Overview of MR-guided Focused Ultrasound Physics & Applications

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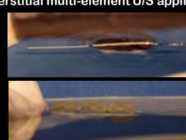
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Emerging and Innovative Ultrasound Technology in Diagnosis and Therapy
AAPM 2014, Austin, TX

Thermal therapy energy sources

- Cryotherapy
- Radiofrequency
- Microwave
- Laser
- **Ultrasound**

Interstitial multi-element U/S applicators

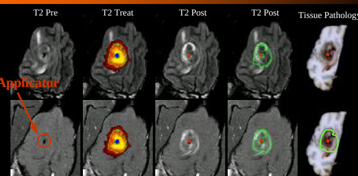


High Intensity Focused Ultrasound (FUS or HIFU)

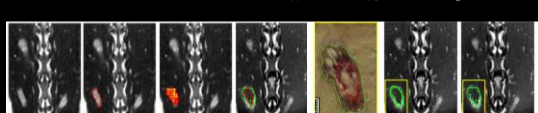
Schlesinger D, et al, MR-guided focused ultrasound surgery, present and future
Med. Phys. 40 (8), August 2013

Modalities for image-guided thermal therapy

- US
- CT
- **MRI**



Multi-element U/S applicator therapy



MRgFUS

Commercial Focused Ultrasound Systems

Ultrasound Guided

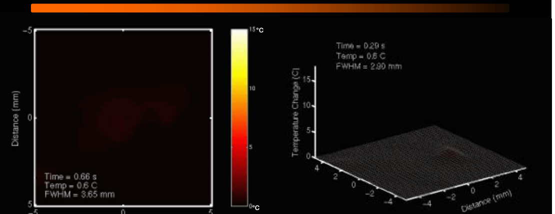
MRI Guided

MRgFUS: uterine fibroids

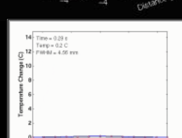
(ExAblate 2000; Insightec, Haifa, Isreal)

Tempany C, et al., Radiology 2003: 226: 897-905

Real-time MRTI for model validation



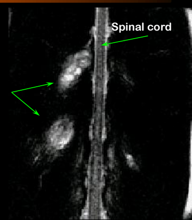
MRTI is a ***non-invasive*** and ***quantitative*** means for spatiotemporal characterization of heating and validation of theoretical models used for treatment planning.



Example: Focused ultrasound heating on 1.5T clinical scanner.

Role of image guidance in thermal therapy

- Facilitate more optimized treatment
  - planning
  - targeting/localizing
  - monitoring/control
  - verification
- Imaging information synergistic with integration of model based simulation
- Endgame
  - increase safety + efficacy
  - facilitate minimally invasive approaches previously not considered possible/safe



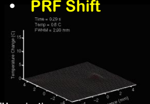
HIFU Ablation in Rabbit Paraspinal Muscle @1.5T

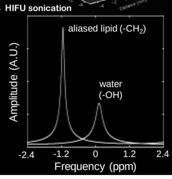
- Treatment prescription
- Prescribed sonication point
- Thermal dose (point)
- Thermal dose (total)

Hazle JD, Stafford RJ, Price RE JMRI 15 (2): 185-94., 2002.

MR Temperature Imaging (MRTI)

- Diffusion
- T1-relaxation
- PRF Shift





- Proton resonance frequency (PRF) of water shifts linearly with temperature
- Sensitivity: -0.01 ppm/°C (water)

Tissue Type (Canine)	Temp. Range (°C)	Temp. Sensitivity (ppm/°C)
Brain	25-59	-0.0102 ± 0.0005
Prostate	32-59	-0.0099 ± 0.0004
Kidney	35-54	-0.0103 ± 0.0006
Liver	35-51	-0.0098 ± 0.0002
Bone (femur)	17-57	-0.0109 ± 0.0002

- Disadvantages
  - Less sensitive at low field strengths
  - Lipid is insensitive to temperature
  - Sensitive to background field changes
    - Motion, susceptibility, etc

