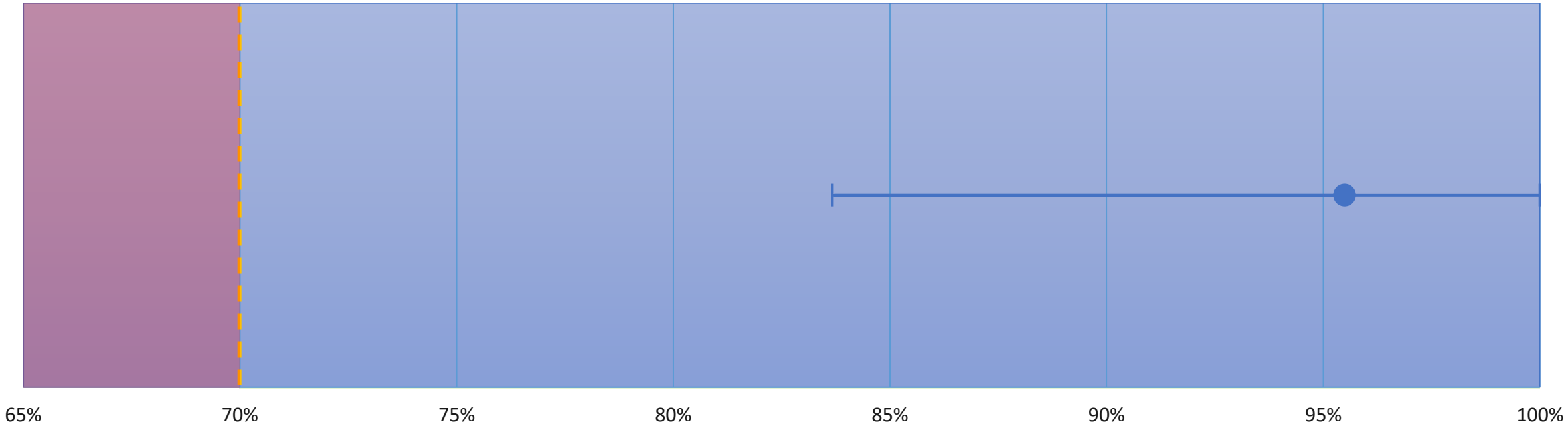
Values presented as mean ± standard deviation or n/N (%) as appropriate; HistoSonics Data on File (CSR2472 Rev. A and supplemental analysis)
Figure adapted from "Portal Vein Embolization as an Oncosurgical Strategy Prior to Major Hepatic Resection: Anatomic, Surgical, and Technical Considerations" by Orcutt, Kobayashi, Sultenfuss, Hailey, Sparks, Satpathy, and Anaya, Front Surg. 2016 Mar 11;3:14, under CC BY 4.0 / Superimposed #HOPE4LIVER data.

CLN2954_rA

Primary Efficacy Endpoint: Technical Success

Definition: Complete tumor coverage with treated volume ≥ targeted tumor via CT/MR imaging at ≤36 hours post-procedure

Efficacy Performance Goal	Lower 95% CI*	Primary Efficacy Success
>70%	**83.7%**	**95.5% (42/44) tumors**



Primary Efficacy Endpoint Met

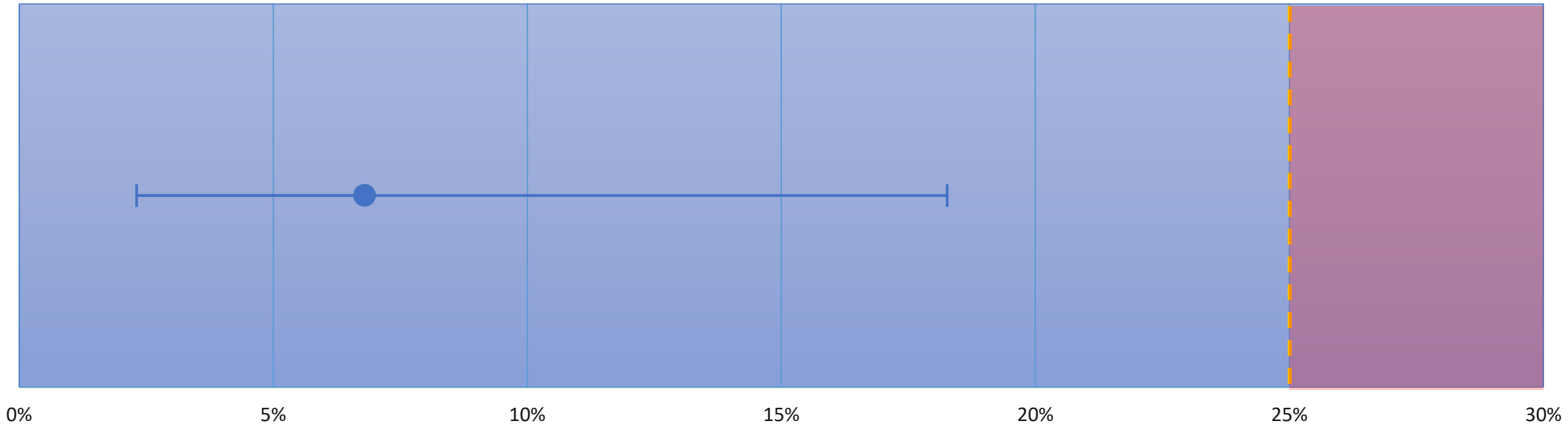
Lower confidence interval of 83.7% > pre-specified performance goal of 70%

