HIFU: Why should a radiation oncology physicist pay attention?

And…why should an ultrasound physicist pay attention to clinical radiation physics?

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Conflicts of Interest

Research Support, Elekta Instruments, AB

Educational Objectives

- Understand the similarities and differences between HIFU and ionizing radiation in terms of physics and biological effects.
- Learn about some of the challenges HIFU faces to achieve regular clinical use.
- Learn how HIFU might benefit from the experience of radiation oncology physicists, and how radiation oncology physics might benefit from working on HIFU.

Warning: Some parts of this talk are opinion. Feel free to disagree.

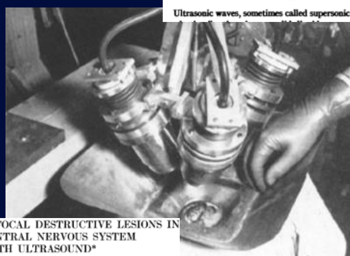
HIFU is not a new idea…

Am J Pathol. 1944 May; 20(3): 637–649.

HISTOLOGY OF CEREBRAL LESIONS PRODUCED BY FOCUSED ULTRASOUND*

JOHN G. LYNN, M.D., and TRACY J. PUTNAM, M.D.
(From the Department of Neurology, Columbia University, New York, N.Y.)

Ultrasonic waves, sometimes called supersonic waves, are mechanical



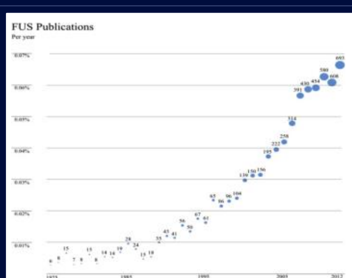
PRODUCTION OF FOCAL DESTRUCTIVE LESIONS IN THE CENTRAL NERVOUS SYSTEM WITH ULTRASOUND*

W. J. FRY, M.S., W. H. MOSBERG, JR., M.D.,†
J. W. BARNARD, PH.D. AND F. J. FRY, M.S.
Bioacoustics Laboratory, University of Illinois, Urbana, Illinois

(Received for publication May 26, 1954)

J Neurosurg. 1954 Sep; 11(5): 471-8.

But its popularity is growing…



Annual number and percentage of overall of publications in Medline dealing with focused ultrasound

Tyshlek *et al. Journal of Therapeutic Ultrasound* 2014

How does HIFU compare to ionizing radiation?

What are some barriers to entry for HIFU

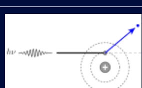
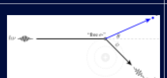
Are there opportunities for clinical medical physicists?

Can HIFU and RadOnc coexist?

Quick, pain-free physics review…..

Part 1: For ultrasound physicists

How do photons interact with matter?

Photoelectric	Compton	Pair -production
		
Energy transferred to e-	Energy transferred to e-	Energy transferred to e-
$E_{e-} = hv\text{-}E_b$	$E_{e-} = hv\text{-}hv'$	$E_{e-}+E_{e+} = hv\text{-}2m_0c^2$
Interaction with inner shell e- Characteristic and Auger e- produced Original photon disappears	Interaction with "free" outer shell electron. Scattered photon can interact elsewhere.	1.02 MeV threshold Produces e- / e+ pair e+ will annihilate, producing two photons Annihilation photons can interact elsewhere

How do photons deposit energy?

KERMA = Kinetic Energy Released per unit Mass

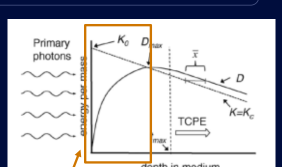
KERMA is the transfer of energy to secondary charged particles from uncharged ionizing radiation

Absorbed dose is the energy imparted to tissue by the charged particles via excitation/ionization

Dose = $E_{absorbed}$ / unit mass

Dose is given in units of Gray (Gy)

1 Gy = 1 Joule / kg



Radiation at the energies used for therapy has a "skin-sparing" effect

S. A. Naqvi, "Photon Interactions," *University of Maryland Resident Physics Review Course*, (2008).

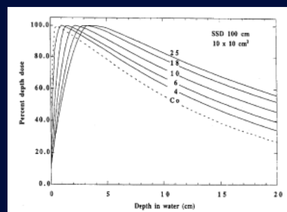
How do photons attenuate with depth?

