

Thank you for the support!

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We thank all participating companies for providing equipment and materials for this workshop!



Ultrasound

Ultrasound waves are mechanical longitudinal pressure waves at a frequency above 20 kHz.





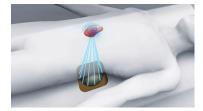
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Diagnostic ultrasound usually employs frequencies in the range of 5–20 MHz.

Lower frequency for industrial applications such as cleaning, plastic welding and bactericidal water purification.

Ultrasound

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The rapeutic ultrasound usually employs frequencies in the range of 1–4 MHz.

High Intensity Focused Ultrasound (HIFU)

High-Intensity Focused Ultrasound (HIFU or **FUS)** is a medical procedure that applies high-intensity focused sonic energy to locally heat and destroy diseased or damaged tissue through ablation.

HIFU is a hyperthermia therapy that uses temperature to treat diseases.

Other ultrasound treatment methods include ultrasoundassisted drug delivery, ultrasound hemostasis, ultrasound lithotripsy, and ultrasound-assisted thrombolysis.

High Intensity Focused Ultrasound (HIFU)

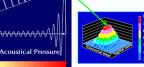
 HIFU therapy utilizes a localized focus of high intensity ultrasound

 \mathbf{D}

Local temperature rise is linearly dependent on the local HIFU intensity
 First publication 1942 (Lynn et al.)





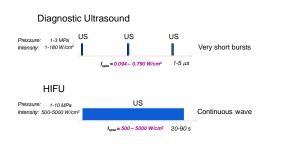




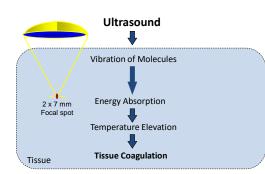


Diagnostic vs. Therapeutic Ultrasound

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Therapeutic US Interaction with Tissue



HIFU induced temperature increase

Pennes' bioheat transfer equation determines the tissue temperature rise induced by HIFU according to

$$\begin{split} \rho C_t \frac{\partial T(\vec{r},t)}{\partial t} &= k \nabla^2 T(\vec{r},t) - W_b C_b(T(\vec{r},t) - T_a) \\ &+ \alpha f \frac{|p(r,t)|^2}{\rho c} \end{split}$$

 $\begin{array}{l} \rho = \mbox{tissue density} \\ C_s = \mbox{tissue specific heat} \\ T = \mbox{tissue temperature} \\ k = \mbox{thermal conductivity} \\ W_u = \mbox{tissue perfusion} \\ C_b = \mbox{block specific heat} \\ T_a = \mbox{arterial block temperature} \\ a = \mbox{tissue absorption} \\ f = \mbox{ultrasound frequency} \\ p = \mbox{ultrasound pressure} \\ c = \mbox{ultrasound speed} \end{array}$

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• For a localized focus, the temperature rise will also be localized but slightly spread by heat conduction, also called heat diffusion

Advantages over other techniques

An important difference between HIFU and many other forms of focused energy, such as radiation therapy or radio surgery, is that the passage of ultrasound energy through tissue has no apparent cumulative effect on that tissue.

The absence of cumulative effects of HIFU on the treated tissue means that the treatment can be repeated in case of first HIFU treatment failure or partial treatment of the prostate.

As a non-ionizing treatment HIFU is also an option to treat cancer recurrence after radiation therapy failure.

Imaging guided HIFU

Clinical HIFU procedures are typically performed in conjunction with an imaging procedure to enable treatment planning and targeting before applying a therapeutic or ablative levels of ultrasound energy.

