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Diagnostic Ultrasound Imaging Quality Control and High-Intensity Focused Ultrasound Therapy Hands-on Workshop

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THE UNIVERSITY OF
CHICAGO

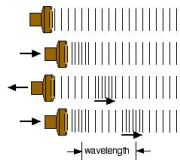
Thank you for the support!

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



Ultrasound

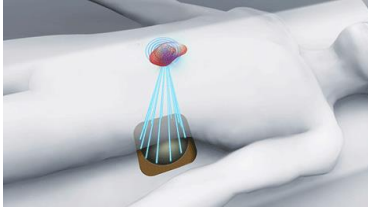
Ultrasound waves are mechanical longitudinal pressure waves at a frequency above 20 kHz



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



Therapeutic 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.

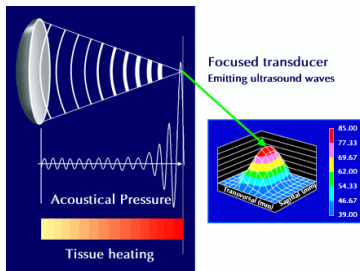
HIFU is a hyperthermia therapy that uses temperature to treat diseases.



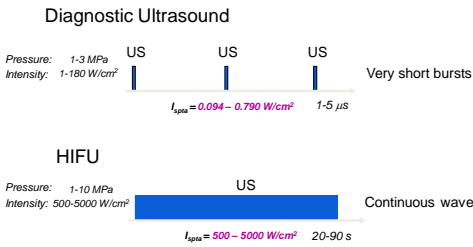
Other ultrasound treatment methods include ultrasound-assisted drug delivery, ultrasound hemostasis, ultrasound lithotripsy, and ultrasound-assisted thrombolysis.

High Intensity Focused Ultrasound (HIFU)

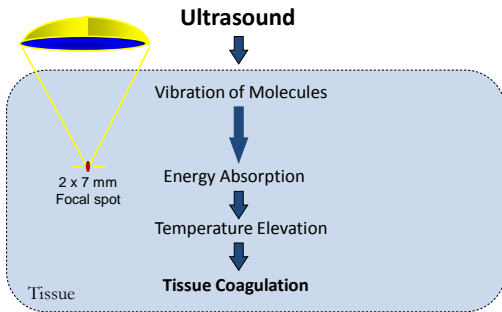
- HIFU therapy utilizes a localized focus of high intensity ultrasound
 - Local temperature rise is linearly dependent on the local HIFU intensity
 - First publication 1942 (Lynn et al.)



Diagnostic vs. Therapeutic Ultrasound



Therapeutic US Interaction with Tissue



HIFU induced temperature increase

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

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

ρ = tissue density
 C_i = tissue specific heat
 T = tissue temperature
 k = thermal conductivity
 W_b = tissue perfusion
 C_b = blood specific heat
 T_a = arterial blood temperature
 α = tissue absorption
 f = ultrasound frequency
 p = ultrasound pressure
 c = ultrasound speed

- 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 effect 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



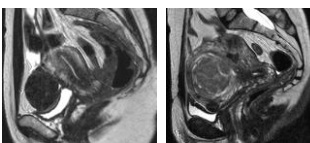
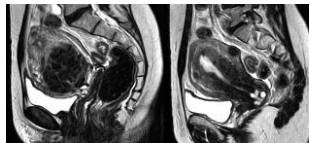
1. "On-line MRI monitored noninvasive ultrasound" by Hyyrynen K., Damianou C., Darkazanli A., Unger E., Levy M., Schenck J. in Proceedings of the annual international conference of the IEEE engineering in medicine and biology society/October 1992.
2. "MR-guided focused ultrasound surgery," Oline HE, Schenck JF, Hyyrynen K, Watkins RD, Souza SP, Jolesz FA. Journal of Computer Assisted Tomography [1992, 16(6):556-65]
3. U.S. Patent #5247935. filed on March 19, 1992. The technology was later transferred to InVivoSight in Haifa, Israel in 1998.