Photons attenuate exponentially with depth

$$I = I_o e^{-\mu z}$$

μ is the linear attenuation coefficient (units cm^{-1})

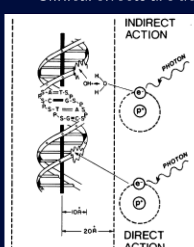
Expresses the fraction of incident photons attenuated or scattered per unit thickness of absorber



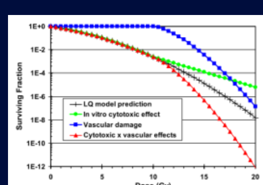
μ depends on photon energy, absorbing medium

Radiobiology of ionizing radiation

Ionizing radiation damages DNA through direct or indirect action
High-dose radiation may additionally cause vascular damage
Clinical effects are delayed and accumulative



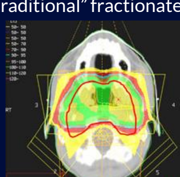
Hall, "Radiobiology for the Radiologist"



J. Kirkpatric, J. Meyer, L.B. Marks
Semin Rad Onc, 18(4), 2008.

How do we leverage radiobiology?

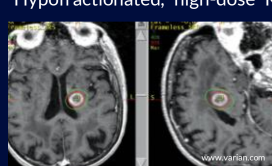
"Traditional" fractionated RT



Cheung, Biomed Imaging Interv J 2006; 2(1):e19

Relies on differential biology

Hypofractionated, "high-dose" RT



Relies on differential targeting

Quick, pain-free physics review…..

Part 2: For radiation oncology physicists

How does ultrasound deposit energy?

Converts mechanical energy into heat

1. Relaxation absorption

Energy converted to heat due to the lag in time it takes molecules to move back into position

Depends on visco-elastic properties of tissue

Prominent effect in tissue

2. Classical absorption

Friction between particles converts mechanical energy into heat

N. Smith, A. Webb, Introduction to Medical Imaging, Cambridge Press, 2011

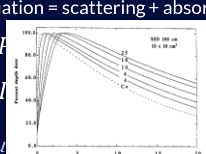
How does ultrasound attenuate with depth?

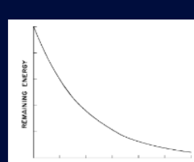
Attenuation = scattering + absorption

F

I

$\mu = \mu$





μ_a = absorption and μ_a = scatter attenuation coefficients

and

$\mu_a = \mu_{a,classical} + \mu_{a,relaxation}$

classical and relaxation scattering coefficients

Note the similarities (and differences) to ionizing radiation!

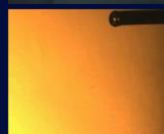
HIFU has multiple physical effects…

Thermal

heating†

Mechanical

acoustic streaming / radiation force‡



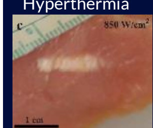
boiling and cavitation*

†Precision Acoustics - https://www.youtube.com/watch?v=kOvKDJS41tI
‡W. Dridi, et al., Laboratorie de mécanique des fluides et d'acoustique
*Video courtesty of Larry Crum, University of Washington

…which cause multiple biological effects…

Thermal

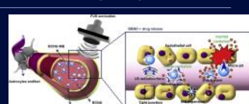
Ablation and Hyperthermia



Zdaric, Med Phys 35(10), 2008

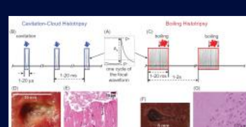
Mechanical

Payload delivery



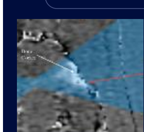
Ting, et al., Biomaterials, 33(2), 2012

Histotripsy



V. Khokhlova, et al., Int J. Hyperthermia 31(2), 2015.

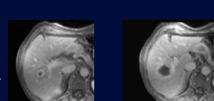
…leading to a variety of potential applications!



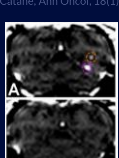
Pain palliation

R. Catane, Ann Oncol, 18(1), 2006.

Solid tumor ablation



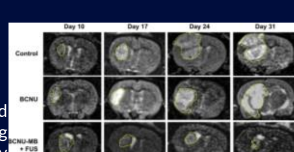
T. Leslie, FUS Summer Course Cargese, 2009



Reversible BBB opening

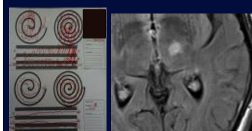
F. Marquet, PLoS One, 6(7), 2011.

Targeted drug delivery



Ting, et al., Biomaterials, 33(2), 2012

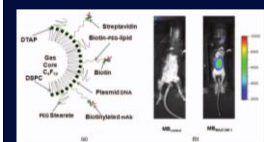
……and even more variety!