Monitoring required for a controlled therapeutic procedure Temperature monitoring can be provided by either MRI (MRIgHIFU) or ultrasound (USgHIFU) guidance

- MRI is much more accurate and reliable
- · First publications on MRI guided HIFU in 1992



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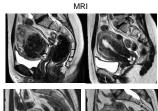
"On-line MRI monitored noninvasive ultrasound" by Hynynen K., Damianou C., Darkazanii A., Unger E., Levy M., Schenck J. in Proceedings of the annual international conference of the IEEE engineering in medicine and holicoy zooley.Ocabet 1992.
 "MR-guide Obusie ultrasound surgery", Olice HE, Schendu CF, Hynynen K. Waitrike RD, Sozza SP, Jusies FA, Journal of Computer Assisted Transgraphy (1992, 168);556-65]
 U.S. Pisetti FS2705. Bied on Mach H, 1992 The technology was later transferred to InsighTec in Halla Israel in 1998.

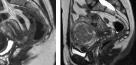
Imaging guided HIFU of Uterine Fibroids

Ultrasound









Computed Tomography

Courtesy of Lizette Warner, Ph.D.

MRI guided HIFU





MRI guided HIFU

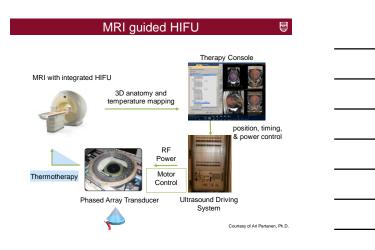
 MRI guided focused ultrasound therapy is based on ultrasound induced local hyperthermia with thermal monitoring using MRI



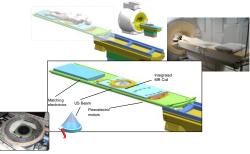
Courtesy of Ari Partanen, Ph.D.

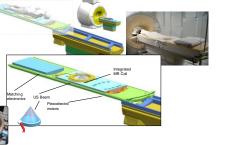
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MRI guided HIFU





MR Thermometry

- · Temperature rise can be measured with several MRI techniques as a number of different MR properties are temperature dependent
 - Spin density
 - T₁-constant
 - Diffusion coefficient
 - Water proton resonance frequency
 - Spectroscopy
 - Gd-contrast enhancement
 - etc.

MR Thermometry

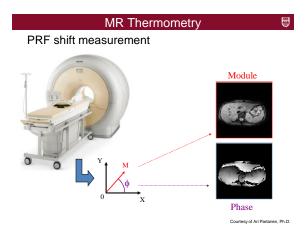
- MRI temperature measurement for HIFU is commonly based on the water proton resonance frequency shift which induces phase differences between dynamic frames.
- Proton resonance frequency shift of lipid hydrogens are independent of temperature. Temperature in lipids can not be measured with the PRF method → fat is suppressed
- · From MR dynamic phase images a relative temperature change can be calculated.



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MR Thermometry

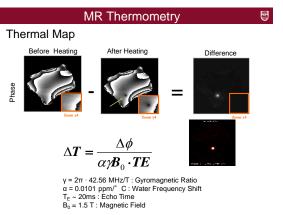
- · Proton Resonance Frequency shift
- · Temperature maps are calculated from phase differences between successive dynamic frames as

$$\Delta T = \frac{\Delta \phi}{\alpha \gamma B_0 \cdot TE}$$

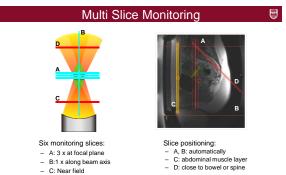
Water Frequency Shift Echo Time Magnetic Field

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· Temperature maps are calculated on-line during sonication and displayed as overlays on the magnitude image



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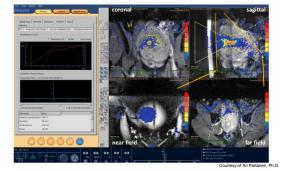
- D: Far field

Multi-shot EPI with TE=20ms, TR=37ms, resolution=2.5x2.5x7mm³, EPI-factor=11 and 121-binomial water-selective excitation; 2.9 s acquisition time for all 6 slices

