HIFU in Radiation Oncology - Dosimetry & Workflow Considerations

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Conflicts of Interest

None

Educational Objectives

Discuss the physical and biological characteristics of RT and ablative HIFU procedures and how they complicate the creation of a unified concept of "dose".

Review recent efforts to directly compare and combine dosimetric models for RT and HIFU.

Summarize some of the implications that combined RT/HIFU treatments may have for treatment planning workflows.

How does HIFU compare to ionizing radiation?

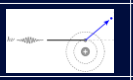
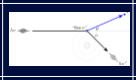
What makes a "combined" dose for RT+HIFU complicated?

Can we represent a combined HIFU/RT Dose?

How might workflow change for RT + HIFU

Quick, pain-free radiation physics and biology review…..

How do photons interact with matter?

Photoelectric	Compton	Pair -production
		
Energy transferred to e-	Energy transferred to e-	Energy transferred to e-
$E_{e^-} = h\nu - E_b$	$E_{e^-} = h\nu - h\nu'$	$E_{e^-} + E_{e^+} = h\nu - 2m_0c^2$
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

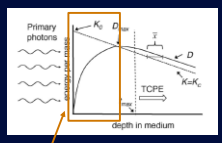
KERMA is the transfer of energy to secondary charged particles from uncharged ionizing radiation

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

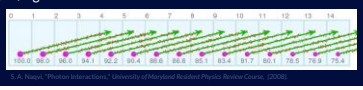
Dose = $E_{absorbed}$ / unit mass

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 Radiation Physics Review Course, (2008)

Radiobiology of ionizing radiation

Ionizing radiation damages DNA through direct ionization or indirect action via free radicals

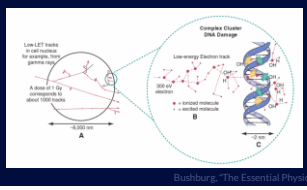
Probability of damage is stochastic

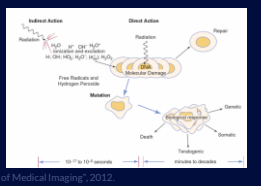
Double-strand breaks are less repairable

Damage can be repaired or can result in mutations

Damage tends to accumulate

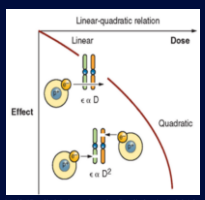
Evident clinical effects are delayed





Bushburg, "The Essential Physics of Medical Imaging", 2012.

The linear-quadratic model



Hall, "Radiobiology for the Radiologist", 2012.

$$S(D) = e^{-(\alpha D + \beta D^2)}$$

Unrepairable DNA damage represented by a dual-strand break.

For low doses:

A double chromosome break requires only a single electron

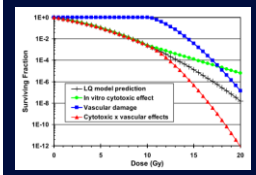
Probability of interaction ~ dose

For high doses:

A double chromosome break can result from two separate electrons

Probability of interaction ~ dose^2

At ablative doses, radiobiology might work differently

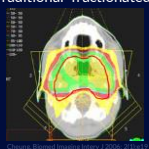


J. Kirkpatric, J. Meyer, L.B. Marks Semin Rad Onc, 18(4), 2008.

Author/Year	Model Name	Strategy
Guerrero and Allen (2004)	Modified LQ model (MLQ)	Linear-Quadratic-Linear
Park, et al. (2008)	Universal Survival Curve	Hybrid LQ and multi-target model
Kavanagh and Newman (2008)	Kavanagh-Newman	Dose-dependent increase in exponential rate of cell kill
Astrahan (2008)	L-QL model	Linear-quadratic linear
Hanin and Zaider (2010)		Microdosimetry model
Wang, et. al. (2010)	Generalized Linear Quadratic Model (gLQ)	Adds a parallel β_2 term to account for less sub-lethal repair at high doses

How does RT leverage radiobiology?

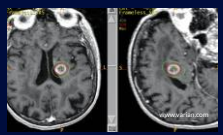
"Traditional" fractionated RT



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

Relies on differential biology

Ablative, hypofractionated RT



Relies on differential targeting

Quick, pain-free therapeutic ultrasound physics and biology review…

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

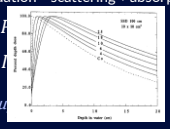
How does ultrasound attenuate with depth?