Functional lesioning

UVA neurosurgery

Stroke



Gene therapy

A. Burgess et al., PLoS ONE 7(8), 2012

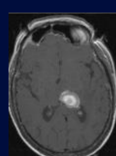
A. Klibanov, University of Virginia

HIFU effects can be immediate

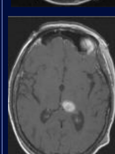
Pre-HIFU ablation

Immediately post-HIFU ablation (~62% non-perfused)

Images courtesy of A. Matsumoto, University of Virginia. Schlesinger, et al., MR-guided focused ultrasound surgery, present and future, Med Phys, 40(8), 2013



Pre-radiosurgery

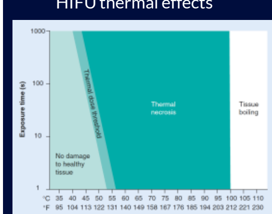


23 days post-radiosurgery (~53% volume reduction)

A. Da Silva et al., JNS 110(3), 2009

HIFU effects can be deterministic

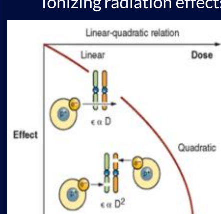
HIFU thermal effects



Above a given time/temperature threshold, proteins denature and cells undergo thermal necrosis

J. Foley et al., Imaging Med (5) 2013

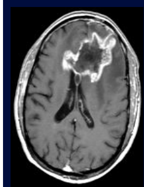
Ionizing radiation effects



Cell death depends on a dose-dependent frequency distribution of DNA strand breaks

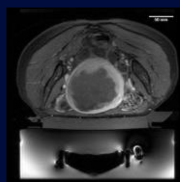
E. Hall, Radiobiology for the Radiologist

HIFU can be repeated



Radiation necrosis

R. Shah, et al, RadioGraphics 32(5), 2012



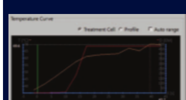
HIFU #1

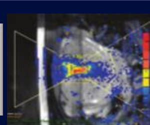
HIFU #2

Uterine fibroid ablation.
Non-perfused volume after treatment #1: ~62%
Non-perfused volume after treatment #2: ~100%

Images courtesy of A. Matsumoto, University of Virginia

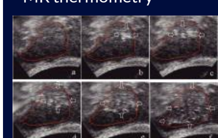
HIFU has real-time treatment monitoring….today!





MR thermometry

Philips Sonalleve



US hyperechogeneity

Images courtesy of J.F. Aubry, F. Wu

Real-time in-vivo imaging of delivered dose still in development

centrodecontroldecancer.com

How does HIFU compare to ionizing radiation?

What are some barriers to entry for HIFU

Are there opportunities for clinical medical physicists?

Can HIFU and RadOnc coexist?

There is not a standard way to describe a HIFU treatment

Basic units for ionizing radiation

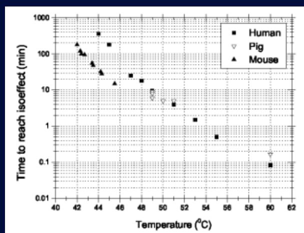
Measurement	Common Units	Official (SI) Unit
Energy	Joules (J), Mega electron-volts (MeV)	Joules (J)
Activity – disintegrations per unit time	Curie (Ci)	Becquerel (Bq)
Exposure – ionization	Roentgen (R)	Coulombs/kg (C/kg)
Absorbed Dose – energy deposited in tissue	Rad	Gray (Gy) 1 Gy = 1 J/kg
Dose equivalent – biological effect	Rem	Sievert (Sv)

Potential dose units for therapeutic ultrasound

Measurement	Units	Potential issues
Intensity (Exposure)	Watts/cm^2	Intensity in free space or water or tissue? Peak or average?
Acoustic dose | dose rate	Joules/kg | Joules/kg·s	Similar to SAR Deposited energy not directly related to biological effect Varies with conditions and beam path
Cavitation dose	# bubbles, integrated cavitation detector signal	How does this relate to biological effect?
Thermal isoeffective dose (CEM/TET)	Minutes	More like a threshold than a dose. Not scalable.

A. Shaw et al., Int. J. Hyperthermia, 31(2), 2015

Thermal isoeffective dose – the default standard



$$t_{43} = \int_{t=0}^{t=final} R^{\left(\frac{43°C - T(t)}{1°C}\right)} dt$$

R = # min required to compensate for a 1° temp change

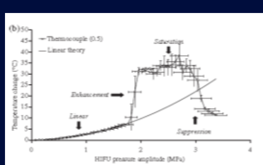
R=0.5, T≥ 43°C
R=0.25, < 43°C

Is this valid for ablative temperatures?
What about non-thermal applications?