Multi Slice Monitoring



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Temperature Map Corrections

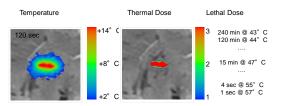
- · Baseline drift
 - Magnetic field drift is corrected for with a zero order correction
 - Uses unheated parts of the image as the baseline
- · Motion detection
 - Detection, no correction
 - Checks for intra-scan motion (changes in temperature std dev)
 - Gives a warning if motion is detected
 - Interscan motion has to be manually checked with $\ensuremath{\mathsf{MR}}$ scans

Thermal Dose

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- · Accumulated temperature over time
- · Tissue effects depend on temperature and time
- Tissue necrosis at 43°C over 240 min.
 - Definition of One Thermal Dose
 - Measure Thermal Dose in 240 equivalent minutes (EM)
 - Time for lethal dose halves with every degree temperature increase



Thermal Dose

• Thermal dose (TD) is calculated as a time integral of temperature increase (Arrhenius Equation), based on temperature maps

$$TD(t) = \overset{t}{0} r^{(43-T(t))} dt \qquad \begin{array}{c} r = 0.25(T < 43^{\circ}C) \\ r = 0.50(T > 43^{\circ}C) \end{array}$$

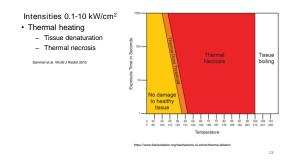
- 0
 240 EM (equivalent minutes) is commonly defined to indicate full and irreversible coagulative necrosis in muscle tissue
- 30 EM is often taken as the threshold for onset of thermal damage

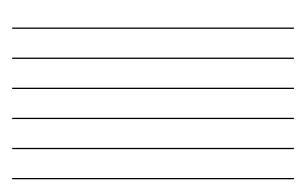
Thermal Dose Limits

- * $0-30 \text{ EM} \rightarrow \text{no thermal damage}$
- * $30-240 \text{ EM} \rightarrow \text{possible}$ thermal damage (mostly reversible)
 - edematous, fragmented cell membranes, varying damage to vasculature
- 240 EM < \rightarrow irreversible coagulative necrosis
 - Generalized thermal coagulation, fragmented cell membranes, necrotic vascularization => no perfusion in CE images
- · Limits depend on tissue type
 - e.g. Brain tissue is more sensitive to temperature than muscle tissue
- · HIFU may occlude blood vessels within the target region
 - Parts of uterine fibroids downstream of such an occlusion may appear non-perfused even though no thermal damage was inflicted to these areas

Thermal Ultrasound Therapy Effects

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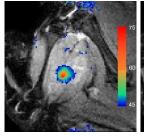


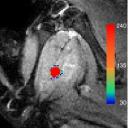


Thermal Map and Thermal Dose Map

Thermal Map (∆T^oC + 37^oC)

Thermal Dose Map (equivalent minutes at 43°C)





Courtesy of Ari Partanen, Ph.D.

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Macroscopic Tissue Effects

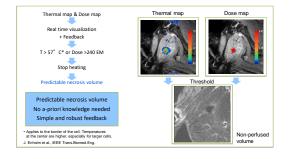


Real Time Feedback

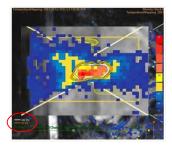


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Thermal Map and Thermal Dose Map



Temperature

- maps
- Discrete color scheme
 Easy to detect near field heating – yellow is getting critical

Iso-dose contours

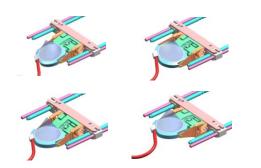
- Thermal dose 30 EM – edema zone
- (orange)
- 240 EM necrosis zone (white)

Focusing the Ultrasound Beam

Ultrasound can be focused into a small focal zone, either via

- 1. a lens (for example, a polystyrene lens), or
- 2. a curved transducer, or
- 3. a phased array
- 4. or any combination of the three