* 95% confidence interval estimated by bootstrap sampling with replacement method to account for potential within-subject tumor correlations. Subject is the bootstrap sampling unit, 1,000,000 iterations for bootstrap resampling were performed, and the bootstrap method was the bias-corrected and accelerated (BCA) method.
HistoSonics Data on File (CSR2472 Rev. A)

Primary Safety Endpoint: Major Complications

Definition: Index procedure related CTCAE grade 3 or higher adverse events up to 30 days post-index procedure

Primary Safety Endpoint	Upper 95% CI*	Safety Performance Goal
6.8% (3/44)	**18.2%**	**<25%**



Primary Safety Endpoint Met

Upper confidence interval of 18.2% < pre-specified performance goal of 25%

*Two-sided 95% Wilson score confidence interval

HistoSonics Data on File (CSR2472 Rev. A)

CLN2954_rA

Primary Safety Endpoint: Major Complications

The observed 30-day index procedure related CTCAE grade ≥ 3 complications were all known risks of focal liver therapies and are not unique to histotripsy

CTCAE Grade 3 Events:

Sepsis: Subject, with stage IVa pancreatic cancer, >20 mets, and indwelling biliary stent developed liver abscess. Resolved 13 days later with treatment.

Pleuritic Pain: Subject, with stage II HCC, developed worsening of pleuritic chest pain that led to readmission 3 days post index procedure. Subject was treated with paracetamol and was discharged home 2 days later.

CTCAE Grade 5 Event:

Hepatic Failure: Subject, with stage IVb breast cancer, developed liver insufficiency and was admitted to the emergency room 12 days post index procedure. Continued deterioration of liver function resulted in hepatic insufficiency. Subject expired 37 days post index procedure.

HistoSonics Data on File (CSR2472 Rev. A)
CLN2954_rA

Limitations

- Small heterogenous patient cohort
- Advanced stage disease, so while the effect of histotripsy tissue destruction was seen, the effect of histotripsy on the disease process was not evaluated
- Extremely stringent inclusion/exclusion criteria limiting patient enrollment
- Lack of randomized comparison

#Hope4Liver Conclusions

The primary safety and efficacy endpoints for the #HOPE4LIVER trials were met, demonstrating successful non-invasive destruction of liver tissue using histotripsy

High rate of technical success (95.5%) indicates that physicians can precisely target and destroy liver tissue

Procedure-related major complications are all well documented risks of focal liver tumor treatment and are not unique to histotripsy

HistoSonics Data on File (CSR2472 Rev. A)
CLN2954_rA

CAIN Trial Update

Professor Charles CAIN

- **A visionary, a fearless leader, and a force to be reckoned with!**
- We are entering the ‘STAR WARS’ era…..

CAIN TRIAL DESIGN

Prospective, multicenter, single-arm, feasibility trial

Objective: Evaluate efficacy & safety of HistoSonics System for treatment of primary renal cancer

CAIN

ClinicalTrials.gov: NCT05432232 & NIHR CRN CPMS 53429

NHS The Leeds Teaching Hospital NHS Trust

CAIN

Follow-up: 36 hours, 14 days, 30 days, 90 days and 6 months

Subjects who are 18 years of age or older with a diagnosis of a solid renal tumor.