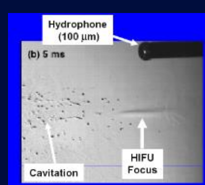
M. Dewhirst, Int J Hyperthermia, 19(3), 2003.

S. Sapareto, W. Dewey, Int J Radiat Oncol Biol Phys, 10(6), 1984

Cavitation is difficult to predict or control



C. Coussios, Int. J. Hyperthermia, 23(2), 2007.



L. Crum, U of Washington.

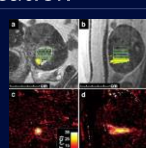
Cavitation causes broadband emission due to scatter off bubbles. Can significantly increase temperature rise, and can also shield deep regions.

Patient motion degrades image guidance and sonication

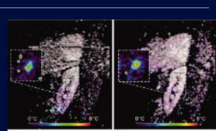
Some treatment monitoring techniques are subtraction-based

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

$$\Delta\phi = \phi - \phi_{baseline}$$

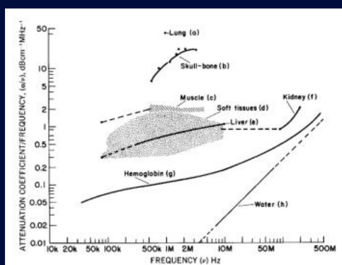


Even if you can compensate on the imaging side, the sonication itself has to adjust to motion



Ries, et al., Magnetic Resonance in Medicine (64), 2010

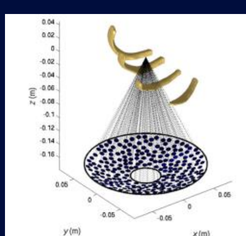
The treatment envelope is often limited by bone and air



- Bone and air attenuate ultrasound much more than other tissue types.
- Current thermal treatment techniques limit ablation to areas distant from bone and avoid air in beampath.

W. Hendee, Medical Imaging Physics, 2002

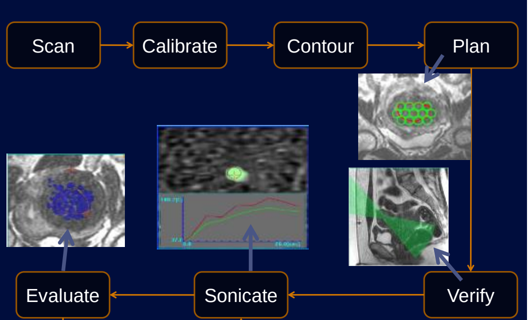
Tissue heterogeneity can complicate delivery



P Gelat, et al., Phys Med Bio (59)2014

- Heterogeneous tissue such as bone in the beampath absorb and scatter HIFU energy
- This can cause unwanted heating in the heterogeneity and in surrounding tissue
- Side-lobe formation can cause unwanted heating away from the focus
- Need improved methods to detect heterogeneities and avoid/adjust

The workflow model is still developing



It is difficult to convince payers to cover HIFU

Systematic Review of the Efficacy and Safety of High-Intensity Focused Ultrasound for the Primary and Salvage Treatment of Prostate Cancer
M. Warmuth, T. Johansson, P. Mad
European Urology (58) 2010

Conclusions: Applying the GRADE approach, the available evidence on efficacy and safety of HIFU in prostate cancer is of very low quality, mainly due to study designs that lack control groups. More research is needed to explore the use of HIFU in prostate cancer.

The situation is not different for Radiation Oncology

THE WALL STREET JOURNAL.

Prostate-Cancer Therapy Comes Under Attack

Some Insurers Stop Covering Expensive Proton Beams to Battle Prostate Cancer

By RON WINSLOW and TIMOTHY W. MARTIN
Aug. 28, 2013 8:09 p.m. ET

Health insurers are pushing back against one of medicine's most expensive technologies amid growing evidence it may not be better for patients than cheaper options.

