

MECHANISMS AND APPLICATIONS OF BOILING HISTOTRIPSY FOR MECHANICAL TISSUE ABLATION IN HIFU

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OUTLINE

- ❖ High intensity focused ultrasound (HIFU): main principles and current challenges
- ❖ Histotripsy – HIFU-based mechanical ablation
 - Cavitation and boiling histotripsy: physical mechanisms
 - Advantages over thermal ablation
 - Instrumentation
- ❖ Clinical applications and preclinical studies of boiling histotripsy
 - Ablation of solid cancers: liver, kidney, pancreas, prostate
 - Evidence for enhanced anti-tumor immune response
 - Release of blood based biomarkers
 - Liquefaction of large hematomas for fine needle aspiration

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) THERAPY

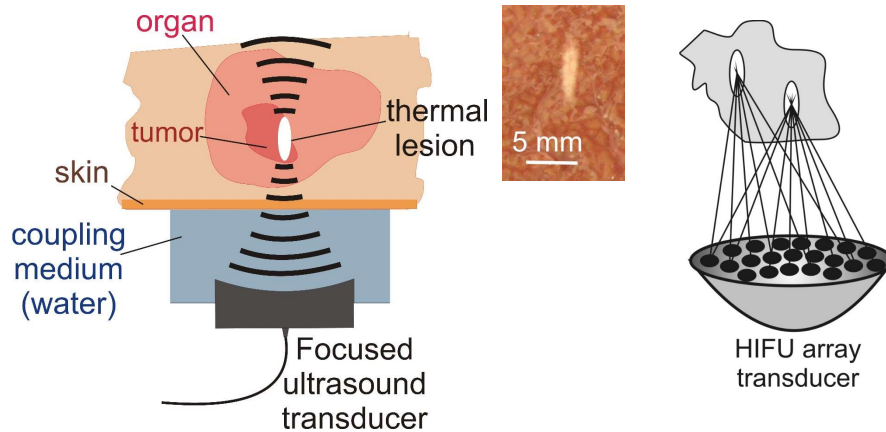
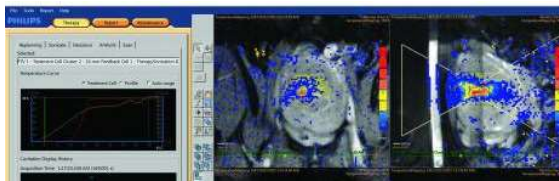


IMAGE GUIDANCE FOR HIFU ABLATION

MRI and MR thermometry

Based on proton resonance frequency shift



FDA-approved:

uterine fibroids
bone tumors
essential tremor

CE mark in Europe:

breast tumors
kidney and liver tumors
pancreas tumors

Challenges: costly, lengthy procedure

Insightech ExAblate

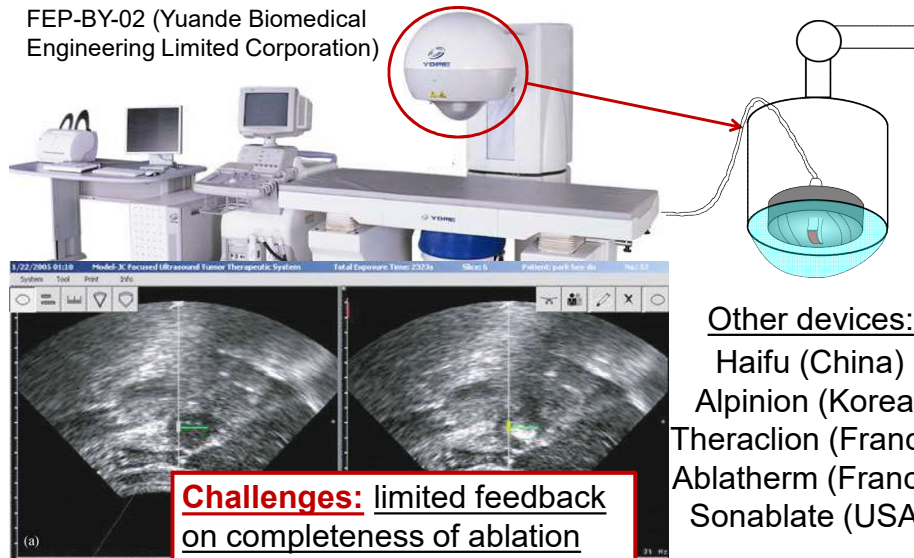


Philips Sonalleve



ULTRASOUND-GUIDED HIFU ABLATION

FEP-BY-02 (Yuande Biomedical Engineering Limited Corporation)



Other devices:
 Haifu (China)
 Alpinion (Korea)
 Theraclion (France)
 Ablatherm (France)
 Sonablate (USA)

CHALLENGES IN HIFU THERMAL ABLATION

- ❖ Near-field heating of the intervening tissues: ribs, skin, muscle, fat
- ❖ Heat sink effect in well vascularized targets: incompleteness of ablation (ultrasound-guided)
- ❖ Cost, lengthy procedure (MR-guided)