Imaging guided HIFU of Uterine Fibroids

Ultrasound

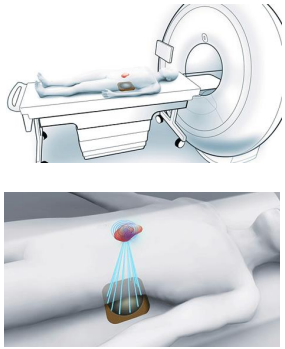


MRI



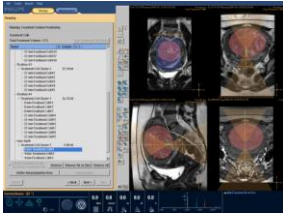
Courtesy of Lizette Warner, Ph.D.

MRI guided HIFU



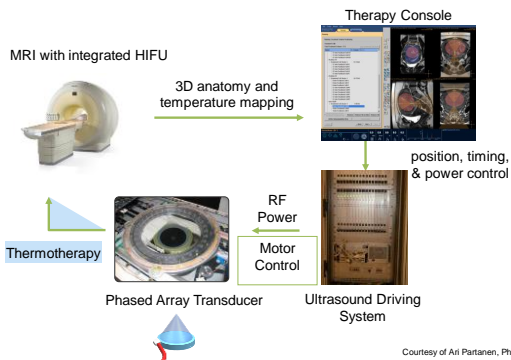
MRI guided HIFU

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



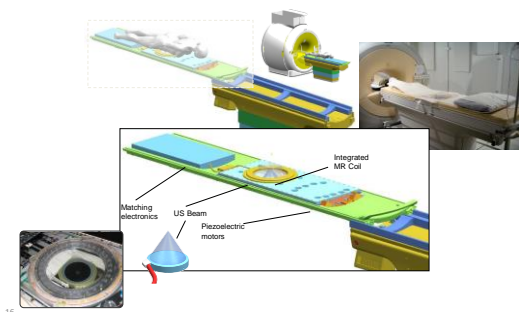
Courtesy of Ari Partanen, Ph.D.

MRI guided HIFU



Courtesy of Ari Partanen, Ph.D.

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
 - T_1 -constant
 - Diffusion coefficient
 - Water proton resonance frequency
 - Spectroscopy
 - Gd-contrast enhancement
 - etc.

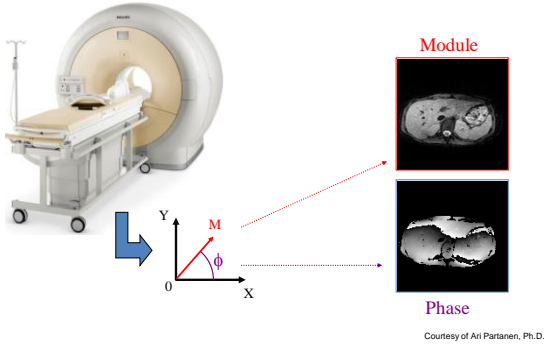


MR Thermometry

- MRI temperature measurement 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

MR Thermometry

PRF shift measurement



MR Thermometry

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

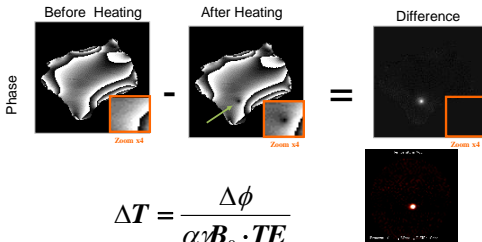
$$\Delta T = \frac{\Delta\phi}{\alpha\gamma B_0 \cdot TE}$$

$\gamma = 2\pi \cdot 42.56 \text{ MHz/T}$ Gyromagnetic Ratio
 $\alpha = 0.0101 \text{ ppm/}^\circ\text{C}$ Water Frequency Shift
 $T_E = 20\text{ms}$ Echo Time
 $B_0 = 1.5\text{T}$ Magnetic Field

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

MR Thermometry

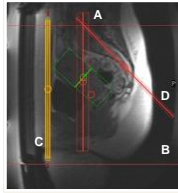
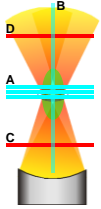
Thermal Map



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

$\gamma = 2\pi \cdot 42.56 \text{ MHz/T}$: Gyromagnetic Ratio
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Multi Slice Monitoring