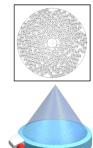
HIFU Transducer



Transducer

Phased Array Transducer

- 256 Independent channels
- Ultrasound Frequency: 1-1.5 MHzPower Max 300 Watts Acoustic
- Advantages
 - Allow electronic displacement along all directions (about ±2cm)
 - Very fast electronic displacement: position update < 10ms
 - Allow to heat a large area without transducer displacement
 - Allow temperature control over large volume



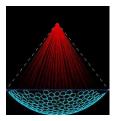
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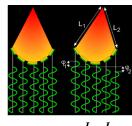
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HIFU Transducer

Electronic displacement of the focal point Phase change of the electronic signal moves the focal point





$$\varphi_2 - \varphi_1 = 2\pi \frac{L_2 - L_1}{\lambda}$$

HIFU Transducer

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High power output (up to 150 W) Adjustable frequency (1~10 MHz) Tailor-made transducers with various focal lengths, aperture sizes



HIFU Transducer

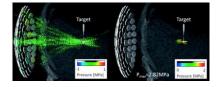
Tissue mimicking gel insonated with a HIFU transducer. The gel shows a lesion in the region of the ultrasonic focus due to the temperature rise.



HIFU Transducer

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Pressure calculation in the tissue mimicking gel insonated with a HIFU transducer.



HIFU Transducer

HIFU tabletop transducer





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Ablation Concepts

Traditional

·Point-by-point ablation •Challenge #1 - treatment time

- Ablation speed limit ~1 ml/ min - Excessive cooling times
- Long procedure times 3h+

•Challenge #2 - tissue properties

- Local variations in tissue properties Inhomogeneous absorption, attenuation, perfusion, diffusion
- - Irregular heating patterns
 Risk of incomplete coverage

Solutions

 Volumetric heating addressing #1 •Real-time feedback addressing #2



- · Point-by-point sonication method: the Treatment point do not change during the sonication
- · Volumetric sonication method: the Treatment point moves outwards from the treatment cell centre along a certain path (trajectory)
 - Single sonication time constant: Regular Cell
 - Single sonication time minimized: Feedback Cell
 - · Treatment point moves along its path, sonication is stopped when a certain predefined temperature and/or thermal dose is reached.

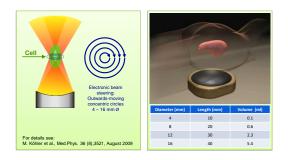
Treatment Cell (TC) is a treated tissue volume of a single sonication

Volumetric Heating

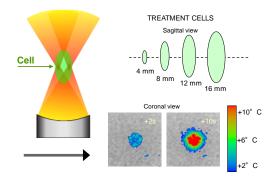
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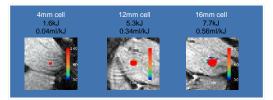
Volumetric Heating





Volumetric Heating

- Larger cells require a longer sonication duration at the same power level, meaning more energy
- · Resulting necrosis volume scales with cell size
- · Treatment energy efficiency improved with cell size



Courtesy of Ari Partanen, Ph.D.

Volumetric Treatment with Feedback

Thermal map & Dose map Real time visualization + Automatic control T > 57° C* or Dose >240 EM Stop heating Reliable necrosis volume



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Ph.D.

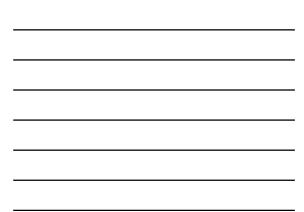
* Applies to the border of the cell. Temperatures at the center are higher, especially for larger cells.



Courtesy of Lizette Warner, Ph.I



https://www.fusfoundation.org/diseases-and-conditions/overview



Clinical Applications

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Uterine fibroids

HIFU treatment for uterine fibroids was approved by the US Food and Drug Administration (FDA) in October 2004.

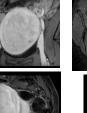
Most patients benefit from HIFU and symptomatic relief is sustained for two or more years. Up to 16-20% of patient will require an additional treatment.