Review: Rieke, V. & Butts Pauly, K. JMRI, 27:376-90 (2008);

Thermal "Dose" & Damage Assessment

- Thermal damage is cumulative effect
  - Isotherm characterization of bioeffects limited
- Damage as function of exposure can be modeled as an Arrhenius rate process (Ω)

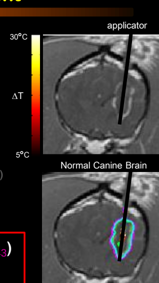
$$\Omega = A\int_0^t e^{\frac{-E_a}{RT(\tau)}}d\tau$$

R = Universal Gas Constant
A = Frequency Factor (3.1 x 10^{98} s^{-1})
E_a = Activation Energy (6.3 x 10^5 J)
(Henriques FC, Arch Pathol, 1947; 43: p. 489.)

- Cumulative Equivalent minutes @ 43°C (CEM_{43})
  - Empirically derived from isoeffects observed in low temperature hyperthermia work:

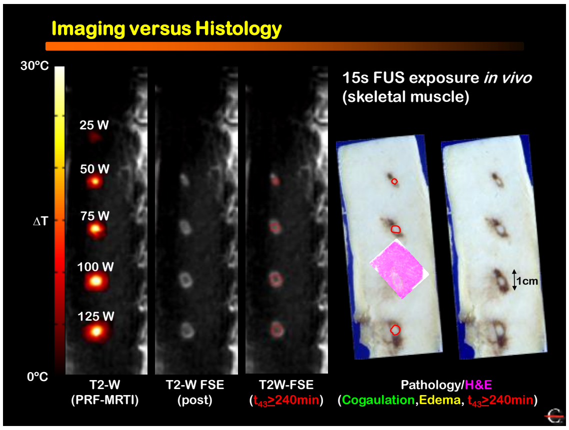
$$\mathrm{CEM}_{43}(t_n) = \sum_{t=0}^{n\cdot\Delta t} \mathrm{R}^{(43-T_n)}\cdot\Delta t, \text{ with } \mathrm{R} = \begin{cases} 0.25 & T_n < 43°C \\ 0.50 & T_n \geq 43°C \end{cases}$$

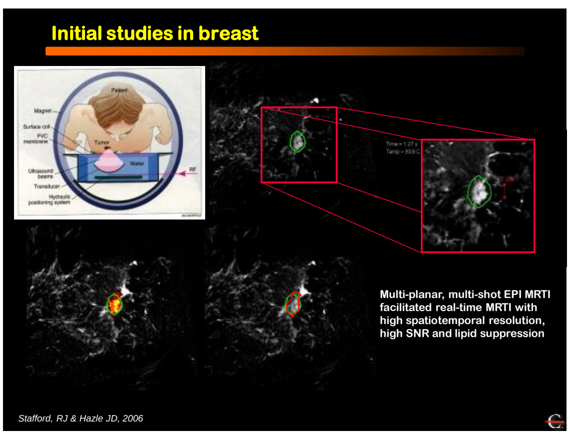
Sapareto SA, Dewey WC Int. J. Rad. Onc. Bio. Phys. 10: 787-800, 1984.