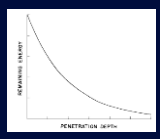
Attenuation = scattering + absorption

$I =$

$I =$

$\mu = \mu$





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‡

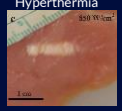
boiling and cavitation*

† 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

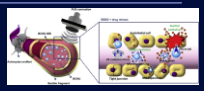
Ablation and Hyperthermia



Zdaric, Med Phys 35(10), 2008

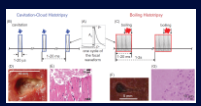
Mechanical

Payload delivery



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

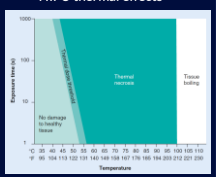
Histotripsy



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

HIFU effects can be deterministic

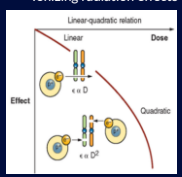
HIFU thermal effects



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

How does HIFU compare to ionizing radiation?

What makes a "combined" dose for RT+HIFU complicated?

Can we represent a combined HIFU/RT Dose?

How might workflow change for RT + HIFU

Just deciding on a "dose" for HIFU by itself is complicated

Basic units for ionizing radiation

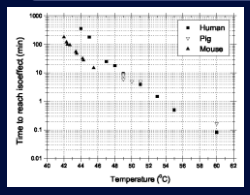
Measurement	Common Units	Official (SI) Unit
Energy	Joules (J), Mega electron-volts (MeV)	Joules (J)
Activity – disintegrations per unit time	Curie (Ci)	Becquerel (Bq)
Exposure – ionization	Roentgen (R)	Coulombs/kg (C/kg)
Absorbed Dose – energy deposited in tissue	Rad	Gray (Gy) 1 Gy = 1 J/kg
Dose equivalent – 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? Similar to SAR
Acoustic dose | dose rate	Joules/kg | Joules/kg·s	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

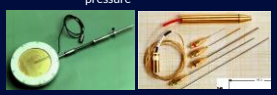
Is this valid for ablative temperatures?
What about non-thermal applications?

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

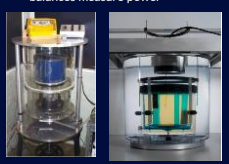
S. Sapareto, W. Dewey, Int J Radiat Oncol Biol Phys, 10(6), 1984

But….what can we measure for HIFU?

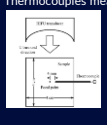
Hydrophones measure pressure



Radiation force and buoyancy balances measure power



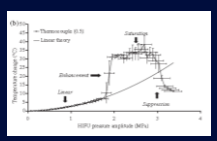
Thermocouples measure temperature



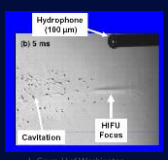
J-C Wang, et al., J Heat Mass Transfer 2014.

Measure pressure and power, calculate intensity!

also…what about those mechanical effects?



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



L. Crum, U of Washington.

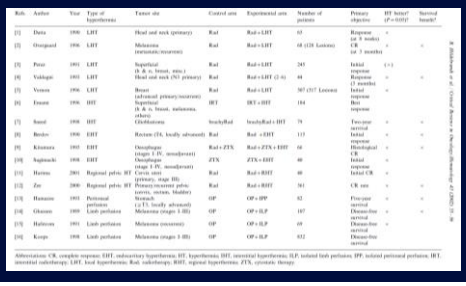
Cavitation causes broadband emission due to scatter off bubbles. Can significantly increase temperature rise, and can also shield deep regions.

Why would you want to use HIFU with ionizing radiation?