Recruitment Target (n=20)

General and Imaging Eligible Criteria

Key Inclusion Criteria

- Subject diagnosed with primary renal cancer (biopsied proven 14 days prior to the index procedure)
- Tumor(s) must be ≤3 cm in longest diameter.
- Maximum of ONE tumors allowed for treatment regardless of number present.
- eGFR ≥45mL/min, ≤14 days prior to the planned index procedure date.
- Subject meets all the following functional criteria at ≤14 days prior to the planned index procedure date:
- • White Blood Cell (WBC) ≥3,000/mm3 • Absolute Neutrophil Count (ANC) ≥1,200/mm3 • Hemoglobin (Hgb) ≥9 g/dL • Platelet count ≥100,000/mm3 (≥100 10*9/L) • White Blood Count (WBC) ≤40 cells/µL via urinalysis • Albumin ≤300,000 mg/L via urinalysis

Key Exclusion Criteria

- Subject has planned cancer treatment prior to 30-day follow-up visit.
- Subject with genetic syndrome e.g. VHL, BHD etc. or solitary kidney.
- Targeted tumor with adequate margin overlaps the renal pelvis, main renal vessel, ureter, or other vital structure.

Co-Primary Endpoints

Primary Efficacy Endpoint: Technical Success at ≤ 36 hours

- Complete tumor coverage (CT/MRI)
- Adjudicated by imaging core lab

Primary Safety Endpoint: Major Complications up to 30 days post-procedure

- Index-procedure related adverse events defined as Clavien-Dindo Classification grade 3 or higher
- Adjudicated by Clinical Events Committee (CEC)

Patients and Methods

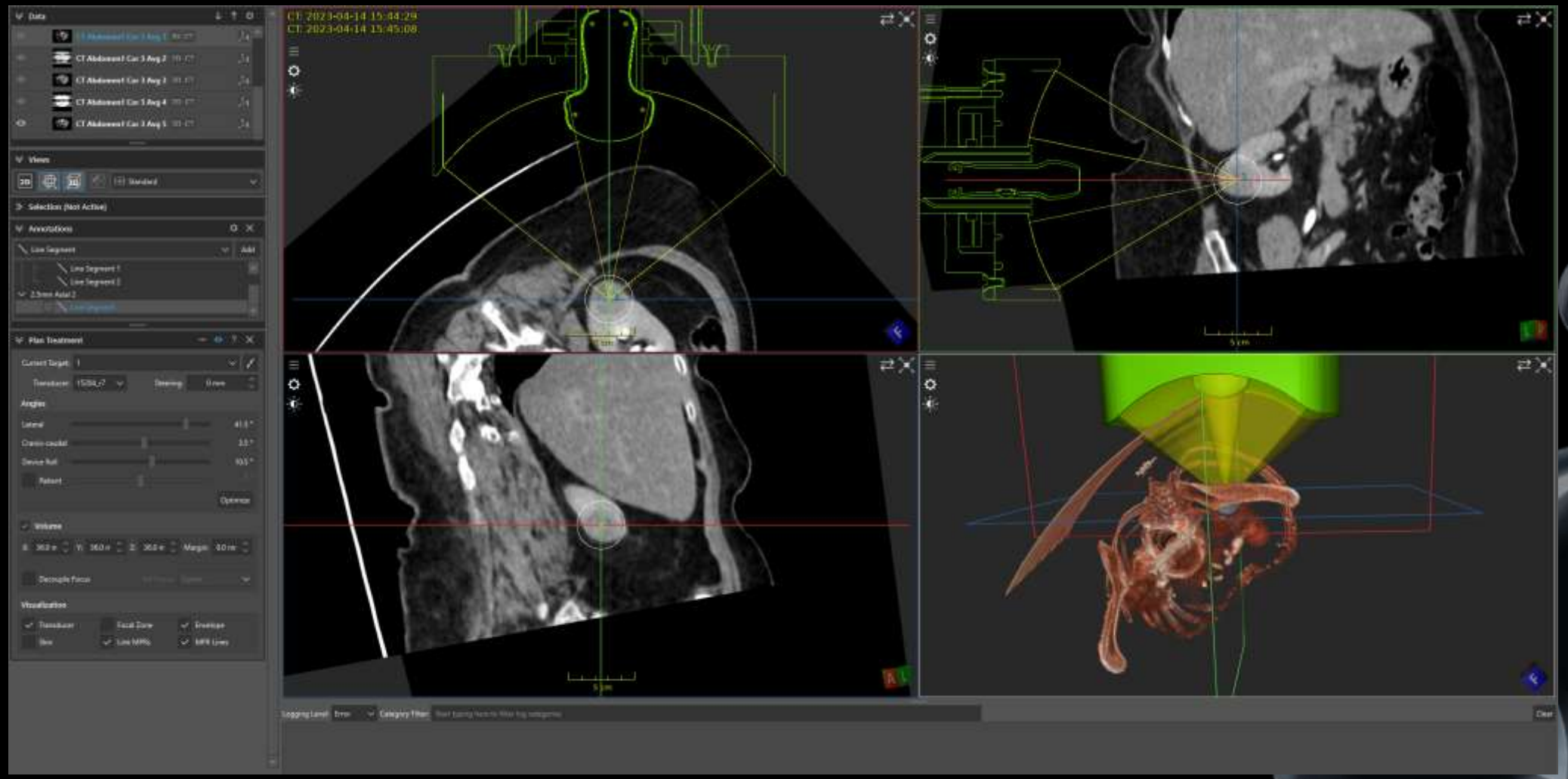
CAIN Trial: Screening for Participants

- Renal Cancer MDT – local and regional
- Caseload ~30-50/week
- Referral to image guided ablation (IGA) 16-20%
- Screening of the IGA group yield around 6-8% participants to be approached for further imaging screening with ultrasound at the outpatient clinic