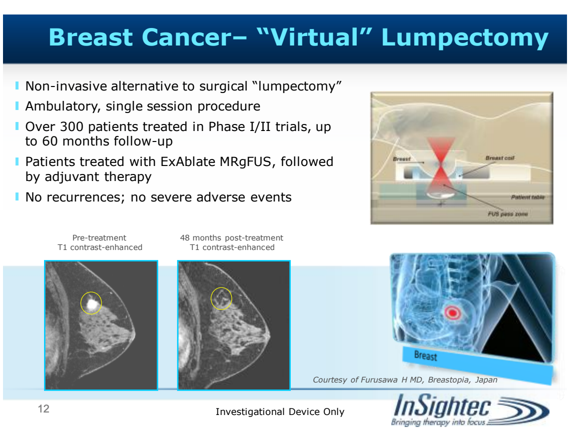


isodose models
Ω ≥ 1
T ≥ 57°C
CEM_{43} ≥ 240 min

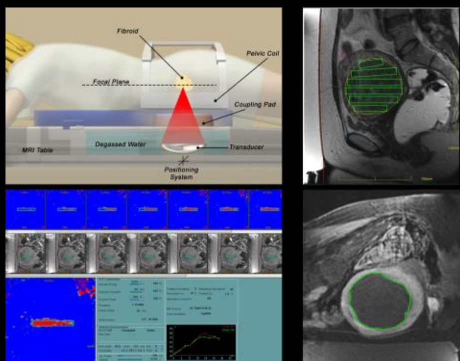
Yung J, et al, Medical Physics 2010


Imaging versus Histology
30°C
ΔT
0°C
25 W
50 W
75 W
100 W
125 W
15s FUS exposure in vivo
(skeletal muscle)
1cm
T2-W
(PRF-MRTI)
T2-W FSE
(post)
T2W-FSE
(t43≥240min)
Pathology/H&E
(Cogaulation,Edema, t43≥240min)


Initial studies in breast
Multi-planar, multi-shot EPI MRTI facilitated real-time MRTI with high spatiotemporal resolution, high SNR and lipid suppression
Stafford, RJ & Hazle JD, 2006

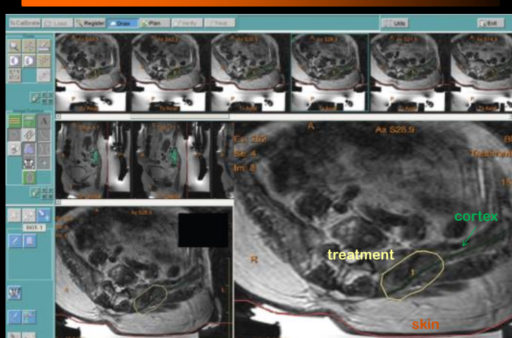

Breast Cancer– "Virtual" Lumpectomy
Non-invasive alternative to surgical "lumpectomy"
Ambulatory, single session procedure
Over 300 patients treated in Phase I/II trials, up to 60 months follow-up
Patients treated with ExAblate MRgFUS, followed by adjuvant therapy
No recurrences; no severe adverse events
Pre-treatment
T1 contrast-enhanced
48 months post-treatment
T1 contrast-enhanced
Breast
Courtesy of Furusawa H MD, Breastopia, Japan
12
Investigational Device Only
InSightec
Bringing therapy into focus

First approved indication: uterine fibroids



Stafford, RJ & Ahrar K, MRI-guided Thermal Therapy Techniques (in Kahn & Busse Interventional MRI, 2012)

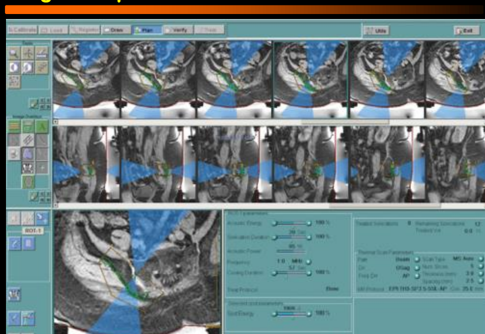
MRgFUS of painful bone mets



Planning: radiologist segmentation

Napoli A, et al, RadioGraphics , 2013

MRgFUS of painful bone mets

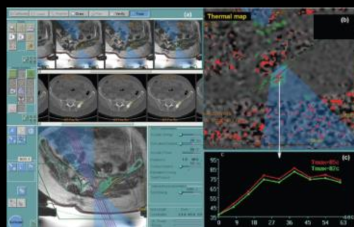


Treatment planning: evaluation

Napoli A, et al, RadioGraphics , 2013

MRgFUS of painful bone mets

Verification step

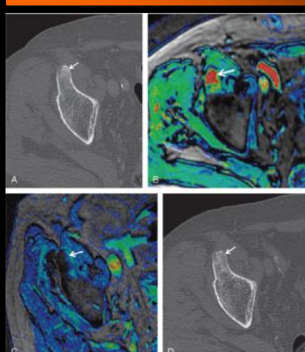


Treatment monitoring

Palliation is achieved by spreading the heat across the surface of the bone to ablate the nerves in the adjacent periosteum.

