Development of an MR-Guided HIFU-Based Pelvic Hyperthermia Program in a Radiation Oncology Environment

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Conflicts of Interest

• None

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Mild hyperthermia therapy (MHT)

- Radioresistance is a significant clinical barrier in improving radiotherapy outcome.
- MHT: heat tissue to 40-45°C and maintains the temperature for an extended period of time (up to 60 minutes).
- MHT is a powerful radiosensitizer.

MHT + RT

- Ex: Cervical Cancer

Ultrasound-mediated MHT

- Many clinical trials have assessed the use of US for MHT.
- Trials analyzed a large array of sites
- Limited MR-guidance, HIFU
High Intensity Focused Ultrasound (HIFU)

- HIFU: Focused ultrasound → local heating
- Non-ionizing, minimally invasive.
- Tissues in between focus and transducer minimally affected
- Focal point:
  - 1-3 mm Ø
  - 10-17 mm length

MR Guided HIFU (MRgHIFU)

- MR can monitor HIFU-induced temp changes
- Proton Resonance Frequency Shift method: Phase change linearly proportional to T change from 0-100ºC
- Relative measure → Requires a baseline phase and temperature
- These changes in T are color mapped to MR images.
- T maps can have lower resolution
- Absolute T measures possible but more difficult

MRgHIFU System

- Sonalleve V2 - Profound Medical
- Independent table slides over MR table (250 lb limit)
- Transducer: 256 PZT elements forming an annulus
- Transducer in oil bath, can move laterally, longitudinally
- MR-based real time temperature monitoring
- Water-based skin cooling system on top of oil bath (DISC)
- Dedicated coil must be utilized
Sonalleve V2

• System designed for pelvic ablation treatments (ex: uterine fibroids), developed use for ablating bone metastasis.
• Modified to perform MHT under MR guidance.

Sonalleve MHT

• Homogenous large volume by mechanical and/or electrical beam steering.

New Technology: Role(s) of Physicist

• Development of new technology (preclinical)
  - Instrumentation, software, etc.
  - Can be vendor driven
• QA
  - AAPM TG-241: MR-Guided Focused Ultrasound (MRgFUS)
  - AAPM TG-333: MR-Guided Focused Ultrasound Quality Assurance
• Clinical Application of Technology (preclinical → clinical)
  - Use of technology
    - Specific application in mind → how to optimize technology for that use
    - Technology developed/acquired → determine best utilization of technology
    - Application of technology (optimize imaging, planning, dosimetry, etc.)
  - Regulatory
    - FDA (IDE, IND, 510k, etc.)
    - IRB
Choice of Treatment Site

- Hypothermia useful (esp. w/ RT)
- Accessible due to table/transducer geometry
  - Transducer centered in table.
  - Good contact w/ transducer required.
  - Depth (8-10 cm), size of target limitations.
  - Motion (respiration, peristalsis, etc.) cause artifacts
- Air, bone in or near beam path will be problematic
- Patient comfort will be key → long TXs
  - Ablation can be done in short bursts
- Market?
  - Vendor partners need to show utility
  - Recruitment of subjects

Site: Cervical Cancer

- Late stage (FIGO IIIB-IV) have poor prognosis even w/ RT (5-year survival < 32% for IIIB, 20% for IVA).
- MHT has shown utility as adjuvant therapy to RT
- Relatively high load of patients at our clinic
- Sonalleve designed for pelvic treatments.
- Potential liabilities: Bony pelvis/femurs limit access windows, depth, potential for organ motion during TX.
- Need to address feasibility, safety, accessibility, and treatment approach for our patient population

Current MRgHIFU MHT Clinical Trials

- Clinical Trial (NCT02528175)¹: MRgHIFU for recurrent rectal cancer +RT compared with RT and oral chemotherapy.
- Chu² et al.: MRgHIFU MHT is feasible and safe for homogeneous targets (muscle in thigh and near rectum) in vivo.
- Not studied: MRgHIFU MHT feasibility and safety in pelvic geometries that would have broader applicability to cervix cancer treatments.

Project Aims

1. Demonstrate feasibility and safety of MRgHIFU induced MHT in vivo in an animal model for various representative cervical cancer target geometries.

2. Analyze potential for accessibility of cervical cancer targets in our patient population using retrospective data.

3. Phase I clinical trial on safety and feasibility of MRgHIFU induced MHT in human patients with late stage (FIGO IIIB-IVA) cervical cancer.

In vivo Target Selection

- 13 MHT treatment sessions in 6 pigs.
- 3 Different Sites (denoted by •):
  - Muscle adjacent to the ventral bladder wall (MVB)
  - Muscle adjacent to the dorsal bladder wall (MDB)
  - Uterus
- Motivation for selection: Representative of clinical target geometries.
Methods

Axial view illustration of the treatment plane and transducer position

- Feasibility: Computational analysis of temperature data
- Safety: Gd-enhanced T1 THRIVE MR images (pre vs post TX) + gross pathology + histopathology using ablation sites for positive controls
- Target = 42°C for 30 minutes.
- 18 mm treatment cell
- Maximum temp threshold = 44°C in near field
- Power = 100 W, Frequency = 1.0 MHz
- Temperature monitoring in 6 planes.
- Thermometry in each plane every 3.7 s

Feasibility Assessment Metrics

- For all voxels in the target ROI, average across all 3.7 s acquired “dynamic” images and calculate:
  - \( T_{\text{avg}} \): Average temperature
  - \( T_{10} \): Temperature that 10% of the voxels reached.
  - \( T_{90} \): Temperature that 90% of the voxels reached.
  - \( \sigma_T \): The standard deviation of the \( T \) of every pixel.
- Temperature metrics:
  - \( \text{Accuracy} = T_{\text{avg}} - 42^\circ \text{C} \)
  - \( \text{Precision} = \sigma_T \)
  - Uniformity = Temporal average of the largest difference between the \( T_{\text{avg}} \) and either the \( T_{10} \) or \( T_{90} \) in each dynamic
  - Temporal variation = Standard deviation of the \( T_{\text{avg}} \) values across all dynamics