CAIN Trial: Recruitment of Participants

- Interventional Oncology (IO) outpatient clinic
- Two stage approach
- First visit: approach patients for willingness to consider participation with ultrasound assessment to assess technical suitability
- Second visit: consent for formal recruitment with tentative treatment date in place

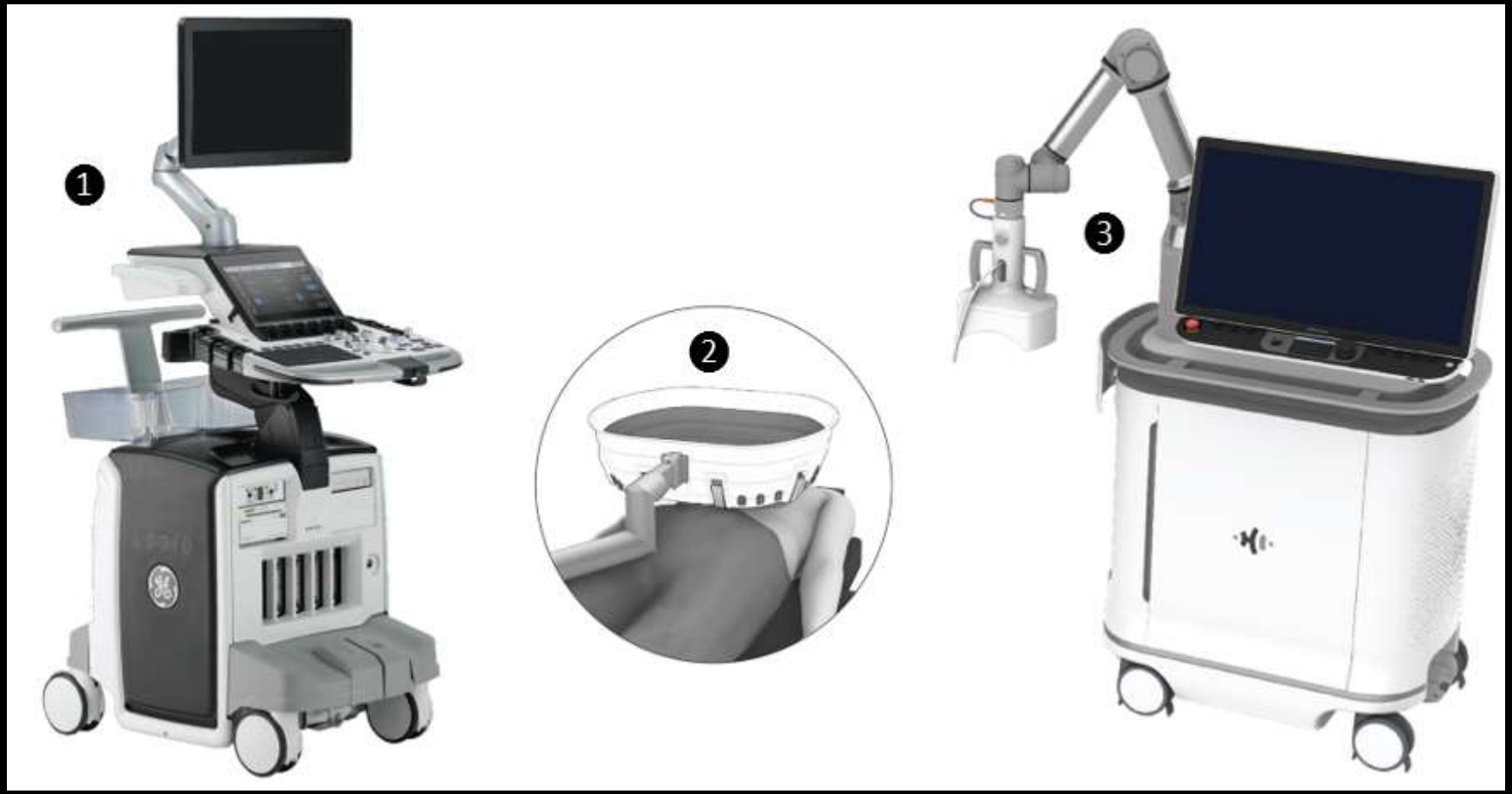
CAIN Trial: Treatment Planning



CAIN Trial: Histotripsy Treatment

- March 2023-March 2024 Cloud Breaker HistoSonics System
- March 2024- Dec 2024 now Edison HistoSonics System