Napoli A, et al, RadioGraphics , 2013

MRgFUS of painful bone mets



Prostate mets in 63 yo male in right anterior-superior iliac spine

Pre-Treatment:
T1W+C MRI => perfused

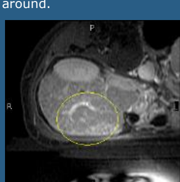
Post-Treatment (3 mo):
T1W+C MRI => non-perfused
CT => increased density in treated area and disappearance of nodular pathologic tissue

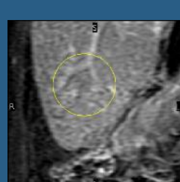
Patient classified as complete responder (MDACC criteria)

Napoli A, et al, Investigative Radiology & Volume 48, Number 6, June 2013

Case Study – Liver HCC

- 67yr old patient with a 2cm HCC primary lesion in segment 5. The liver because it was so large pushed segment 5 well below the ribs providing a reasonable treatment position.
- Although not an ideal first position, because of some anaesthesia issues due to patient chest problems, it was decided to leave the position and try to work around.





Images courtesy of Sapienza University - Rome

Investigational Device Only

InSightec Bringing therapy into focus

Case Study – Liver HCC

- A total of 32 sonications with an average energy of 2445 joules with a 15second sonication time.
- Apnea time was 27seconds with a minimum of 60 seconds ventilation time between sonications.
- Total treatment time from sonication 1 to sonication 32, 1hour 30 minutes.
- Non perfuse volume of lesion. 100%
- No post procedure problems

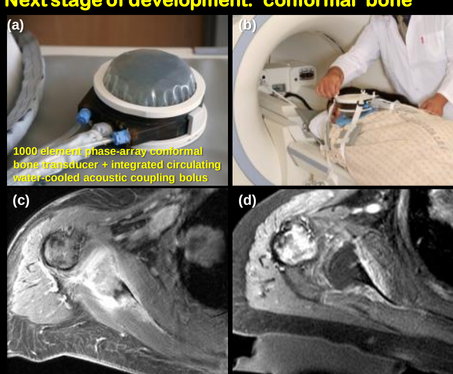
Post contrast subtraction right and left. Middle – thermal dose map

Images courtesy of Sapienza University - Rome

Investigational Device Only

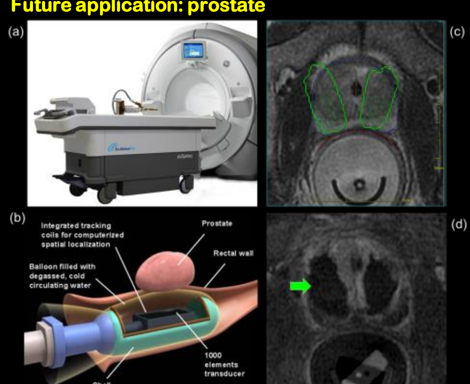
InSightec Bringing therapy into focus

Next stage of development: 'conformal' bone



Stafford, RJ & Ahrar K, MRI-guided Thermal Therapy Techniques (in Kahn & Busse Interventionall MRI, 2012)

Future application: prostate



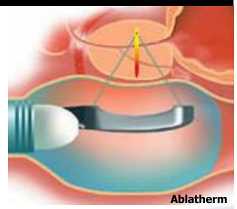
(Images courtesy Insightec, Inc. and Chris Cheng MD, National Cancer Centre, Singapore)

Prostate HIFU technology

(Courtesy Rajiv Chopra, PhD)

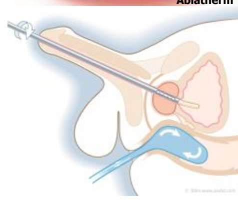
Transrectal Devices[1,2]