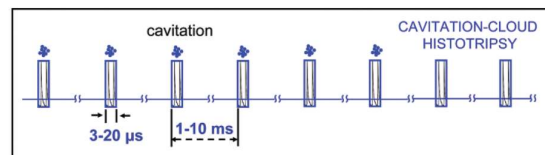
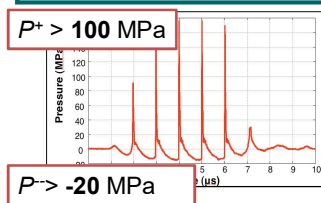
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HIFU FOR NON-INVASIVE TISSUE EROSION – “HISTOTRIPSY”

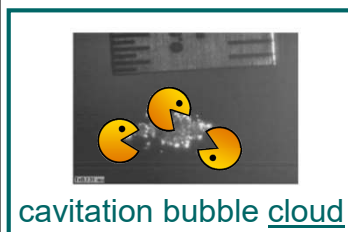
Mechanical damage to tissue without significant thermal effects

University of Michigan, since 2004

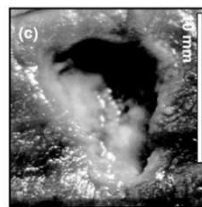


Fluid-filled void in tissue

Ultrasound guidance

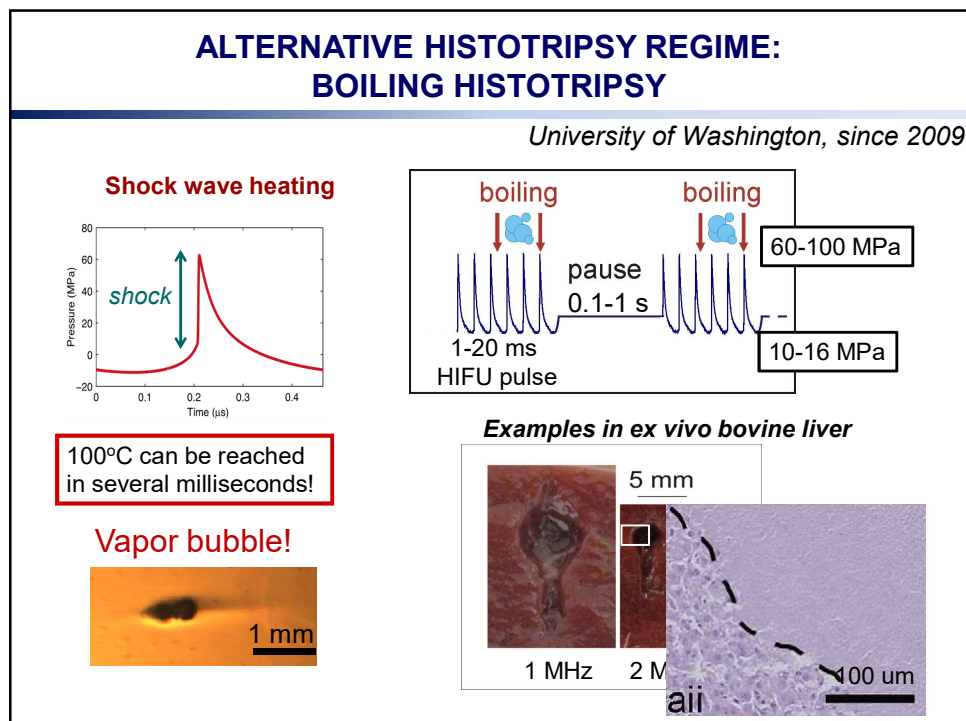
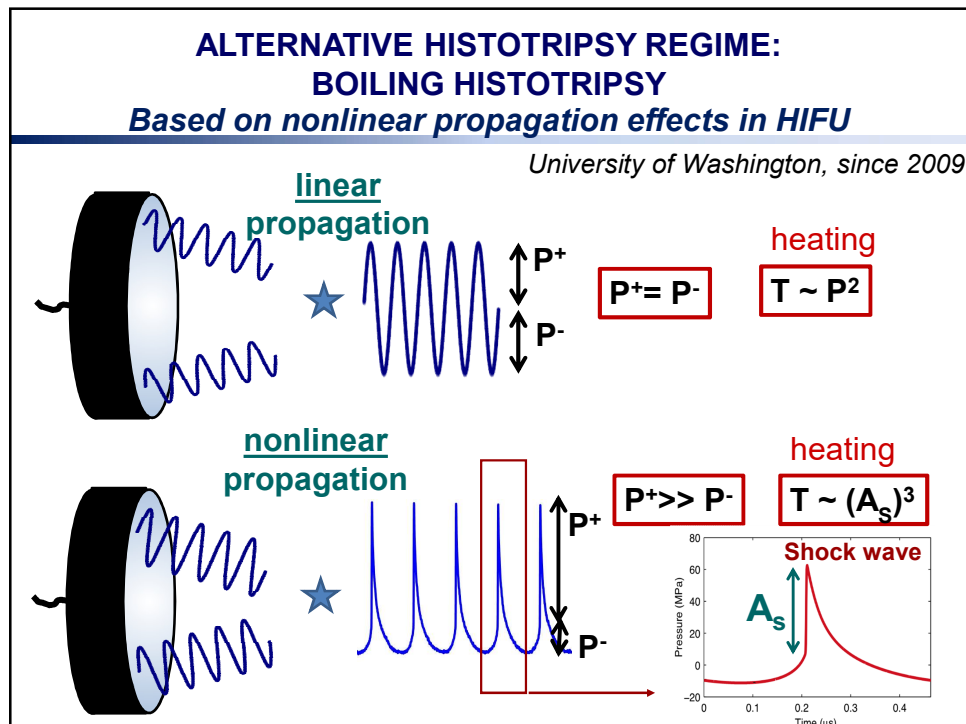