Edison HistoSonics System



Courtesy of HistoSonics

Procedure related workflow

TARGET & LOCALIZE

1. Integrated ultrasound allows the user to target treatment area
2. 3D DICOM viewing and ultrasound/MRI/CT fusion and robotic image acquisition/navigation

PLAN

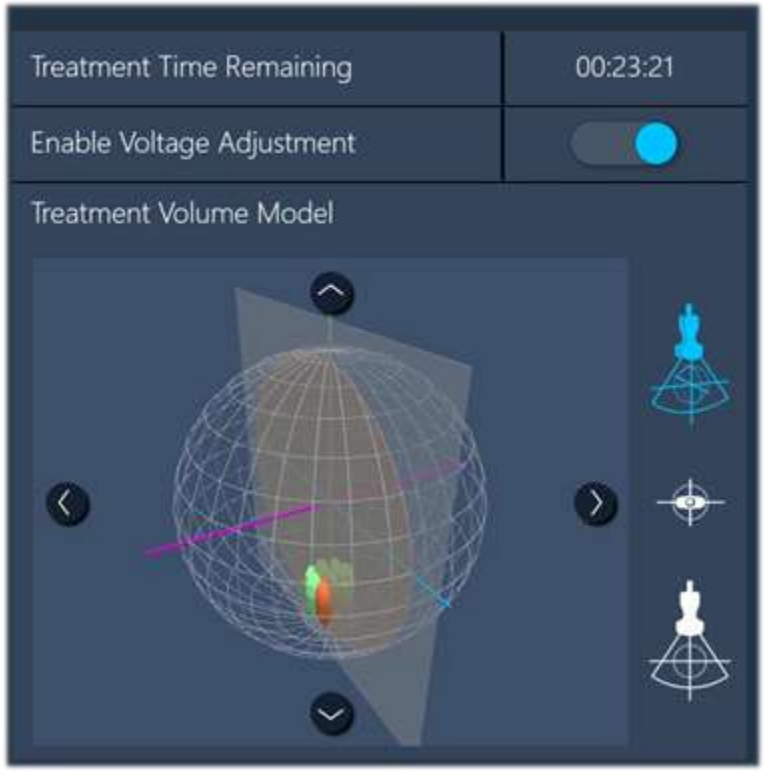
1. User contours and plans treatment (target/margin)
2. Cavitation threshold sensing used to determine patient specific treatment settings
3. Settings are set based on unique treatment scenario including target location/pathway and plan dimensions/shape