Possibilities for HIFU + Radiation

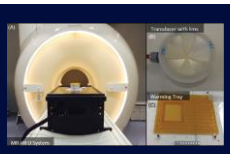
- HIFU as salvage for local failure after radiotherapy
- Radiotherapy as salvage for local failure after HIFU
- Local tumor debulking with HIFU + wide-field radiation therapy for "micrometastases"
- Radioactive drug delivery using HIFU+carrier
- Radiosensitization using HIFU hyperthermia timed with radiation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

Evidence for hyperthermia



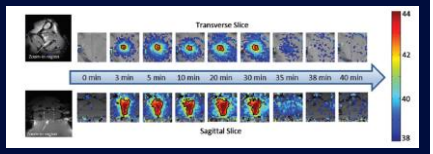
B. Hildebrandt et al., Crit Reviews in Oncology 43, 2002

"Local" hyperthermia with HIFU



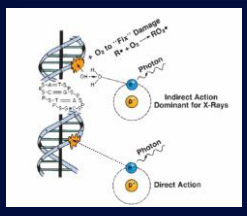
MR-guided HIFU system with acoustic lens to spread out focal spot

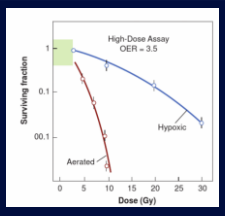
In-vivo studies demonstrated ability to locally raise and hold temperature over clinically significant times



C. Bing et al., Int J. Hyperthermia 31(8), 2015

HIFU might address problems with RT and hypoxia



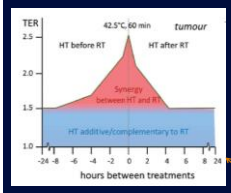


Molecular O2 can make DNA damage irreparable
Ionizing radiation is much less effective in hypoxic tissues

E. Hall, Radiobiology for the Radiologist

What happens when heat and radiation interact in a patient?

Hyperthermia and ionizing radiation



H. Crezee, et al., Int. J. of Hyperthermia (32), 2016.

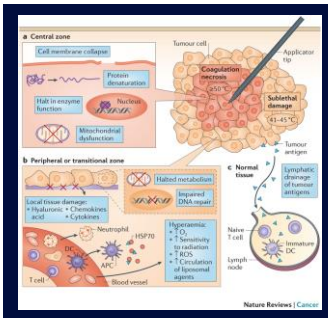
Heat can have a synergistic effect with ionizing radiation:

Direct cell killing: especially of hypoxic cells

Reoxygenation: increased perfusion of O2 to tumor

Inhibition of DNA repair: enhance therapeutic ratio

Sequence and time interval are critical to the magnitude of the effect



K.F. Chu et al., Nature Reviews Cancer(14), 2014.

In reality, things are much more complicated!

Especially for HIFU!

Ablative HIFU treatments have a central necrotic zone and a surrounding sublethal zone.

There is a complicated set of biological and immune effects in play.

Even when only considering thermal effects, dose for combined RT+HIFU is complicated!

Complicated hasn't stopped people from trying!

How does HIFU compare to ionizing radiation?

What makes a "combined" dose for RT+HIFU complicated?

Can we represent a combined HIFU/RT Dose?

How might workflow change for RT + HIFU

1. Extend the LQ model to account for heating

Radiosensitivity params adjusted for achieved temperature/time interval (Gy^{-1}, Gy^{-2})

Protraction factor for repair during RT

Equivalent EBRT dose (Gy)

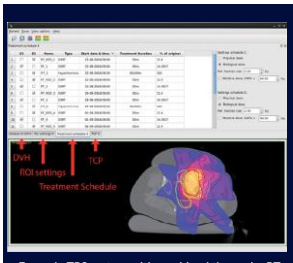
Total dose (Gy)

$$EQD_{RT} = \frac{\alpha(T, t_{int}) \cdot D + \beta(T, t_{int}) \cdot D^2 \cdot G}{\alpha_{37°} + \beta_{37°} \cdot d_{ref}}$$

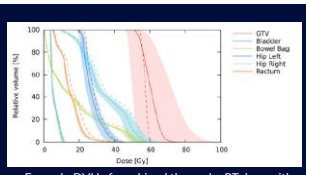
Radiosensitivity params at 37°C.

Fraction size of reference treatment

C.M. van Leeuwen et al., Intl. J. Hyperthermia, 2016.



Example TPS system with combined thermal + RT dose modeling

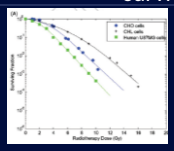


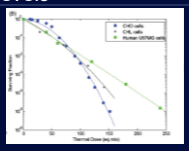
Example DVH of combined thermal + RT dose with confidence intervals

Including expanded LQ model easily supported in treatment planning systems with biological optimization

C.M. van Leeuwen et al., Intl. J. Hyperthermia, 2016.