- Focused ultrasound transducers
- Ultrasound imaging guidance
- Long history (>2,000 treatments)
- Long treatment times



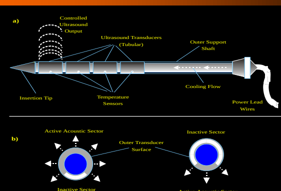
Interstitial/Transurethral[3,4,5]

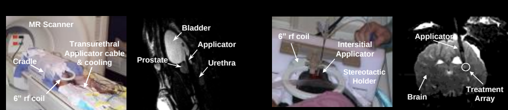
- Cylindrical/planar transducers
- MRI-guidance
- No focusing capabilities
- Shorter treatment times



1. Gelet et al 1996, 2. Foster et al 1993, 3. Diederich et al 1996, 4. Lafon et al 1998, 5. Hazle et al 2002

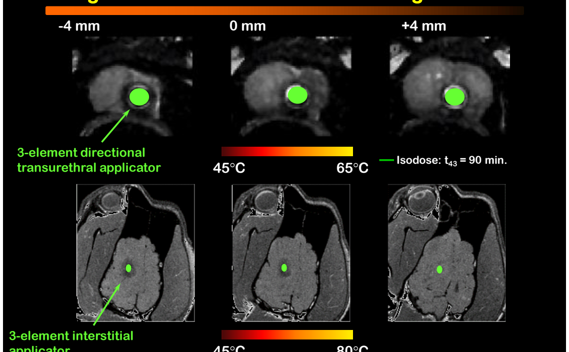
Interstitial ultrasound applicators for MRgTT





Hazle JD, et al. JMRI, 2002; Kangasniemi M, et al, JMRI, 2002

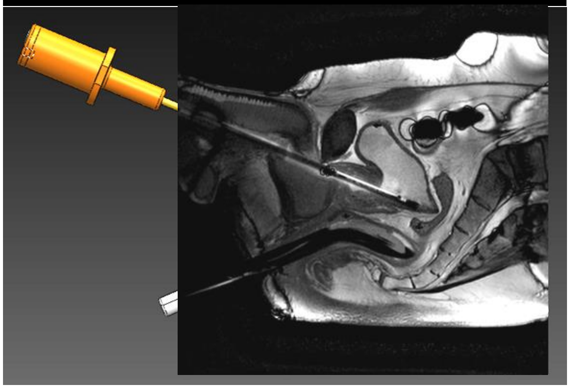
MR-guided interstitial ultrasound heating



Stafford RJ, et al, JMRI 2004; Diederich CJ, et al, Medical Physics, 2004; Hazle JD, et al. JMRI 15 (4): 409-17., 2002; Kangasniemi M, et al, JMRI, 2002

Precise Localization with MRI

(Courtesy Rajiv Chopra, PhD)

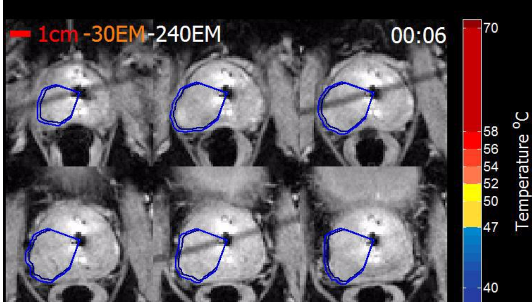


Transurethral Ultrasound Ablation in Prostate

www.profoundmedical.com

Real-time temperature control

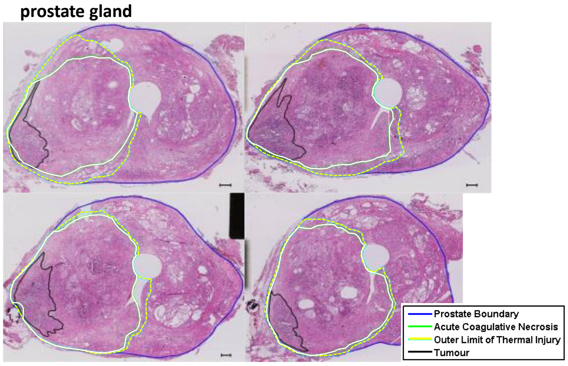
(Courtesy Rajiv Chopra, PhD)