cavitation bubble cloud



UNIVERSITY OF MICHIGAN

Maxwell et al., Acoustics today 2012



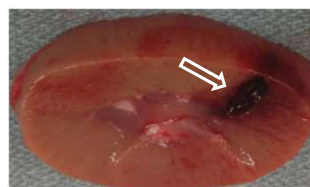
B-mode Ultrasound guidance

In vivo porcine kidney



Hyperechoic region
corresponds to vapor bubbles

Post-treatment



DIFFERENTIAL ABLATION THRESHOLD AND CONNECTIVE TISSUE STRUCTURE SPARING

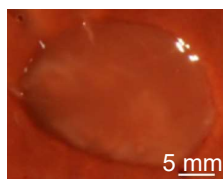
**Volumetric BH lesions
in ex-vivo bovine liver**
(produced by Phillips Sonalleve)

Treatment time: 30 min
Lesion volume: 6 cc

With contents

Contents removed

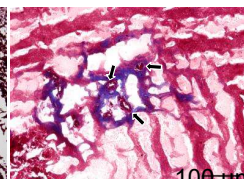
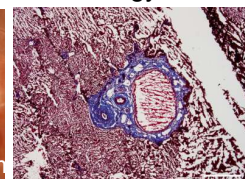
Histology: Masson's trichrome stain



5 mm



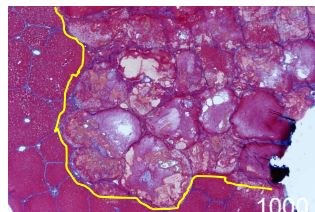
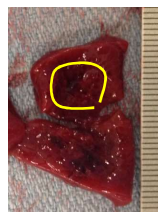
5 mm



100 μ m

All larger caliber vessels (~ 1 mm) and some of smaller (~ 100 μ m) vessels preserved

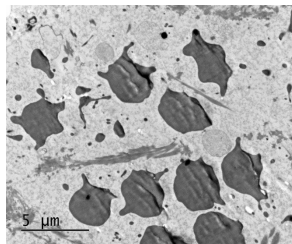
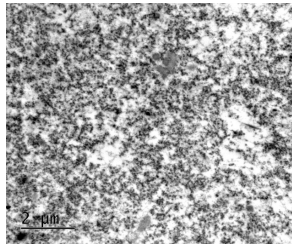
**Volumetric BH lesions
in-vivo porcine liver:**
lobules and ducts
preserved



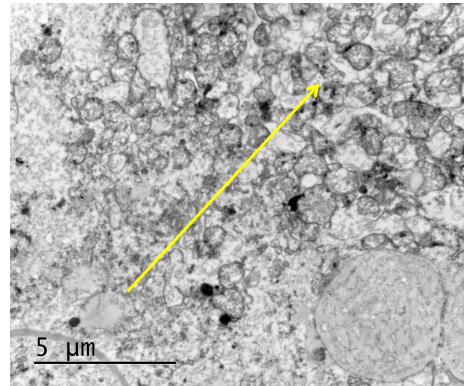
100 μ m

TEM IMAGING OF BOILING HISTOTRIPSY LESIONS

Lesion contents



Lesion border

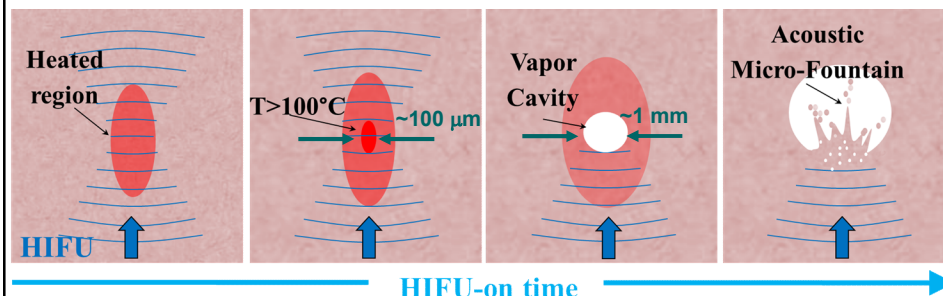


Transition zone from fully intact to completely destroyed tissue ~20 μm

MECHANISM OF TISSUE FRACTIONATION BY BOILING HISTOTRIPSY

How does a mm-sized bubble fractionate tissue down to subcellular level?

