Overview of MR-guided Focused Ultrasound Physics & Applications

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Department of Imaging Physics

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

Thermal therapy energy sources
- Cryotherapy
- Radiofrequency
- Microwave
- Laser
- Ultrasound


Modalities for image-guided thermal therapy
- US
- CT
- MRI

MRgFUS

Tissue Pathology
- T1 Pre
- T1 Treat
- T1+C Post
- T1+C Post

Applicator
- Isodose: t43 = 50 min.
Commercial Focused Ultrasound Systems

ExAblate (EDAP TMS, Lyon, France)
ExAblate OR (Insightec, Haifa, Israel)
Sonablate 500 (SonaCare Medical, Charlotte, NC)
Sonalleve MR-HIFU (Philips Healthcare, Guildford, UK)
Ablatherm (EDAP TMS, Lyon, France)

Ultrasound Guided
MRI Guided


MRgFUS: uterine fibroids

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

Imaging information synergistic with integration of model based simulation

Endgame
- increase safety + efficacy
- facilitate minimally invasive approaches previously not considered possible/safe

MR Temperature Imaging (MRTI)

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

<table>
<thead>
<tr>
<th>Tissue Type (Carotid)</th>
<th>Temp. Range (°C)</th>
<th>Temp. Sensitivity (ppm/°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>25-59</td>
<td>0.0102 ± 0.0005</td>
</tr>
<tr>
<td>Prostate</td>
<td>32-54</td>
<td>0.0102 ± 0.0005</td>
</tr>
<tr>
<td>Kidney</td>
<td>36-54</td>
<td>0.0102 ± 0.0006</td>
</tr>
<tr>
<td>Uterus</td>
<td>36-51</td>
<td>0.0102 ± 0.0002</td>
</tr>
<tr>
<td>Bone (femur)</td>
<td>17-57</td>
<td>0.0102 ± 0.0002</td>
</tr>
</tbody>
</table>

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

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

\[ \Omega = A_e^{nT} \exp \left( \frac{-E_a}{RT} \right) \]

- Cumulative Equivalent minutes @ 43 °C (CEM43)
  - Empirically derived from isoeffects observed in low temperature hyperthermia work:

\[ \text{CEM}(T) = \sum_{T_1}^{T_2} \frac{R^{1.2}}{0.25} \Delta t, \text{ with } R = 0.50 \text{ at } 43°C \]

- isoDF models

Yung J, et al, Medical Physics 2010

HIFU Ablation in Rabbit Paraspinal Muscle @ 1.1 T

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

12s HIFU sonication


Tissue Type (Canine) Temp. Range (°C) Temp. Sensitivity (ppm/°C)

| Brain | 25-59 | 0.0102 ± 0.0005 |
| Prostate | 32-54 | 0.0102 ± 0.0005 |
| Kidney | 36-54 | 0.0102 ± 0.0006 |
| Uterus | 36-51 | 0.0102 ± 0.0002 |
| Bone (femur) | 17-57 | 0.0102 ± 0.0002 |

Amplitude (A.U.)

Frequency (ppm)

0.0 1.2 2.4

-1.2 -2.4

12s HIFU sonication

Aliased lipid (CH2)

Water (OH)
**Imaging versus Histology**

15s FUS exposure in vivo (skeletal muscle)

<table>
<thead>
<tr>
<th>W</th>
<th>°C</th>
<th>ΔT</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>50</td>
<td></td>
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<tr>
<td>100</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>100</td>
<td></td>
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</table>

**Initial studies in breast**

Multi-planar, multi-shot EPI MRTI facilitated real-time MRTI with high spatial/spatial resolution, high SNR and lipid suppression

**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

Investigational Device Only
First approved indication: uterine fibroids

MRgFUS of painful bone mets
Planning: radiologist segmentation

MRgFUS of painful bone mets
Treatment: evaluation
Palliation is achieved by spreading the heat across the surface of the bone to ablate the nerves in the adjacent periosteum.

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)

Case Study – Liver HCC

67 yr 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.
Case Study - Liver HCC

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

Images courtesy of Sapienza University - Rome

Next stage of development: ‘conformal’ bone


Future application: prostate

Images courtesy Insightec, Inc. and Chris Cheng MD, National Cancer Centre, Singapore
Prostate HIFU technology

Transrectal Devices\textsuperscript{1,2}
- Focused ultrasound transducers
- Ultrasound imaging guidance
- Long history (>2,000 treatments)
- Long treatment times

Interstitial/Transurethral\textsuperscript{3,4,5}
- Cylindrical/planar transducers
- MRI-guidance
- No focusing capabilities
- Shorter treatment times


Interstitial ultrasound applicators for MRgTT


MR-guided interstitial ultrasound heating

Precise Localization with MRI

Transurethral Ultrasound Ablation in Prostate

Real-time temperature control

www.profoundmedical.com
Histological Analysis
(Courtesy Rajiv Chopra, PhD)

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

Future applications: transcranial MRgFUS


Blood brain barrier disruption (animal model)

Future applications: transcranial MRgFUS
Essential Tremor Treatment

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

(Courtesy Jessica Foley, PhD)

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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)

(Typan blue in rat)

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Minimally-Invasive Thermal Therapies

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

PC3 Xenograft
Immunohistochemical staining

HSP 70
HSP 27

MR Temperature Imaging (HSP expression models)
Another approach

Thermosensitive liposome

Focused ultrasound
Deep penetration of tumors

Radiosensitization

Radiosensitization

(courtesy Sunil Krishnan, MD)
### Summary

- 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.

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### Global Development Landscape

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Reimbursement</th>
<th>FDA Approval</th>
<th>Outside US Approval</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Parkinosis/rejection</td>
<td>Yes</td>
<td>No</td>
<td>Yes (Parkinosis/rejection)</td>
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<tr>
<td>Oncological</td>
<td>Prostate Cancer</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Prostate Cancer)</td>
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<tr>
<td>Musculoskeletal</td>
<td>Osteoarthritis</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Thyroid Nodules</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Thyroid Nodules)</td>
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### Anecdotal

<table>
<thead>
<tr>
<th>Field</th>
<th>Surgery</th>
<th>Dialysis</th>
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<tbody>
<tr>
<td>Urology</td>
<td>Prostate Nodules</td>
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<tr>
<td>Ophthalmology</td>
<td>Aphakia</td>
<td>Yes</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>Avoid Pain</td>
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### Preclinical

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Field</th>
<th>Preclinical</th>
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</thead>
<tbody>
<tr>
<td>Ophthalmology</td>
<td>Cataract</td>
<td>Yes</td>
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<tr>
<td>Dermatology</td>
<td>Psoriasis</td>
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<tr>
<td>Gastroenterology</td>
<td>Ulcer</td>
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### Conceptual

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Field</th>
<th>Conceptual</th>
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<tbody>
<tr>
<td>Neurology</td>
<td>Alzheimer's Disease</td>
<td>Yes</td>
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<tr>
<td>Cardiology</td>
<td>Heart Failure</td>
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</tr>
<tr>
<td>Urology</td>
<td>Bladder Cancer</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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*(Courtesy Sunil Krishnan, MD)*

*(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 (UMich)
Chris Diederich (UCSF)
Randy King (FDA)
Chris Missen (Utrecht)
Dennis Parker (UAB)
Rares Solome (Geneva)
David J. Schaeffer (U Virginia)
Gert R. ter Haar (Royal Marsden)

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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