Clinical Applications

Pre and post HIFU contrast Enhanced MRI of Uterine Fibroids

Left: Pre-procedure C+ cedure C+ MR-HIFU as indicate non-perfused







Very large uterine fibroid • 40/F, urinary frequency, pain • 123 x 103 x 92 mm³ = 599.5 ml

Treatment • Treatment time: 163 minutes • Ablation speed: 179 ml/h





Clinical Applications



Planning Fast TSE T2w 3D DRIVE

Uterine fibroid





Courtesy: Samsung Medical Center, Seoul, Korea & AIOG 2011;205:292.e1-5

Clinical Applications

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Functional Neuro Surgery

Transcranial Magnetic Resonance-guided Focused Ultrasound Surgery (tcMRgFUS) is a technology for the non-invasive treatment of various brain disorders such as Essential Tremor, Neuropathic Pain and Parkinson's Disease.

Preliminary results demonstrate the ability to effectively ablate targets deep in the brain with high precision.

Clinical Applications

Delivering drugs to brain

In current research, HIFU is being used to temporarily open the blood-brain barrier, allowing absorption of drugs into the brain. It is most effective when used in combination with a calcium channel blocker like verapamil.

Treatment of atrial fibrillation

HIFU has been used to treat the most common heart arrhythmia, atrial fibrillation (AF). A minimally invasive catheter based system designed to ablate heart tissue responsible for propagating AF has been approved for use in Europe and is undergoing an FDA approved phase III pivotal efficacy trial in the United States.

Clinical Applications

Cancers

HIFU has been successfully applied in treatment of cancer to destroy solid tumors of the bone, brain, breast, liver, pancreas, rectum, kidney, testes, prostate. At this stage, cancer treatments are still in the investigatory phases as there is a need to find more about their effectiveness.

HIFU has been found to offer palliative care. CE approval had been given in the past for palliative treatment of bone metastasis and recently Insightec's ExAblate received also FDA approval. Experimentally, a palliative effect was found in cases of advanced pancreatic cancer.

Several thousand patients with different types of tumors have been treated in China with HIFU using ultrasound imageguided devices built by several different companies.

Clinical Applications

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Prostate cancer

HIFU prostate treatment is administered through a trans-rectal probe and relies on heat developed by focusing ultrasound waves.

Promising results approaching those of surgery have been reported in large series of prostate cancer patients. These treatments are performed under ultrasound imaging guidance, which allows for treatment planning and some minimal indication of the energy deposition.

Transrectal MR-HIFU of the Prostate



Clinical Applications

Prostate cancer

HIFU may also be used to ablate the entire prostate gland using a transrectal probe. This is an outpatient procedure that usually lasts 1-3 hours. First results show that it greatly reduces some of the side effects common with other treatments for prostate cancer.

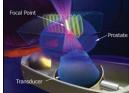
During HIFU, the entire prostate is ablated, including the prostatic urethra.

While the urethra is an important anatomical structure, the sphincter and bladder neck are more important to maintaining the urinary function. During HIFU the sphincter and bladder neck have to be identified and avoided.

Transrectal MR-HIFU of the Prostate

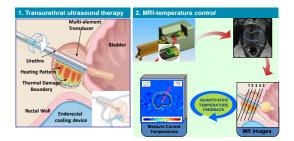
Transrectal HIFU uses sound waves produced by a rectal probe to ablate cancer. Since the urethra runs through the treatment area, urinary infections, bladder obstruction, and incontinence are relatively common side effects.





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Transurethral MR-HIFU of the Prostate 5



Courtesy of Ari Partanen, Ph.D.

Transurethral

8 elements

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Transurethral Applicator



Table top assembly (on standard Achieva table top):

Transducer catheter in holder and rotation device (white)
Positioning system (grey), Interface box (pink)

Courtesy of Ari Partanen, Ph.D.