1. Shock-wave super-focusing and heating within ms to 100°C
2. Interaction of shocks with vapor cavity: acoustic micro-fountain and sub-surface cavitation

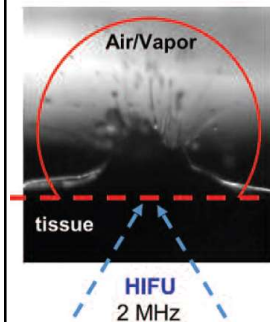


Why is there no measurable thermal effect?

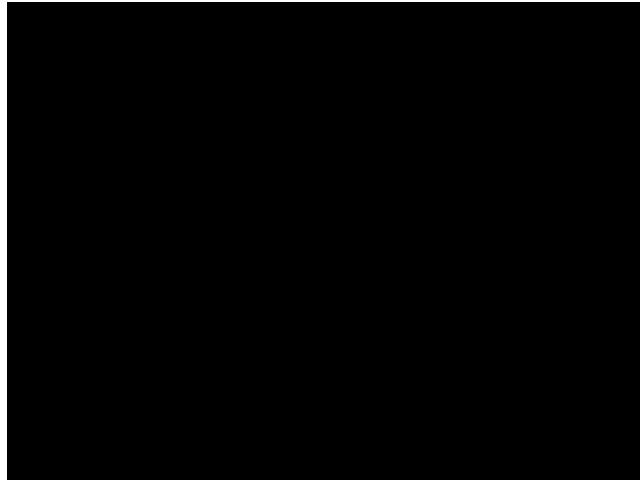
Super-heated area is much smaller (~100 μm) compared to the vapor bubble (~1 mm) and the resulting cavity (~2-5 mm)

Simon et al. Phys Med Biol 2012

EX-VIVO TISSUE ATOMIZATION BY HIFU



Focusing HIFU
on the free tissue-
air interface



Simon et al. Phys Med Biol 2012

ADVANTAGES OVER THERMAL HIFU

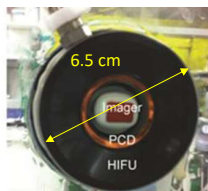
- ❖ Less potential for damaging intervening tissues (ribs, skin, muscle)
- ❖ Ablation not affected by heat-sink effect
- ❖ Real-time B-mode ultrasound imaging of the bubbles (hyperecho) and outcome (hypoecho)
- ❖ Sparing of connective tissue structures (ducts, vessels, fascial planes), tissue selectivity
- ❖ Tissue lysate resorbed without fibrosis
- ❖ Tumor lysate may provide benefits in terms of enhanced antitumor immune response

BOILING HISTOTRIPSY INSTRUMENTATION

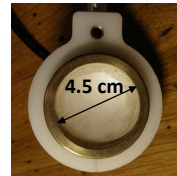
Pulse duration: 1-20 milliseconds
 Duty factor: 0.5-2%
 Transducer F#: 0.75 (90° sector) – 1.4 (40° sector)
 Frequency: 1-3 MHz
 Peak input power: 300 Watts – 4000 Watts



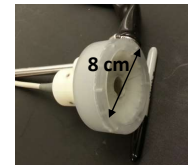
Philips Sonalleve
256-element
phased array



Alpinion VIFU2000
small animal system



+



+

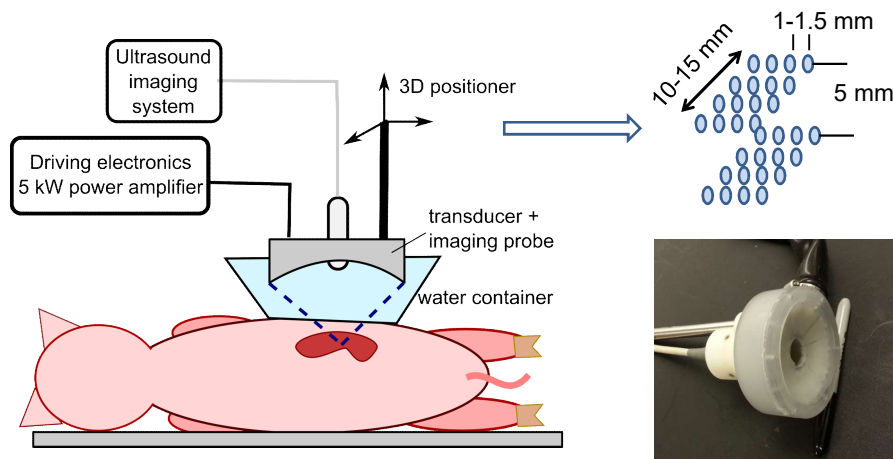


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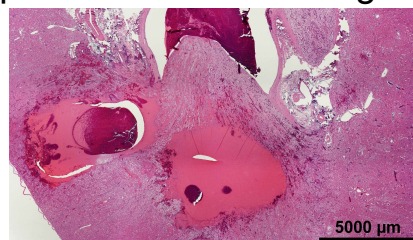
***In vivo* histotripsy of pig liver and kidney**

