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

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Conflicts of Interest

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- None

Special Acknowlegements

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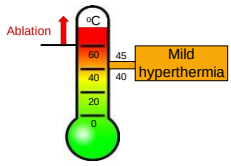
- Hong Chen, Ph.D. – Assistant Professor of Radiation Oncology and Biomedical Engineering, Washington University in St. Louis.

Mild hyperthermia therapy (MHT)

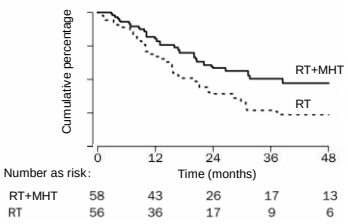
- Radioresistance is a significant clinical barrier in improving radiotherapy outcome
- MHT: heat tissue to 40-45ºC and maintains the temperature for an extended period of time (up to 60 minutes)
- MHT is a powerful radiosensitizer



Partanen A et al. *Int J Hyperthermia*. 2012;28(4):320–36.

MHT + RT

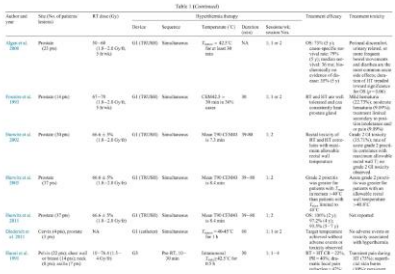
- Ex: Cervical Caner



van der Zee, J. et al. *Lancet, 2000*, 355(9210), 1119–1125.

Ultrasound-mediated MHT

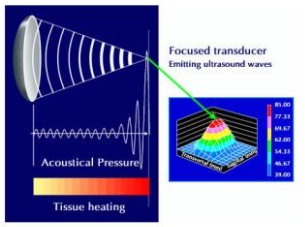
- Many clinical trials have assessed the use of US for MHT.
- Trials analyzed a large array of sites
- Limited MR-guidance, HIFU



Zhu L, et al. Ultrasound Med Biol. 2019;45(5) pp. 1025-1043.

High Intensity Focused Ultrasound (HIFU)

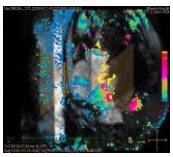
- HIFU: Focused ultrasound → local heating
- Non-Ionizing, minimally invasive.
- Tissues in between focus and transducer minimally effected
- Focal point:
  - 1-3 mm Ø
  - 10-17 mm length



Focused ultrasound generating heat in a targeted area.

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

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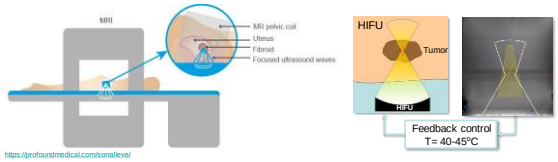

- System designed for pelvic ablation treatments (ex: uterine fibroids), developed use for ablating bone metastasis.
- Modified to perform MHT under MR guidance.

Sonalleve MHT

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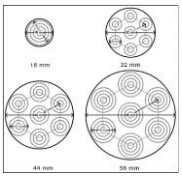
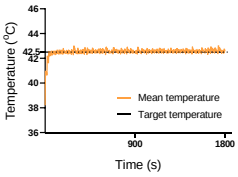
- Homogenous large volume by mechanical and/or electrical beam steering.

Hyperthermia heating cells



Temperature curve for 1-hour MHT



* Tillander M et al. *Medical physics*. 2016;43(3):1539–49.

New Technology: Role(s) of Physicist

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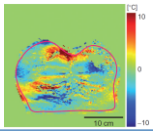
- Development of new technology (preclinical)
  - Instrumentation, software, etc.
  - Can be vendor driven
- QA
  - AAPM TG-241: MR-Guided Focused Ultrasound (MRgFUS)
  - AAPM TG-333: MR-Guided Focused Ultrasound Quality Assurance
- Clinical Application of Technology (preclinical → clinical)
  - Use 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

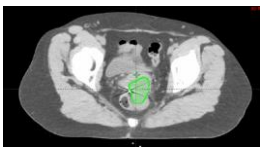
Choice of Treatment Site

- 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 Caner

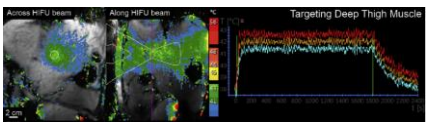
- Late stage (FIGO IIIB-IVA) have poor prognosis even w/ RT (5-year survival < 32% for IIIB, 20% for IVA)[1].
- MHT has shown utility as adjuvant therapy to RT
- Relatively high load of patients at our clinic
- Sonalleve designed for pelvic treatments.
- Potential liabilities: Bony pelvis / femurs limit access windows, depth, potential for organ motion during TX.
- Need to address feasibility, safety, accessibility, and treatment approach for our patient population



1. http://www.ssdhospital.in/indian-woman-and-cancer-cervical-cancer/

Current MRgHIFU MHT Clinical Trials

- Clinical Trial (NCT02528175)[1]: MRgHIFU for recurrent rectal cancer +RT compared with RT and oral chemotherapy.
- Chu[2] 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.

1. https://clinicaltrials.gov/ct2/show/NCT02528175
2. Chu W, et al. Int J Radiat Oncol Biol Phys. 2016;95(4):1259–67.

Project Aims

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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

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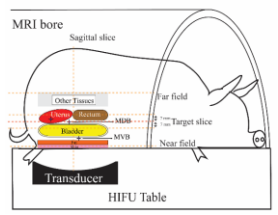

- 13 MHT treatment sessions in 6 pigs.
- 3 Different Sites (denoted by ✦):
  - Muscle adjacent to the ventral bladder wall (MVB)
  - Muscle adjacent to the dorsal bladder wall (MDB)
  - Uterus
- Motivation for selection: Representative of clinical target geometries.