TREAT & MONITOR

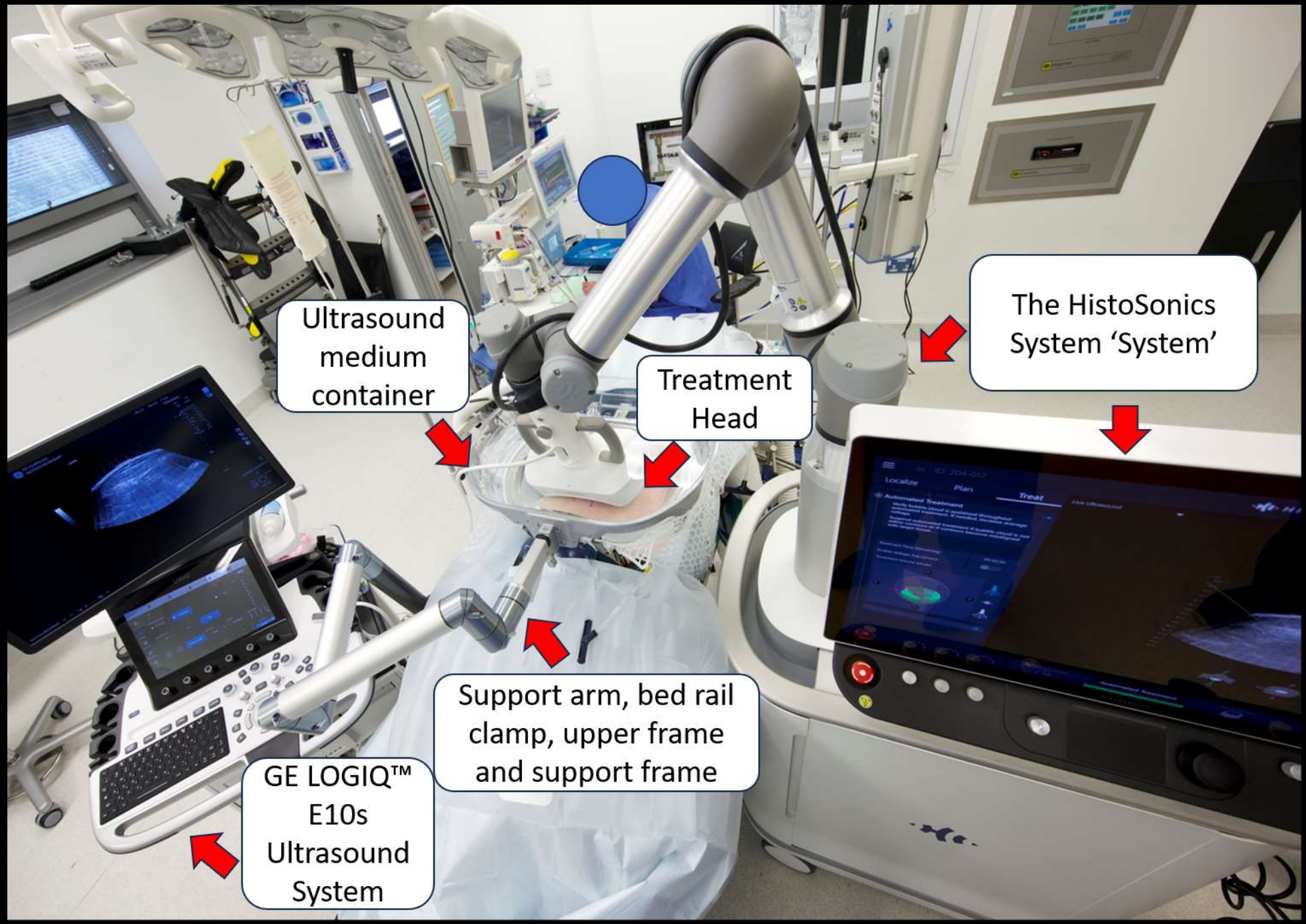
1. Dynamic amplitude treatment is delivered autonomously
2. Physicians monitor treatment bubble cloud and tissue effect in real-time
3. Systems provides real-time status/progress updates

Courtesy of HistoSonics

Automated Treatment with Continuous Visualization



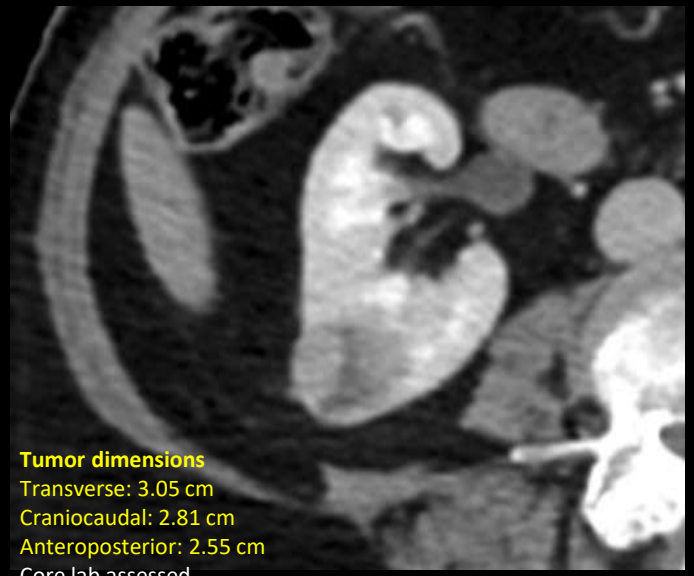
Courtesy of HistoSonics


Ultrasound medium container
Treatment Head
The HistoSonics System ‘System’
Support arm, bed rail clamp, upper frame and support frame
GE LOGIQ™ E10s Ultrasound System

Case Report

Case JP: Clinical History/Pre-treatment Imaging

Pre-Treatment



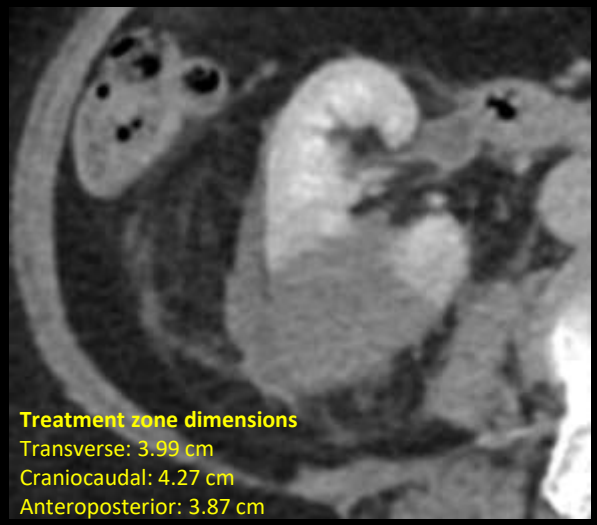
- 80-year-old female presented with a 3 cm clear cell renal cell carcinoma in the lower pole of the right kidney.
- The tumor was classified as low complexity based on the R.E.N.A.L. nephrometry score.