Goals: Evaluate feasibility of transcutaneous and transcostal ablation
Evaluate boiling histotripsy “dose” – number of pulses per spot – for different tissues

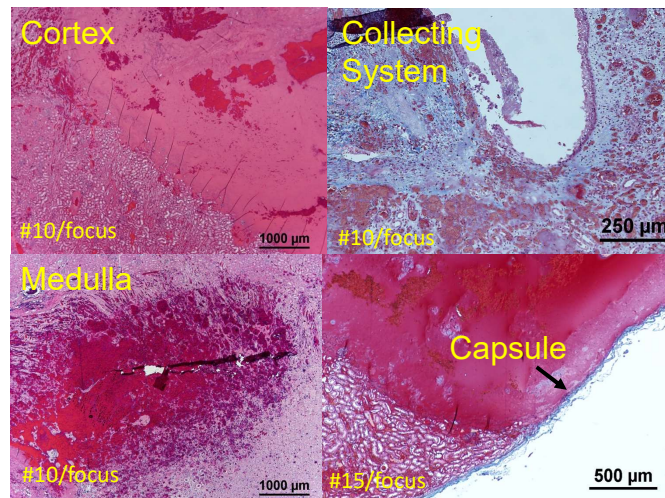


Results: kidney

- ❖ Treatment feasible in 11 targeted kidneys
 - Power threshold 600-1000W (2-fold vs *ex-vivo*)
 - 50% rib coverage feasible (additional 2-fold increase)
- ❖ No hematuria, no prefocal heating/bruising
- ❖ Differential sensitivities: cortex > medulla > collecting system > capsule
- ❖ Precise targeting despite no motion tracking
- ❖ Ablation rate
 - up to 27 cc/hour

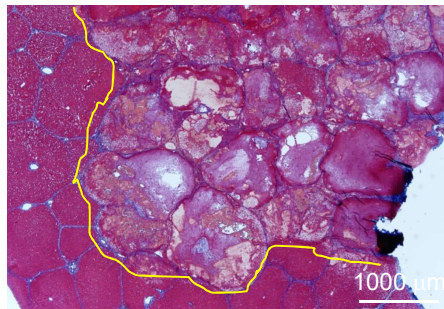


Differential sensitivities of renal tissues



Human renal tumor tissue more sensitive than benign renal tissues (separate ex vivo study)

Results: liver



- ❖ Lesion shape more irregular due to respiratory motion and lobular structure
- ❖ Lesion visualization more challenging
- ❖ At higher output powers, collateral damage to fat layer

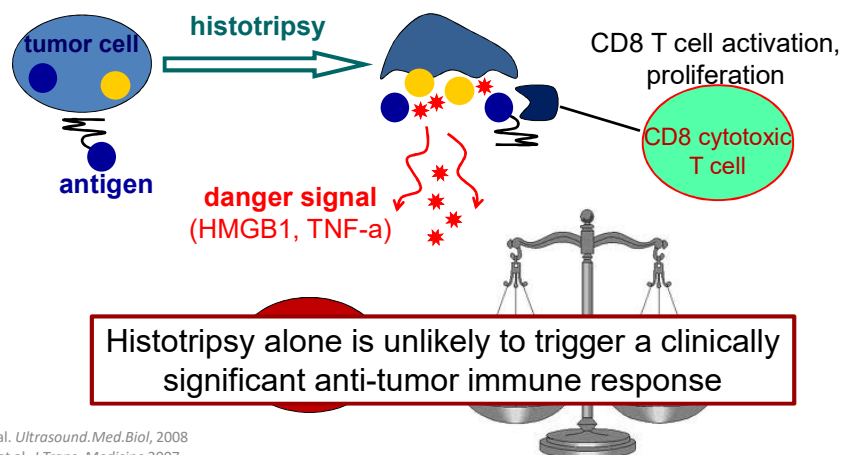
Challenge: aberration and defocusing by soft tissues, primarily fat
Aberration correction strategies needed

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HISTOTRIPSY-INDUCED IMMUNE RESPONSE

Hypothesis: mechanical effects of HIFU cause the response, which is CD8+ T-cell mediated



1.F. Wu et al. *Ultrasound Med Biol*, 2008
 2.P. Zhong et al. *J Trans. Medicine* 2007