At least three major insurers have recently decided to stop covering proton beam therapy for early stage prostate cancer or are reviewing their policy, saying that while it is an effective treatment, it is much less cost-effective when compared to the price of

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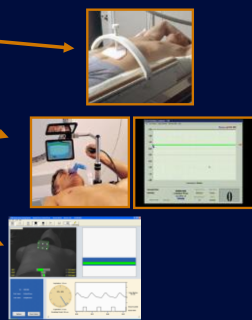
Experience with motion mitigation

- Abdominal compression
  - Forces shallow breathing
- Controlled breath-hold
  - Stabilizes tumor within the respiratory cycle
- Tumor tracking
- Gated beam-on devices
  - Treatment only given when tumor located within the beam
  - Respiratory tracing used



Slide images + text courtesy of Stan Benedict, UCDavis

Clinical metrology and QA standardization

Clinical Standards

ASTRO

ESTRO

American Association of Neurological Surgeons

Rad Physics

TG-51: Calibration
TG-142: QA
TG-106: Beam data collection

The American Association of Physicists in Medicine

HIFU

TG-241: MRgFUS

Technical Standards

NIST

IEEE

IEC

Characterizing and mitigating uncertainty

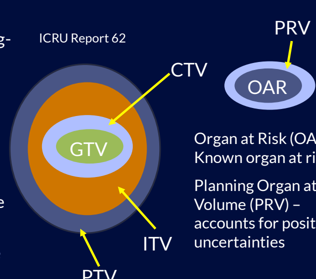
Gross Tumor Volume (GTV) – Known (imaging-evident) tumor

Clinical Target Volume (CTV) – uncertainty in tumor extent

Internal Target Volume (ITV) – uncertainty in size/shape/position (due to motion)

Planning Target Volume (PTV) – uncertainty in setup and delivery

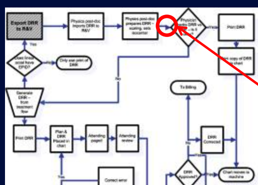
ICRU Report 62



Organ at Risk (OAR) – Known organ at risk

Planning Organ at Risk Volume (PRV) – accounts for positional uncertainties

Experience analyzing procedural risk



TG-100 style analysis

Possible effect: Treatment to wrong location!

RPN score: 160 (*RPN=SxOxD* = 8x5x4)

S: Severity (*No Harm 1 … 10 Severe Harm*)
O: Frequency of occurrence (*Low 1 ... 10 High*)
D: Detectability (*Easily Detected 1 … 10 Undetectable*)
Risk Priority Number, *RPN = S x O X D*

E. Ford, Evaluation of safety in a radiation oncology setting using failure mode and effects analysis. IJROBP 74(3), 2009.

Inventing phantoms and QA detectors for any occasion!

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Possibilities for HIFU + Radiation

- HIFU as salvage for local failure after radiotherapy
- Radiotherapy as salvage for local failure after HIFU
- Local tumor debulking with HIFU + wide-field radiation therapy for "micrometastases"
- Radioactive drug delivery using HIFU+carrier
- Radiosensitization using HIFU hyperthermia timed with radiation therapy
- HIFU to treat hypoxic areas of tumor + radiation therapy for tumor bulk

Perhaps surgery is a good model

Hybrid adaptive surgery

Image courtesy of Brainlab, AG

Develop systems to support surgeons in performing subtotal resections.

For HIFU, aim would be to ablate/erode enough tumor close to critical structures or hypoxic areas to make subsequent radiation safe and more effective.

Conclusions

HIFU has many hurdles to clear…

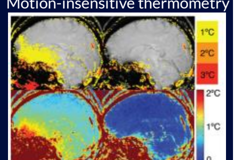
Med Phys. 2011 Jul;38(7):3909-12.
Point/counterpoint. High intensity focused ultrasound may be superior to radiation therapy for the treatment of early stage prostate cancer.
Benedict SH, De Meerleer G, Orton CG, Stancanello J.

- Reimbursement
- Proving superiority over existing technologies
- Calibration standards
- QA standards
- Time of treatment
- Motion management
- Tissue inhomogeneity

…but there are many innovations on the way

Time of treatment	Volumetric ablation
Accuracy of treatment	Volumetric image guidance
Tissue inhomogeneity	Phase aberration correction / MR bone imaging
Motion management	Referenceless thermometry
Nonthermal applications	Radiation-force imaging
Superiority of treatments	Indication-specific transducers

Motion-insensitive thermometry



Single-baseline vs single-baseline+hybrid MR thermometry. Temperature map (top), uncertainty map (bottom) for patient moving tongue.

Rieke, et al., J. Magn Reson Imaging 38(6), 2013

Take advantage of the synergies

Both directions!

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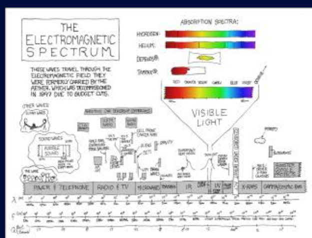

http://www.xkcd.com