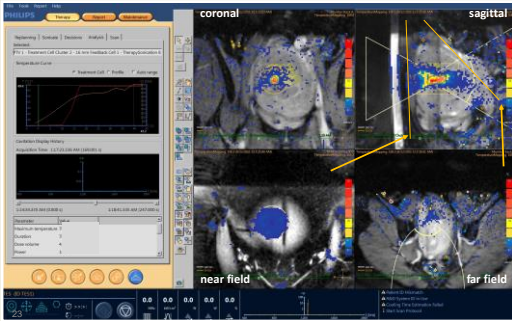


- Six monitoring slices:
- A: 3 x at focal plane
 - B: 1 x along beam axis
 - C: Near field
 - D: Far field

- Slice positioning:
- A, B: automatically
 - C: abdominal muscle layer
 - D: close to bowel or spine

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



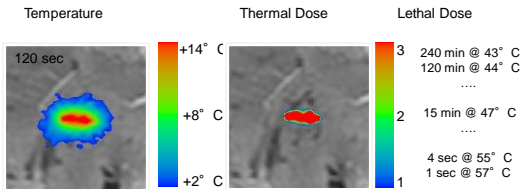
Courtesy of Ari Partanen, Ph.D.

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 MR scans

Thermal Dose

- 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

$$TD(t) = \int_0^t r^{(43-T(t))} dt \quad \begin{array}{l} r=0.25(T < 43^\circ\text{C}) \\ r=0.50(T > 43^\circ\text{C}) \end{array}$$

- 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

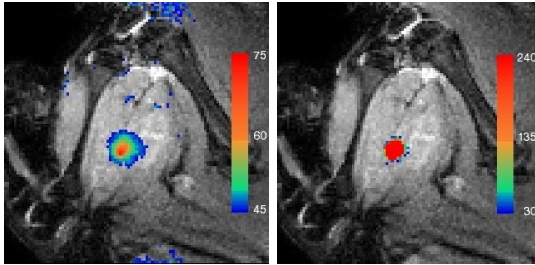
Thermal Dose Limits

- 0 – 30 EM → no thermal damage
- 30 – 240 EM → possible thermal damage (mostly reversible)
 - edematous, fragmented cell membranes, varying damage to vasculature
- 240 EM < → 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 Map and Thermal Dose Map

Thermal Map
($\Delta T^{\circ} C + 37^{\circ} C$)

Thermal Dose Map
(equivalent minutes at $43^{\circ} C$)

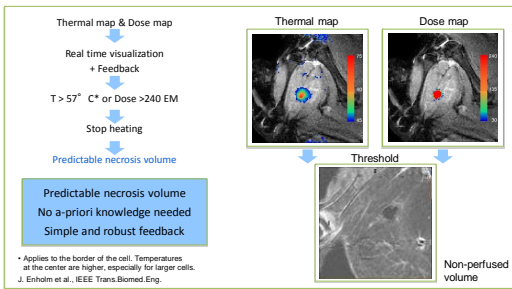


Courtesy of Ari Partanen, Ph.D.

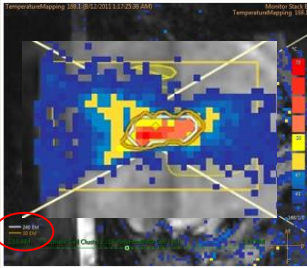
Macroscopic Tissue Effects



Real Time Feedback



Thermal Map and Thermal Dose Map



Temperature maps

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

Iso-dose contours

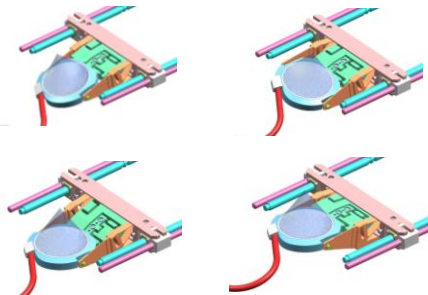
- Thermal dose
- 30 EM – edema zone (orange)
- 240 EM – necrosis zone (white)

Focusing the Ultrasound Beam

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

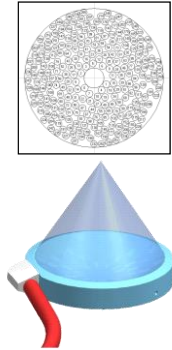
1. a lens (for example, a polystyrene lens),
2. a curved transducer, or
3. a phased array
4. or any combination of the three

HIFU Transducer



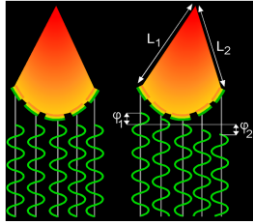
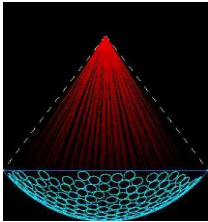
Transducer