ANIMAL MODEL : EKER RAT

Naturally occurring syndromic RCC model¹

Tsc2 tumor suppressor gene

Autosomal dominant: 100% penetrance by 1 yr

Similar biology to human clear cell^{2,3}

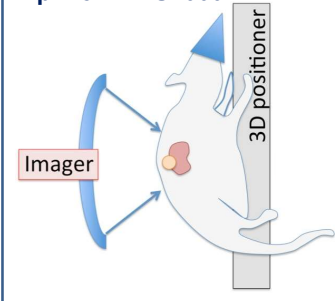
Upregulated HIF-2 α

Overexpression of VEGF

Increased MTOR signaling

Bilateral tumors, rare metastases

Alpinion VIFU2000



25-50% of the tumor liquefied by boiling histotripsy

Rats survived for 1,2,7,14 and 56 days

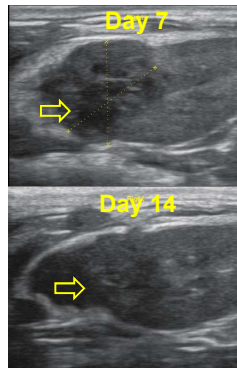
1) McDorman KS and Wolf DC. *Toxicol Path.* 2002; 30: 675-80.

2) Liu MY, et al. *Cancer Res* 2003; 63: 2675-80.

3) Habib SL, et al. *Genes Cancer* 2011; 2: 1051-60.

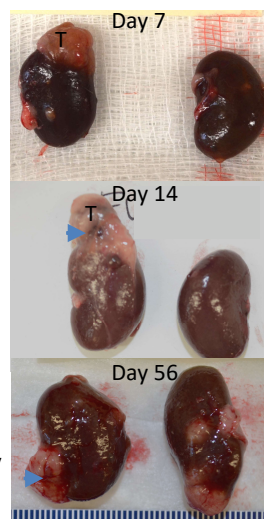
EVOLUTION OF THE TREATED AREA

B-mode ultrasound

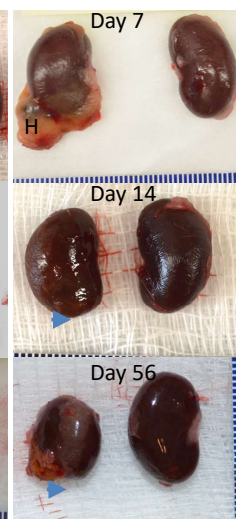


Hypoechoic cavity peaks on day 7
 - disappears by day 14
 - correlates with contraction grossly
Kidney appears healed by day 56

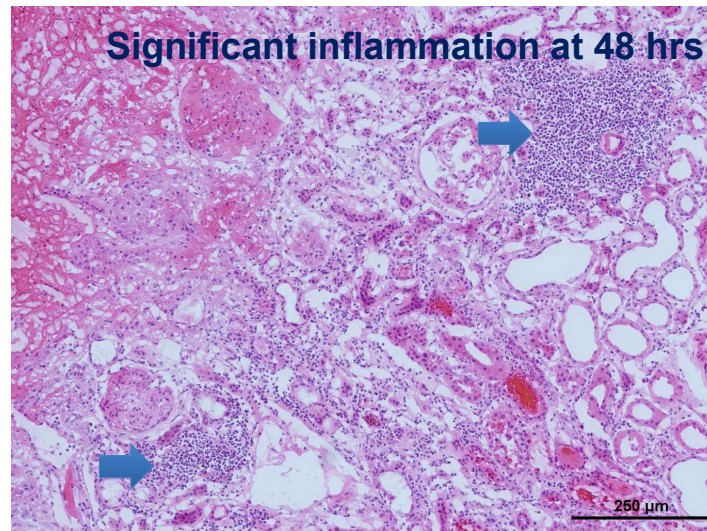
Eker rat



Wild-type rat

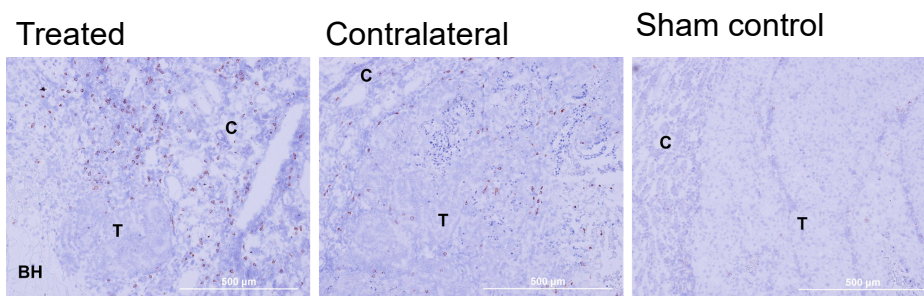


POST-TREATMENT INFLAMMATION



Tumor Infiltrating Leukocytes (48 h)