- CEM43\( T_{90} \): The cumulative equivalent time in minutes that 90% of the voxels reached 43°C.
  \[ \text{equiv min } T_{43} \text{°C} = \sum_{i=0}^{\text{post}} R(T_{43} - T) \Delta t \]
  - \( R=2 \) for \( T>43^\circ \text{C} \)
  - \( R=4 \) for \( T\leq 43^\circ \text{C} \)
- The time needed for the temperature to reach \( \geq 41^\circ \text{C} \) after the start of sonication.
- The time needed for the temperature to decrease to \( \leq 40^\circ \text{C} \) after the end of sonication.
Planning and Treatment

Target ROIs overlaid on coronal MRIs

$T_{\text{avg}}$ maps

$T$ curves during MHT sessions

Results - Feasibility

- Overall temperature accuracy $0.45 \pm 0.32^\circ C$.
- Average values for all parameters clinically acceptable.
- No statistically significant differences between sites ($p<0.05$, Mann-Whitney U test).

Results - Feasibility

- No statistically significant difference in CEM43T$_{90}$ between sites ($p>0.05$, Mann-Whitney U test).
- Both the time for the temperature to reach $>41^\circ C$ at the beginning and fall $<40^\circ C$ at the end of MHT are clinically reasonable.
Results - Safety

- In all MHT sessions, no difference between pre- and post-MHT MR images.
- No damage seen at MHT targets, skin, or along the beam path in gross pathology.
- Ablation sites show stark differences between MHT targets on MR and pathology.

H&E Example: Uterus

- MHT targets show minimal to mild congestion (as denoted by ↑).
- Ablation sites show permanent damage, including severe edema, hemorrhage, and the separation of epithelium and lamina propria.

H&E Example: Muscle

- MHT targets showed no significant lesions.
- Ablation sites show permanent damage, including degeneration, necrosis, and fragmentation of skeletal muscle fibers.
Summary – Feasibility and Safety Study

- MRgHIFU-mediated MHT utilizing the Sonalleve is feasible and safe for an array of pelvic targets with varying anatomical geometries.
  - All treatments showed accuracy within 1°C of target.
  - All other tabulated parameters seem clinically reasonable.
  - No statistically significant differences between parameters for any of the target sites.
  - Imaging and gross pathology showed no differences between MHT treatment sites and untreated controls, but sharp differences between MHT and ablated sites.
- The Sonalleve could potentially be used to deliver MHT to cervical cancer malignancies in human patients.

Retrospective Study

Patient Cohort

- 14 FIGO Stage IIIIB to IVA cervical cancer patients
- Received at least a PET-CT and a simulation CT for RT planning.
- Metabolic tumor volume (MTV) identified by PET/CT used as the target volume
  - Treatment of MTV is an independent prognostic factor for disease-free survival in cervical cancer patients.

Methods

- MTV burned into simulation CT images.
- CT orientation manipulated as needed
  - Only anterior and posterior orientations considered in this preliminary analysis
- CT images imported to HIFU treatment planning system (TPS) for planning and analysis.

Targetability Criteria

Criteria for targetable cells:
1. Deeper than 1 cm from the skin.
2. Depth of the cell less than:
   - 9.5 cm targeting posteriorly
   - 11 cm targeting anteriorly
3. No bone allowed in the direct beam path.
4. No bone or spinal cord in the far field < 1 cm in the direction of the beam path.
5. The tumor is considered conditionally targetable if gas-containing structure(s) exist in the beam path.
Classification of Targets

Targets categorized into 3 types:

1. Directly targetable without intervention.
2. Potentially targetable with a reasonable intervention
   - Rectal filling with balloon
   - Bladder filling with Foley catheter or having patient drink water
3. Not targetable

Treatment Cell Placement

- Contour OAR/avoidance structures in beam path.
- In the coronal plane, cover the MTV uniformly with targetable cells.

- Review the beam path of every sonicated cell and delete any that violate the pre-set criterion.
Results: Targetability

- 93% of patients analyzed at least potentially targetable
- No patients directly targetable
- Primary factors limiting targetability:
  1. Bone blocking beampath
  2. Target Depth
  3. Scar tissue blocking beam entrance pathway

Targetable anteriorly
2 Patients

Targetable both ways
8 Patients

Targetable posteriorly
3 Patients

Summary: Retrospective Study

- ≥90% of analyzed patients with stage IIIB-IVA cervical cancer are potentially targetable with intervention.
- Limitations: Assumptions about patient positioning/compression, not considering target deformation w/ positional change.
- Future directions: Analyze more patients, analyze additional orientations (including slight decubitus positioning), refine depth criteria with imaging data.
- Given potential accessibility of targets, along with the in vitro feasibility and safety results can proceed to Phase I safety and feasibility study in human patients.

Conclusion

- MRgHIFU MHT is a potentially useful technology for enhancing the efficacy of RT treatments.
- Physicists are involved in many parts of the process for translating new technology such as MRgHIFU from preclinic into clinical implementation
- Late stage cervical cancer may provide a reasonable target site
- The Sonalleve V2 system is feasible and safe to use for an array for cervical cancer target geometries
- ≥90% late stage cervical cancer targets in our clinic may be partially accessible with MRgHIFU-mediated MHT with some form of intervention
- Next step: Phase I clinical trial for MRgHIFU MHT treatment of late stage cervical cancer in human patients
Bibliography

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