Transurethral Applicator



-Axially rotating applicator under robotic control -Eight colinear 0.5cm elements (f= 3Mhz, max P_{ac}= 4W) -Cooling via circulating degassed water

Courtesy of Ari Partanen, Ph.D.

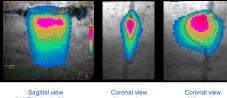
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Transurethral Applicator

Phantom study

Real-time temperature imaging with simultaneous sonication and motor rotation



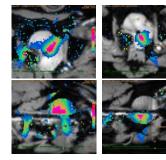
Sagittal view 240 EM depth: 50 mm (necrosis zone, white) (Transducer visible as signal void)

Coronal view No rotation 240 EM depth: 40 mm

Coronal view 90° rotation 240 EM depth: 55 mm

Preliminary Results





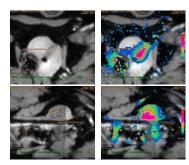
Axial temperature

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Sagittal temperature

Preliminary Results

Dose images



HIFU Mediated Drug Delivery

HIFU may be used to create high temperatures not necessarily to treat the cancer alone, but in conjunction with targeted delivery of cancer drugs.

For example, HIFU and other devices may be used to activate temperature-sensitive liposomes, filled with cancer drug "cargo" to release the drug in high concentrations only at the tumor site(s) only where triggered to do so by the hyperthermia device.

This novel approach is resulting in drug concentrations 10 times or more than traditional chemo with a fraction of the side effects since the drug is not released system-wide.



Journal of Controlled Release, Volume 161, Issue 2, Pages 317-327 (2012). ThermoDox, a heat-sensitive liposcome, rapidly changes structure when heated to a specific temperature, creating openings which release downubicin directly into the targeted tumor.

HIFU Mediated Drug Delivery

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HIFU with special drug delivery vehicles, called lowtemperature-sensitive liposomes (LTSL), to more effectively deliver chemotherapy to tumors.

These LTSL circulate in the blood stream and release contents (i.e. chemotherapy) above ~40 °C, allowing localized chemotherapy delivery to cells in tissue regions (e.g. tumor) that are heated by HIFU.

Since drugs and radiation are often ineffective in central regions of large tumors that are poorly perfused, HIFU could be employed to directly destroy these central regions while drugs released from LTSL kill cancer cells in surrounding regions.

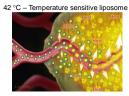
HIFU Mediated Drug Delivery

Liposomes: Temperature sensitive nanoparticles

- · Temperature sensitive liposomes (TSL) rapidly release their therapeutic payload with heat
 - For use with low temperature hyperthermia (40 45 °C)
 Enhanced drug delivery
 - For use with ablative hyperthermia (> 60 °C)
 - Deposit drug in thermal margin → Increase treatment volume

37 °C – Stealth liposome





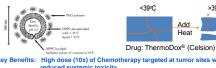
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HIFU Mediated Drug Delivery

<39°C

Low Temperature Sensitive Liposomes (TSL) - Hyperthermia







≈Release rates

· Stable for > 7 days



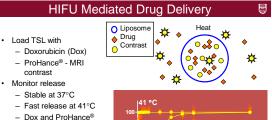


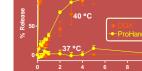
Add Heat

Drug extravasates under HIFU Heat & Pressure

Drug released locally by HIFU Heat & Pressure

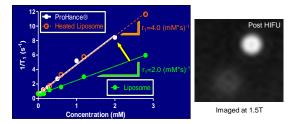
>39°C



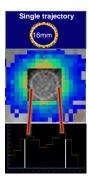


HIFU Mediated Drug Delivery

- Relaxivity
 ¹ (2x) with heating
- Relaxivity of heated liposome~ProHance®
- · Release is visualized with MR-HIFU