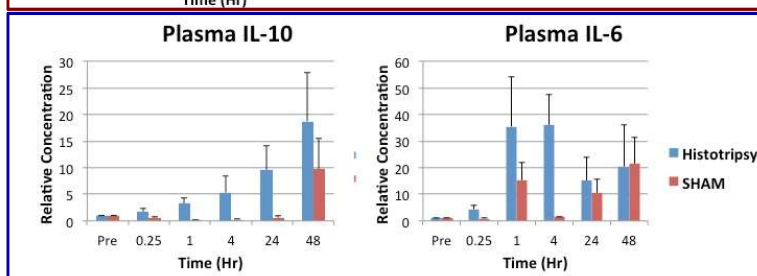
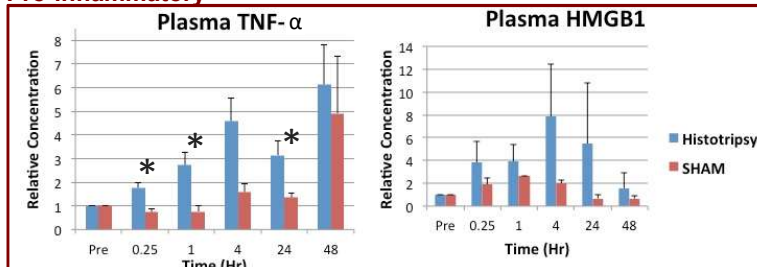
Immunohistochemistry: CD8+ T-cells (stained brown) increased in treated tumor and contralateral kidney, but not in sham-treated control



T=tumor, BH=liquefied lesion, C=benign kidney cortex

Plasma Cytokine Profile (up to 48 hrs)

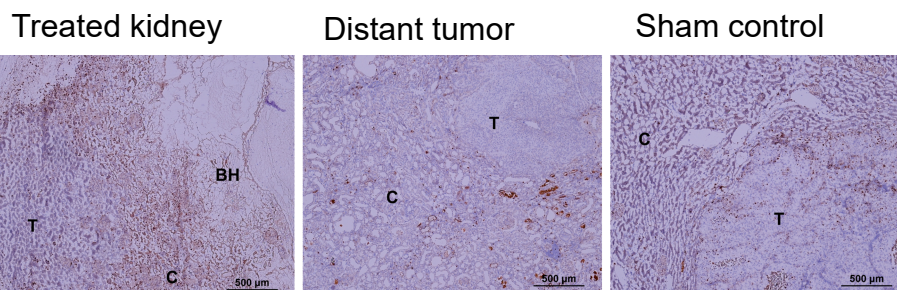
Pro-inflammatory



Anti-inflammatory

Proliferation marker Ki67 (48 h)

Boiling histotripsy ablation of the renal tumor does not appear to stimulate tumor proliferation



T=tumor, BH=liquefied lesion, C=benign kidney cortex

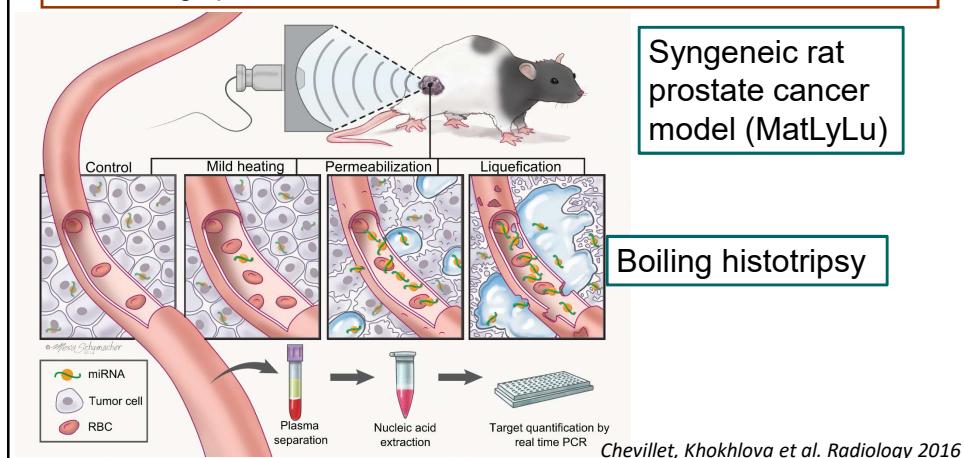
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BOILING HISTOTRIPSY AS NON-INVASIVE LIQUID BIOPSY TOOL