- **Phased Array Transducer**
 - 256 Independent channels
 - Ultrasound Frequency: 1-1.5 MHz
 - Power 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



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

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



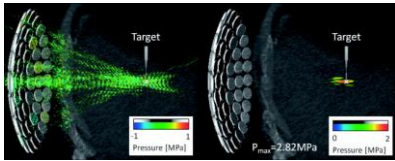
HIFU Transducer

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

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

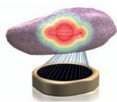


HIFU Transducer

HIFU

tabletop

transducer



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

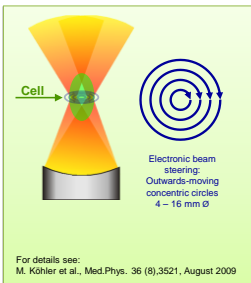
- Volumetric heating addressing #1
- Real-time feedback addressing #2

Point-by-Point vs. Volumetric Treatment

- 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.

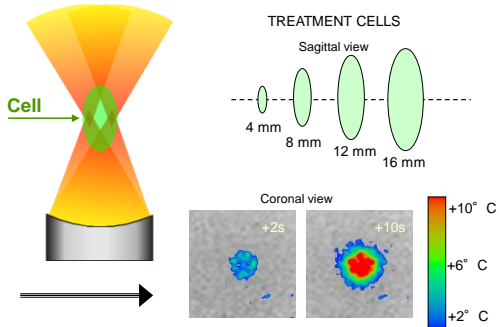
Treatment Cell (TC) is a treated tissue volume of a single sonication

Volumetric Heating



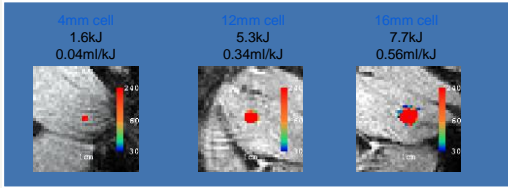
Diameter (mm)	Length (mm)	Volume (ml)
4	10	0.1
8	20	0.6
12	30	2.3
16	40	5.4

Volumetric Heating



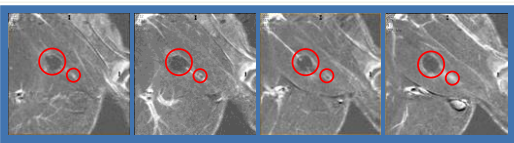
Volumetric Heating

- 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.

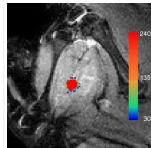
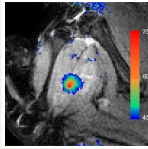
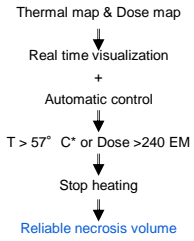
Volumetric Heating



Single point:		Volumetric:
Small cell: Ø2 mm		Large cell: Ø16 mm:
Power: 115W	~ same	Power: 110W
Sonication: 20 s	x 4.5	Sonication: 90 s
Volume ~ 0.2 ml	x 20.5	Volume ~ 4.1 ml
0.087 ml/kJ		0.414 ml/kJ

Courtesy of Ari Partanen, Ph.D.

Volumetric Treatment with Feedback



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

Courtesy of Ari Partanen, Ph.D.

Clinical Applications



Courtesy of Lizette Warner, Ph.D.

Clinical Applications

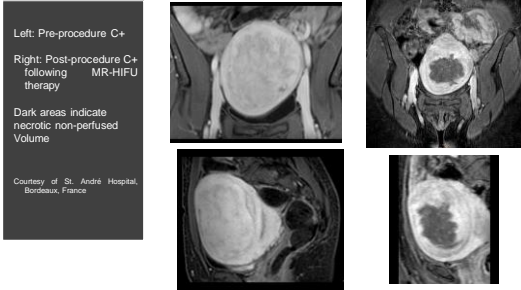
Uterine fibroids

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



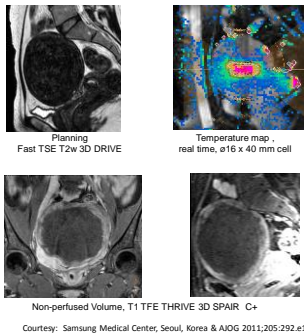
Clinical Applications

Uterine fibroid

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

Post treatment
 • Large Non-perfused Volume:
 • 568 ml
 • 89% reduction



Clinical Applications

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.