In vivo Target Selection

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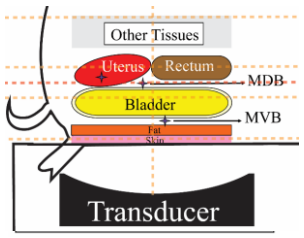

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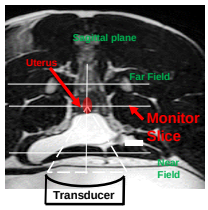
Methods



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 Assement Metrics

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

Feasibility Assement Metrics

- CEM43$_{T90}$: The cumulative equivalent time in minutes that 90% of the voxels reached 43°C.

$$\text{equiv min } T_{90}\ 43^{\circ}\text{C} = \sum_{t=0}^{t=\text{final}} R^{(T_{90}-43)}\Delta t$$

R=2 for T>43° C;
R=4 for T≤43° C.

- The time needed for the temperature to reach ≥41ºC after the start of sonication.
- The time needed for the temperature to decrease to ≤ 40ºC after the end of sonication.

Planning and Treatment

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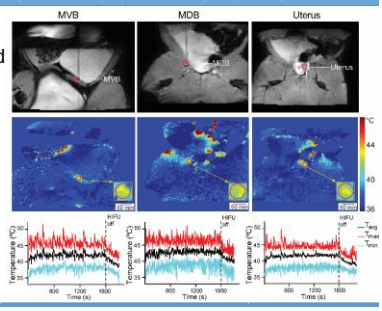
Target ROIs overlaid on coronal MRIs

T_{avg} maps

T curves during MHT sessions



Results - Feasibility

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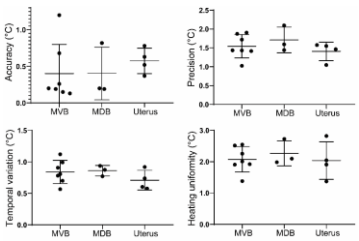

- Overall temperature accuracy 0.45 +/- 0.32°C.
- Average values for all parameters clinically acceptable.
- No statistically significant differences between sites ($p<0.05$, Mann-Whitney U test).

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Results - Feasibility

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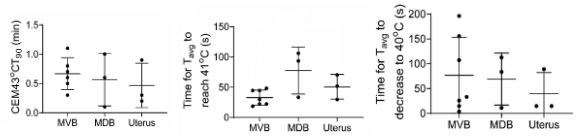

- No statistically significant difference in CEM43T_{90} between sites ($p<0.05$, Mann-Whitney U test).
- Both the time for the temperature to reach >41°C at the beginning and fall <40°C at the end of MHT are clinically reasonable.

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Results - Safety

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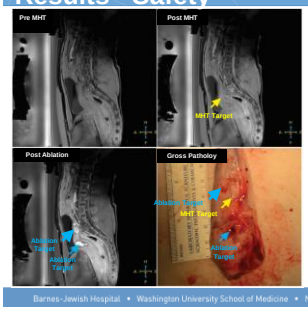

- In all MHT sessions, no difference between pre- and post-MHT MR images
- No damage seen at MHT targets, skin, or along the beam path in gross pathology.
- Ablation sites show stark differences between MHT targets on MR and pathology

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H&E Example: Uterus

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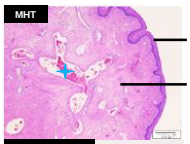

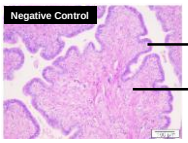

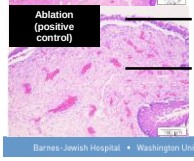

- MHT targets show minimal to mild congestion (as denoted by +).
- Ablation sites show permanent damage, including severe edema, hemorrhage, and the separation of epithelium and lamina propria.

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H&E Example: Muscle

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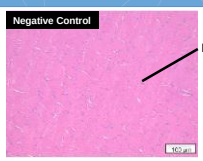

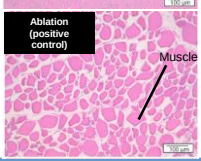

- MHT targets showed no significant lesions.
- Ablation sites show permanent damage, including degeneration, necrosis, and fragmentation of skeletal muscle fibers.

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 IIIB to IVA cervical cancer patietns
- 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 independed 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.

1. Chung HH, et al. *Gynecol Oncol* 2011; 120: 270–274

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

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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

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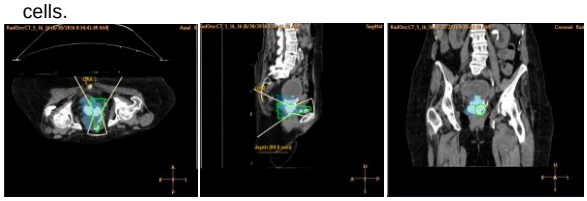
- Contour OAR/avoidance structures in beam path.
- In the coronal plane, cover the MTV uniformly with targetable cells.



Transverse Sagittal Coronal

Treatment Cell Placement

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- Review the beam path of every sonicated cell and delete any have violate the pre-set criterion.

Transverse Sagittal Coronal

Results: Targetability

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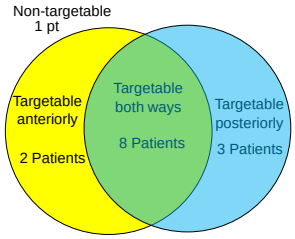
- 93% of patients analyzed at least potentially targetable
- No patients directly targetable
- Primary factors limiting targetability:
  1. Bone blocking beampath
  2. Target Depth
  3. Scar tissue blocking beam entrance pathway



Summary: Retrospective Study

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- ≥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

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- 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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Thank You!

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