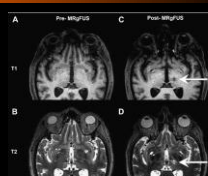
Histological Analysis

(Courtesy Rajiv Chopra, PhD)

- Continuous pattern of thermal damage extends to boundary of prostate gland



Future applications: transcranial MRgFUS



Neuropathic pain: 2-3mm focal lesion in right side of thalamus @ 1 day post-treatment

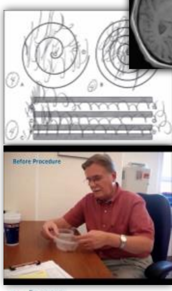
Malietzis G, et al. Br J Radiol 2013;86:20130044.

Blood brain barrier disruption (animal model)

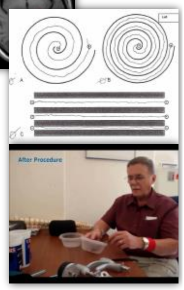
Future applications: transcranial MRgFUS

Essential Tremor Treatment

(Courtesy Jessica Foley, PhD)

- Awake, no anesthesia
- No incisions
- No burr holes
- No electrodes
- No infection
- No blood clots
- No brain damage

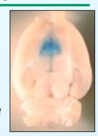


FOCUSED ULTRASOUND FOUNDATION

(Courtesy Nathan McDannold, PhD)

BBB disruption with focused ultrasound:

Mechanisms
- Tight junction widening
- Active transport via vesicles
- Associated with temporary vasospasm
- Sometimes leakage through microvessel damage (presumably due to inertial cavitation)



Trypan blue in rat

rabbit rat mouse

 Slide 35

Minimally-Invasive Thermal Therapies

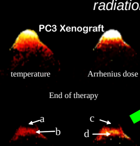
Tissue Temperature

-40°C 0°C 37°C 100°C

38°C to 50°C

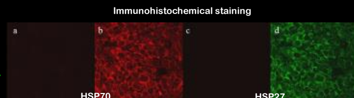
- *Heat* based mechanisms:
  - Low temperatures: Hyperthermia
    - *Goal(s): Modulate perfusion, permeability, tumor micro-environment, enzyme activation, heat shock protein expression, necrosis, apoptosis (induction/inhibition), sensitization to radiation or chemotherapy, targeted drug release, etc*

MR Temperature Imaging



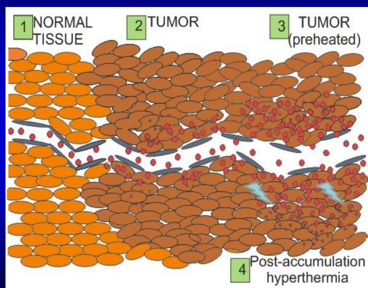
(HSP expression models)

Immunohistochemical staining



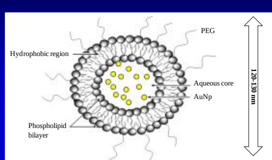
Rylander MN, Feng Y, Zhang Y, Bass J, Stafford RJ, et al, J Biomedical Optics, 2006
Rylander MN, Stafford RJ, Hazle J, Whitney J, Diller KR, Int J Hyperthermia. 2011

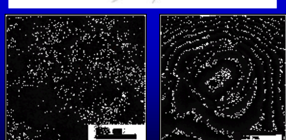
Another approach

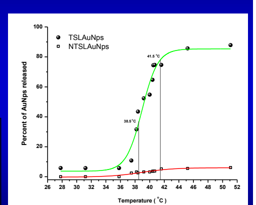


(courtesy Sunil Krishnan, MD)