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.

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 image-guided devices built by several different companies.

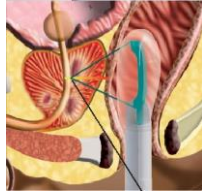
Clinical Applications 

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

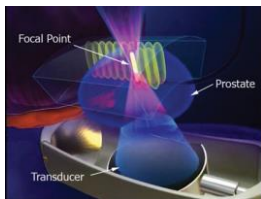
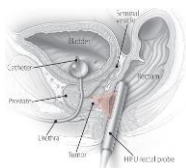
HIFU may also be used to ablate the entire prostate gland using a transrectal probe. This is an outpatient procedure that usually lasts 1–3 hours. First results show that it greatly reduces some of the side effects common with other treatments for prostate cancer.

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

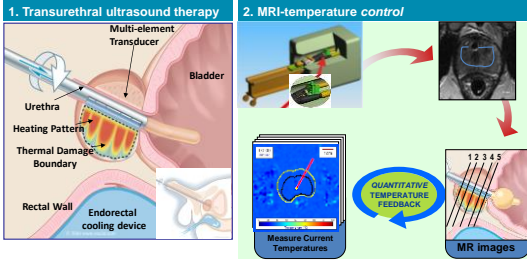
While the urethra is an important anatomical structure, the sphincter and bladder neck are more important to maintaining the urinary function. During HIFU the sphincter and bladder neck have to be identified and avoided.

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.

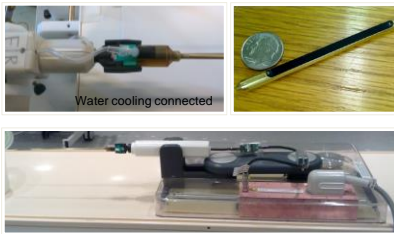


Transurethral MR-HIFU of the Prostate



Courtesy of Ari Partanen, Ph.D.

Transurethral Applicator

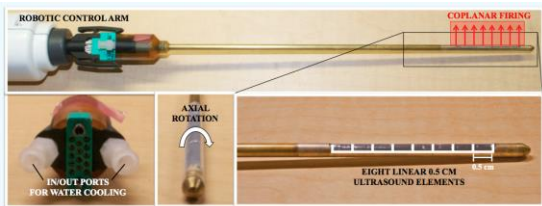


- Transurethral Transducer**
- 8 elements
 - Active part 40 mm
 - OD 4.7 mm
 - Cooling channels

- 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



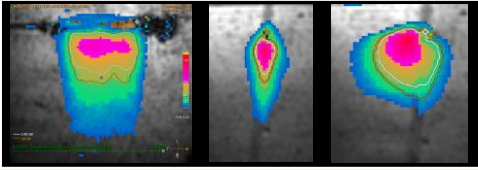
- Axially rotating applicator under robotic control
- Eight colinear 0.5cm elements ($f= 3\text{Mhz}$, $\text{max } P_{\text{ac}}= 4\text{W}$)
- Cooling via circulating degassed water

Courtesy of Ari Partanen, Ph.D.

Transurethral Applicator

Phantom study

Real-time temperature imaging with simultaneous sonication and motor rotation



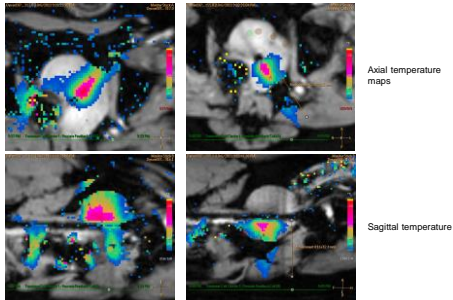
Sagittal view
240 EM depth: 50 mm
(necrosis zone, white)
(Transducer visible as signal void)

Coronal view
No rotation
240 EM depth: 40 mm

Coronal view
90° rotation
240 EM depth: 55 mm

Preliminary Results

Temperature maps

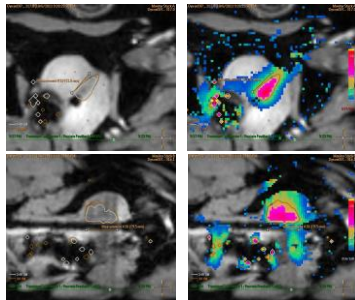


Axial temperature maps

Sagittal temperature

Preliminary Results

Dose images



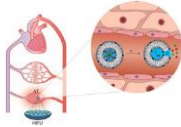
HIFU Drug Delivery



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 liposome, rapidly changes structure when heated to a specific temperature, creating openings which release doxorubicin directly into the targeted tumor.*

HIFU Drug Delivery



HIFU with special drug delivery vehicles, called low-temperature-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.