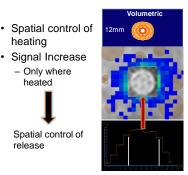
HIFU Mediated Drug Delivery



heating Signal Increase - Only where

heated

Spatial control of release



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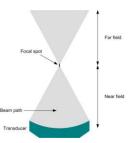
Limitations of HIFU

- - avoided in beam path
- Scar tissue is also problematic due to high absorption and lack of perfusion

 - Rapid heating and no cooling mechanism through perfusion (only cooling through heat diffusion)
 Large scars, cesarean sections, etc. must be avoided in beam-path

Limitations of HIFU

- · Scars, bone, metallic objects, and air-filled cavities in the high-energy near-field part of the beam path need to be avoided
- · Objects can be within the beam path in the far-field - Provided distance from focus is sufficient so that little energy remains in the beam



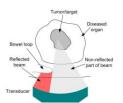
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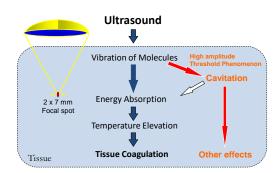
Limitations of HIFU

Air filled cavities

- · Ultrasound cannot propagate in air Ultrasound waves that encounter a tissue-air interface will be fully -reflected
 Reflected beam is also partially
- absorbed in tissue
- absorbed in tissue Can cause unpredictably large temperature rise in tissues close to air-interfaces Air-pockets, skin-folds, belly-button, bowels, intestines, lungs, etc. must be avoided in beam path since temperature rise may be fast and unexpected



Therapeutic US Interaction with Tissue 5





What is cavitation?

- · Interaction of ultrasound field and microbubbles within a medium or tissue
- · Oscillation of bubbles
 - Stable or non-inertial cavitation → sub-harmonic US emission
 - · Stable oscillation



- Instable or inertial cavitation → broadband US emission
 - · Typically fast bubble growth and violent collapse
 - · Mechanical tissue damage, thermal effects, free radicals



Cavitation

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Cavitation in HIFU

- Harmful inertial cavitation is unlikely with diagnostic ultrasound, but may occur at intensities used in HIFU
- Factors increasing risk of cavitation:
 - High sonication power/intensity
 Pre-existing bubbles in beam path
 - Long pulse lengths or continuous wave sonication (such as in HIFU)

 - High temperatures
 - Low ultrasound frequency
- · Risk of thermal effects of cavitation may be reduced by: using degassed water/gel and avoiding bubbles within the ultrasound beam path
 - using high ultrasound frequencies
- · Risks may be mitigated using cavitation detection - i.e. listening for broadband emission

Tissue Liquefaction with Histotripsy

Most clinically advanced focused ultrasound therapies use heat to destroy unhealthy tissue, histotripsy is a non-thermal ultrasonic method that mechanically destroys target tissue using high intensity pulses from 2 to 20 microseconds in length. Histotripsy controls cavitation to mechanically fractionate soft tissue through high pressure (>10 MPa), short duration (<20 $\mu s)$ ultrasound pulses at low duty cycles (<1%).

- Mechanical ablation with shock-induced microbubble clouds¹ Clinical trial to treat benign prostatic hyperplasia²
- 3ader Ultrasound Med Biol 2016

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· Need methods to monitor treatment progress Limited heating observed with histotripsy³
 Need mechanical equivalent to thermal dose



Khokhlova et al. Int J Hyper 2015 ClinicalTrials.gov Identifier: NCT01896973 Kieran J Utol 2007



Summary

High-Intensity Focused Ultrasound (HIFU) is a hyperthermia therapy procedure that applies highintensity focused sonic energy to locally heat and destroy diseased or damaged tissue through ablation.

Temperature monitoring for a controlled therapeutic procedure can be provided by MRI (MRIgHIFU).

MRIgHIFU can be used to effectively deliver chemotherapy to tumors with temperature-sensitive liposomes.

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- 4. American Institute of Ultrasound in Medicine (AIUM)
- 5 Philips Healthcare

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