Thermosensitive liposome

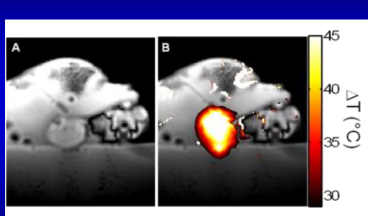






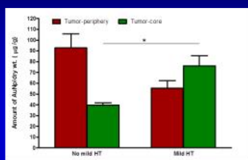
(courtesy Sunil Krishnan, MD)

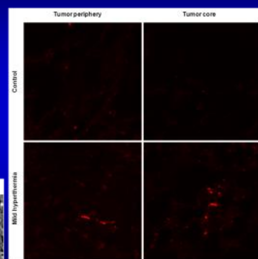
Focused ultrasound

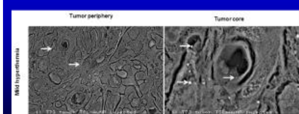


(courtesy Sunil Krishnan, MD)

Deep penetration of tumors

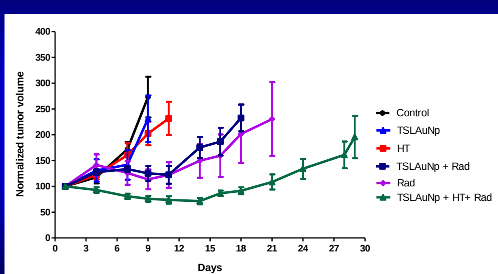






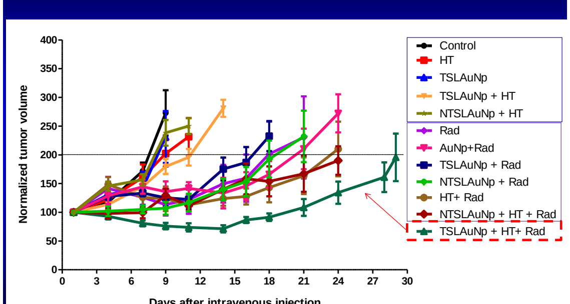
(courtesy Sunil Krishnan, MD)

Radiosensitization



(courtesy Sunil Krishnan, MD)

Radiosensitization



(courtesy Sunil Krishnan, MD)

Summary

MD Anderson Cancer Center

- Delivery of nanoparticles using thermosensitive liposomes enhances deep penetration of nanoparticles when triggered by hyperthermia
- Deep penetration of gold nanoparticles improves radiosensitization independent of the effect of hyperthermic radiosensitization
- In principle, this could be a class solution for a variety of tumors accessible by ultrasound

(courtesy Sunil Krishnan, MD)

Global Development Landscape

(Courtesy Jessica Foley, PhD)

Global Development Landscape

(Courtesy Jessica Foley, PhD)

Task Group No. 241 MR-Guided Focused Ultrasound

Charge

- Identify methodology, phantoms, and software for performance assessment of MRgFUS
- Areas of technical assessment include intrinsic MRgFUS characteristics, quantitative metrics of MRgFUS, and identification of quality assurance measures and procedures

Membership

Keyvan Farahani (NIH)

Rajiv Chopra (UT Southwestern) (Chair)
R. Jason Stafford (UT MDACC) (Co-Chair)

Stanley H. Benedict (UC Davis)
Paul Carson (U Mich)
Chris Diederich (UCSF)
Randy King (FDA)
Chrit Moonen (Utrecht)
Dennis Parker (Utah)
Rares Solomir (Geneva)
David J. Schlesinger (U Virginia)
Gail R. ter Haar (Royal Marsden)

Kim Butts-Pauly (Stanford)
Lili Chen (FCCC)
Arik Hananel (FUS Foundation)
Nathan McDannold (BWH)
Eduardo Moros (Moffit)
Ari Partanen (Philips)
Steffen Sammet (U Chicago)
Robert Staruch (Philips)
Eyal Zadicario (Insightec)

The diseases which medicines cannot cure, excision cures: those which excision cannot cure, are cured by the cautery; but those which the cautery cannot cure, may be deemed incurable.

- Hippocrates Aphorisms (400 BCE)

Thank you for your time!

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