CAIN Trial is sponsored by HistoSonics, Inc. (Plymouth, MN, USA); Clinicaltrials.gov identifier NCT05432232 & NIHR CRN CPMS 53429

Treatment Options/Results

- Histotripsy treatment time was 83 minutes.
- No immediate complications were reported.
- Post-procedure CT imaging showed the histotripsy treatment zone completely covered the tumor and the treatment zone maximum diameter was 4.27 cm.

Post-Treatment (36 hr)



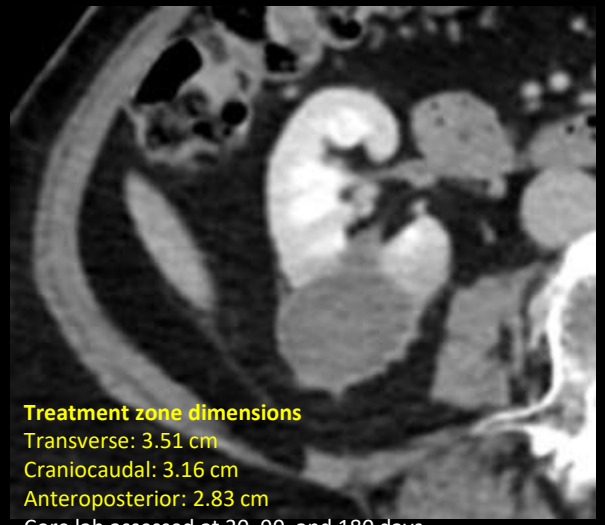
Core lab assessed

Preliminary data as of 20Mar2024; CAIN trial results subject to change based on continued data collection, monitoring, and adjudication.

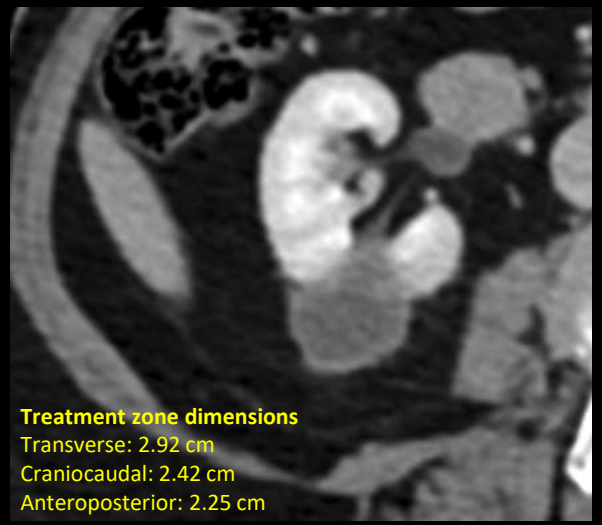
Treatment Options/Results

- There was no evidence of residual or recurrent tumor on CT imaging at 30-, 90-, or 180-day follow-up.
- No index procedure-related Clavien-Dindo Grade ≥3 complications were reported prior to study exit at 168 days.
- Four procedure-related minor complications (Grade I) were reported (haematuria, blister, lower abdominal pain, and vomiting).