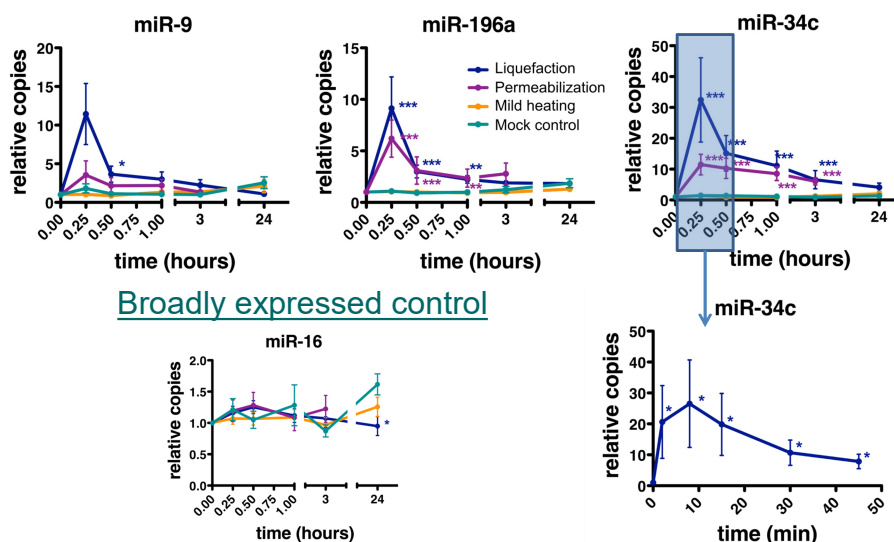
Blood-based cancer biomarker – a cancer-specific molecule secreted by the tumor into the patient's circulation

Problem: concentration of nucleic biomarkers (miRNA, mRNA, DNA) with high predictive value is often low, at the limit of detection



BH-STIMULATED TUMOR miRNA RELEASE

Tumor-associated miRNAs



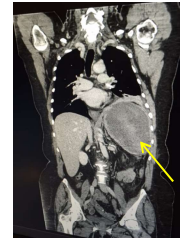
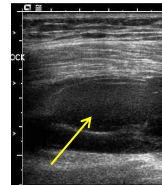
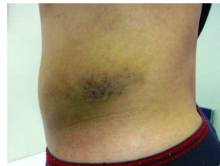
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Motivation

Hematoma – a collection of blood outside of blood vessels

Causes: sharp and blunt trauma, surgical procedures, muscle sprain and overuse in sports

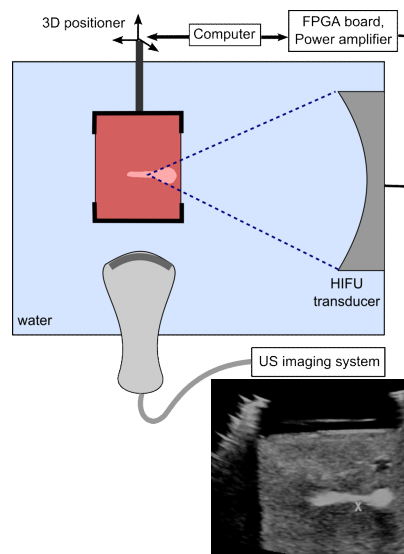


Health effects of large hematomas: PAIN, risk of infection, risk of compartment syndrome

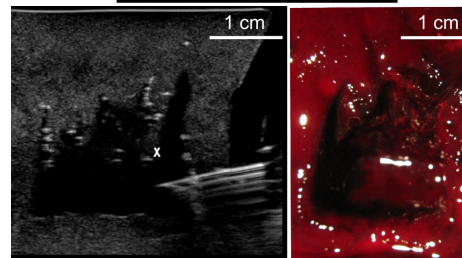
Clinical management: Rest, Immobilization, Compression, Elevation (RICE)
Indwelling catheters (ineffective)
Surgical evacuation (e.g. fasciotomy)

Goal: use histotripsy methods to rapidly (15-20 minutes) liquefy large (~20-50 cc's) hematoma volumes for fine needle aspiration

BH liquefaction of hematomas *in vitro*



Fine needle aspiration



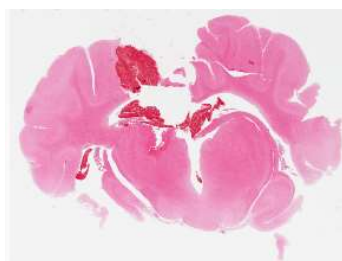
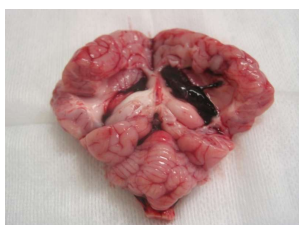
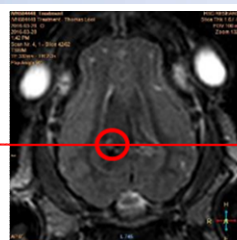
Liquefaction rate up to 1.3 cc/minute

Thrombolysis of Intraventricular Hemorrhagic Clot with BH

In vivo Porcine Study



Philips Sonalleve V1 system



Courtesy: T. Looi *et al.* ASA 2016

Hospital for Sick Children, University of Toronto

SUMMARY

- ❖ Boiling histotripsy is a non-invasive, non-thermal HIFU-based ablation method
- ❖ Can be implemented with existing clinical HIFU systems
- ❖ Precise treatment, sharp lesion borders
- ❖ Real-time and post treatment ultrasound guidance
- ❖ Differential threshold for damage depending on tissue type
- ❖ Liquefied tissue reabsorbs quickly without fibrosis
- ❖ Stimulates anti-tumor immune response

ACKNOWLEDGEMENTS