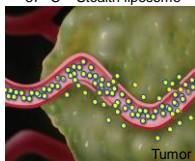
HIFU Drug Delivery



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**

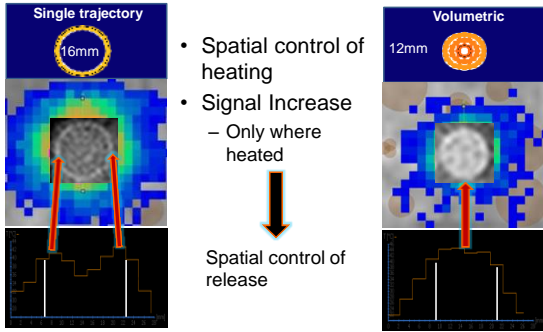
37 °C – Stealth liposome



42 °C – Temperature sensitive liposome



HIFU Drug Delivery

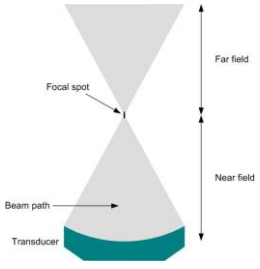


Limitations of HIFU

- **Bone and metallic objects** are problematic due to very high absorption, and speed of sound
 - High absorption coefficient may cause rapid and significant temperature rise even when local intensity is relatively low
 - Very different speed of sound than soft tissues may cause significant refraction and diffraction
 - Unpredictable wave propagation in tissues beyond the bone
 - Local intensity maxima or foci may be produced in unexpected locations causing significant local heating in unintended regions
 - Due to the above reasons bone and surgical clips must be 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

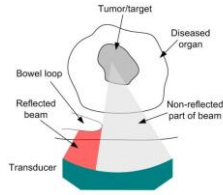
- Scars, bone, metallic objects, and air-filled cavities in the high-energy near-field part of the beam path need to be avoided
- Objects can be within the beam path in the far-field
 - Provided distance from focus is sufficient so that little energy remains in the beam



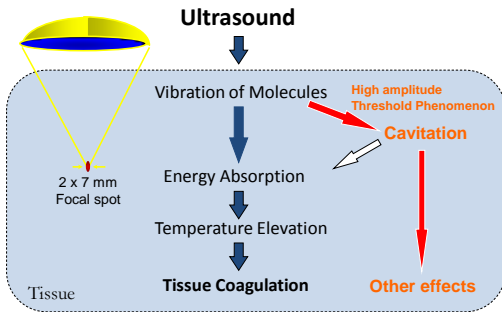
Limitations of HIFU

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**
 - 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

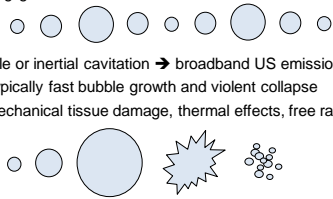


Therapeutic US Interaction with Tissue

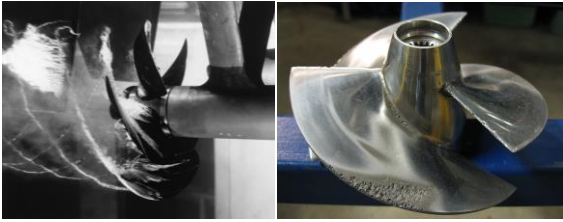


What is cavitation?

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



Cavitation



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

Summary



High-Intensity Focused Ultrasound (HIFU) is a hyperthermia therapy procedure that applies high-intensity 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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CANCER RESEARCH FOUNDATION



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AAPM Annual Meeting - High-Intensity Focused Ultrasound Therapy Hands-on Workshop
 MO-A-144-02 - August 5th, 2013 - Indianapolis, IN

**High-Intensity Focused
 Ultrasound Therapy
 Hands-on Workshop**

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