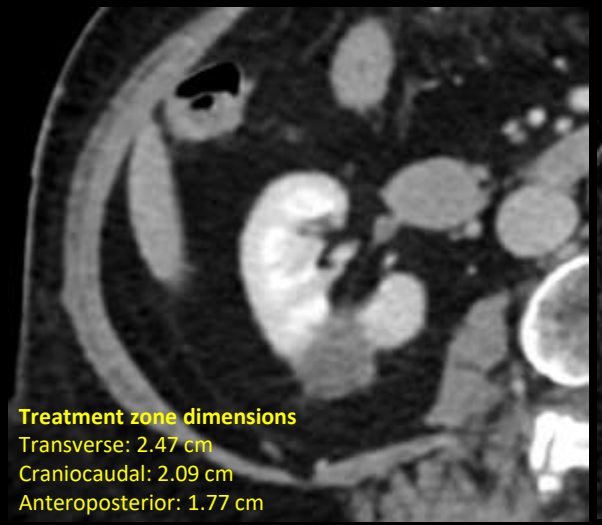
30 days



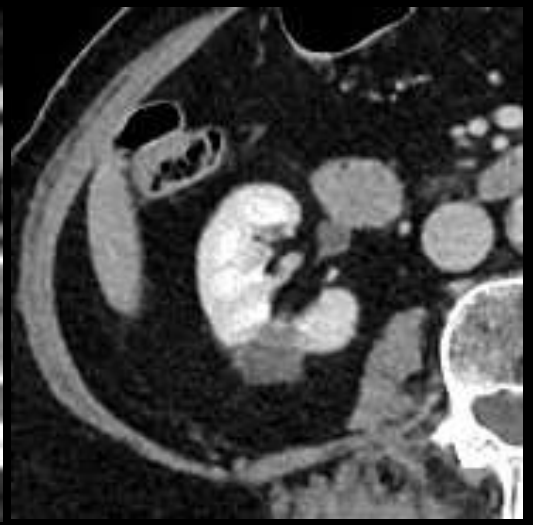
90 days



180 days



1 year



Core lab assessed at 30, 90, and 180 days

Preliminary data as of 20Mar2024; CAIN trial results subject to change based on continued data collection, monitoring, and adjudication.

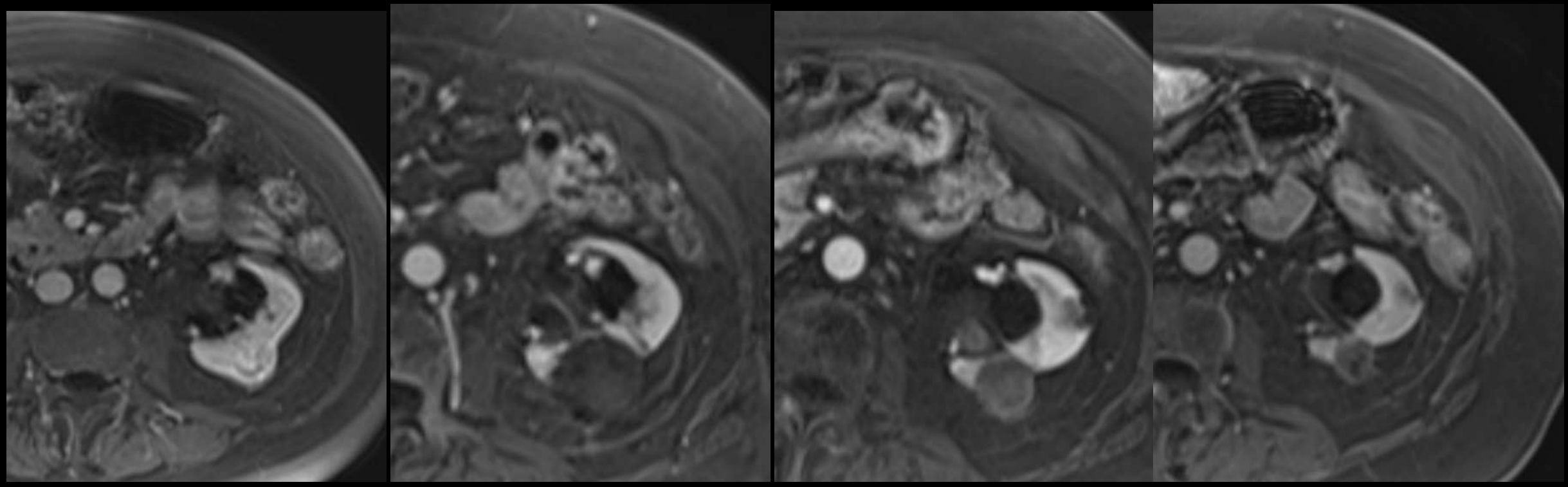
Discussion

- As with any new therapy, there is a learning curve when adopting histotripsy, which uses externally delivered energy, differentiating it from current IO procedures.

- Patient selection, pre-procedural planning, intra-procedural patient positioning and motion management are vital components to consider when embarking on this novel treatment in renal cancer.

Case BW: Global First Patient with Edison ‘Buzzsaw’ Cloud

81 years old had right renal CRYO and left renal Histotripsy



Baseline

36 hours

One month

Three months

Take Home Messages

- **#Hope4Liver trial**
  - FDA approval in October 2023
  - Awarded the Innovative Device Access Pathway (IDAP) by UK Government Feb 2024
- **CAIN trial**
  - Initial experience has shown safety and potential efficacy in treating renal tumour with image guided histotripsy
  - Pivotal study (#Hope4Kidney) to validate this further

Thank you

Contact emails:
tze.wah@nhs.net or T.M.Wah@leeds.ac.uk