2. Directly map thermal and RT doses based on cell survival at ablative levels





Fit RT studies to universal survival curve

$$lnS = \begin{cases} -n\left(\alpha * D_r + \beta * {D_r}^2\right) & for D_r \le D_T \\ -n\left(\frac{1}{D_0} D_r - \frac{D_q}{D_0}\right) & for\ D_r \ge D_T \end{cases}$$

Fit thermal studies to a similar linear quadratic based on damage index:

$$\Omega = \ln\frac{N(0)}{N(t)} = \ln\frac{1}{S}$$

$$lnS = -aD_t + bD_t{}^2 \quad \Rightarrow \quad \Omega = aD_t + bD_t^2$$

D. Schlesinger et al., Intl. J. Hyperthermia, 2017.

Parameters after fitting published cell survival curves to Universal Survival and Damage Index models

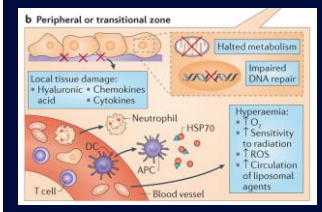
gLQ fit (radiation dose)	α (1/Gy)	β (1/Gy²)	α/β (Gy)	D_q (Gy)	D_o (Gy)	D_T (Gy)	R^2
CHO	0.043	0.062	0.69	2.93	1.23	6.19	0.993
CHL	0.11	0.026	4.12	5.23	1.33	12.22	0.995
GBA	0.14	0.094	1.53	1.81	1.06	4.28	0.996
Exponential fit (thermal dose)	**a (1/CEM)**		**b (1/CEM²)**		**a/b (CEM)**		**R^2**
CHO	0.0047		0.00049		9.6		0.994
CHL	0.035		0.00017		210		0.992
GBA	0.044		9.1e-6		4800		0.998

Radiation dose required
CHO: 17 Gy
CHL: 21 Gy
GBA: 14 Gy

"ablation"
To achieve a survival fraction of 10^{-5}

Thermal dose required
CHO: 149 CEM_{43}
CHL: 178 CEM_{43}
GBA: 250 CEM_{43}

D. Schlesinger et al., Intl. J. Hyperthermia, 2017.



But again…it's complicated!

Above methods are based on in-vitro models of cell survival.

Whole organisms have complex interactions that are not well represented in the model

Perhaps model based on observed tumor responses?

K.F. Chu et al., Nature Reviews Cancer(14),2014.

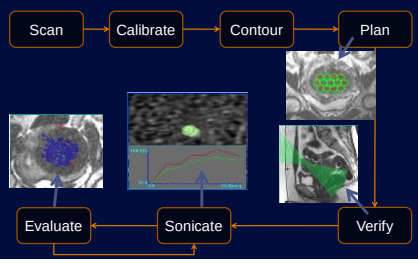
How does HIFU compare to ionizing radiation?

What makes a "combined" dose for RT+HIFU complicated?

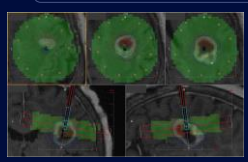
Can we represent a combined HIFU/RT Dose?

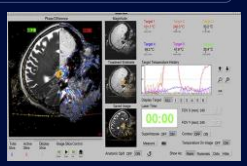
How might workflow change for RT + HIFU

Current workflow looks like RadOnc



Future HIFU workflows may be more procedural





Snapshots of workstations for MR-guided laser interstitial thermal therapy (LITT) systems.

LITT follows a more procedural workflow than the scan-plan-treat workflow found in radiotherapy and current MR-guided HIFU systems.

Lagman et al., J. Clin Neuroscience (36), 2017.

Perhaps surgery+radiosurgery is a good model

Hybrid adaptive surgery

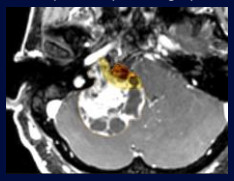


Image courtesy of Brainlab, AG

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

There are several potentially synergistic effects for HIFU and radiotherapy

Creation of unified concept of "dose" remains a work in progress due to the complex biological processes involved.

Existing workflows for surgery/radiosurgery and LITT may serve as a guide to future workflows for HIFU

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