

Towards a Completely Non-Invasive Treatment of Tumors in Children AAPM 2017, Denver, Colorado

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Image-Guided Non-Invasive Therapeutic Energy (IGNITE)

GOAL: Replace traditional pediatric surgery with techniques that are more precise, less invasive and pain free. Therapeutic Ultrasound is one such technique:



MR-HIFU = Integrated MRI & Ultrasound

- MRI Scanner
 - Visualize target
 - Plan treatment
 - Visualize temperature increase
 - Adjust treatment based on thermal feedback



- Generate high intensity sound waves
- Focus soundwaves on target
- Acoustic energy heats target tissue
- Tissue destroyed via coagulative necrosis





Bio-effects of Therapeutic Ultrasound

• Thermal

- Ablation
 - Temperatures > 55° C
 - Coagulative Necrosis
- Tissue hyperthermia
 - Temperatures > 39-45° C:
 - Enhanced drug delivery
- Mechanical
 - Shear stress
 - Histotripsy and Cavitation



Current Treatment Approaches for Pediatric Tumors

- Medical = Systemic Chemotherapy
- Surgical = Tumor resection
- Radiation = Often Combined
- Image-Guided Therapy
 - Minimally Invasive
 - Non Invasive
 - GAP in availability and utility



Potential Pediatric Oncology Applications

- Benign, Symptomatic Tumors
 Osteoid Osteoma
- Locally Aggressive, Symptomatic Lesions
 Desmoid
- Refractory/Relapsed Metastatic Lesions
 - Bone and Soft Tissue Sarcoma
 - Ablation
 - Enhanced Drug Delivery

Non-invasive MR-HIFU Therapy: Clinical Workflow

- 1. Position patient on device w/ good coupling
- 2. Plan treatment
- 3. Perform therapy
 - Adjust based on real time thermal feed back
- 4. Confirm treatment completion
- 5. Therapy may be repeated

Patient Positioning and Treatment Planning



Pre-treatment planning reduces procedure time Positioning aides are required to avoid pressure points Gel pads and liquid gel needed for good coupling free of air-water interfaces.

Benign: Osteoid Osteoma

Osteoid Osteoma

- A benign but painful bone tumor that predominantly occurs in children and young adults
- Dx: Classic clinical history Classic imaging

• Tx:

- °D.
- NSAID Pain Medications
- Surgery: collateral damage and long recovery
- Radiofrequency Ablation: high clinical success (95%)
 BUT: Invasive + ionizing radiation exposure
- MR-HIFU offers an <u>entirely non-invasive</u>, more <u>precise</u>, and radiation free alternative

Osteoid Osteoma: CT guided RFA



5 year old with an osteoid osteoma in the femur (yellow arrows)

Bone drill and probe are placed percutaneously with CT guidance Probe is then heated to 90° C for 6 minutes to destroy the nidus

No visual feed-back or confirmation of treatment success

Feasibility and Safety of MR-HIFU Ablation for Painful OO in Pediatrics

- Prospective, Phase I trial, 12 patients
- FDA monitored and IRB approved
- Clinicaltrials.gov NCT02349971
- · Eligibility
 - Age < 25 years
 - Radiologically confirmed diagnosis
 - Acoustically accessible lesion, excludes skull and spine
- Primary: Safety and Feasibility
- · Secondary: Early clinical response
- · Secondary: Imaging response

Screening and Enrollment



Osteoid Osteoma Patient 2

- 10 yo active girl (swimmer) who presented with left hip pain for 7 months.
 - No injury
 - Pain often prevents her from sleeping without medication
 - No longer swims
 - Partial pain relief with Ibuprofen (3x/day)

OO Patient 2 - Treatment



OO Patient 2: Clinical Response

- Day 7 Night pain improved
- Day 28: Pain resolved, not taking ibuprofen, sleeping well, and participating in swimming
- 6 Months: Asymptomatic without medications Sleeping well and active in sports
- 12 Months: Asymptomatic without medications Continues to swim Nidus not visible on follow up MRI
- No Serious Adverse Events





Locally Aggressive: Desmoid

Desmoid Tumors

- Locally aggressive, infiltrative, monoclonal proliferation of myofibroblasts
 - Pain
 - Motor/sensory neurological deficits
 - Contracture
- Medical therapies not very effective
- Recurrence after surgery
 - 50% after complete surgical resection
 - Combined with radiation therapy



Patient 1

- 15 yo active girl soccer and basketball
- Wide surgical resection at age 12
- Post surgery radiation therapy
- Recurrence 2 years later
 - Meloxicam
 - Sorafenib
 - Worsening symptoms and dose limiting toxicities



MR-HIFU: Desmoid Tumor



MR-HIFU: Desmoid Tumor





Desmoid: Patient 3



Metastatic Tumors: Relapsed or Refractory Sarcoma

Recurrent or Relapsed Sarcoma



- Prognosis for children with metastatic or recurrent solid tumors remains unacceptably poor
- Acute and late effects of chemotherapy and radiation are substantial
- HIFU offers non-invasive, non-ionizing, and spatially precise ablation of large-volume tumors

Patient 2

- 7 yo dx with large pelvic RMS at age 3
- Chemotherapy & surgical resection
- Post surgery radiation therapy
- Recurrence at age 6
 - Size increase of two focal metastatic sites despite chemo X 3
 - Increasing pain with walking
 - Goal: Pain palliation and local control



Recurrent Metastatic Rhabdomyosarcoma



Beyond Thermal Ablation...

- HIFU ablation has limitations
 - Anatomical
 - Physics
- Hyperthermia
 - Can enhance drug delivery
- Combined
 - Ablation
 - Enhanced drug delivery
 - More complete treatment



MR-HIFU Hyperthermia Enhanced Local Drug Delivery

- Mild regional hyperthermia (40-45°C) increases extravasation of liposomal drugs out of the tumor microvasculature and increases overall drug accumulation in tumors
 Supervisite offset with best and above thereast
- Synergistic effect with heat and chemotherapy



Imaging Enhanced Drug Delivery: Preclinical Before Injection After Injection After Heating During Heating



• Where heated: Preferential enhancement ↑Dox in heated area

MR-HIFU: Summary of CNMC Experience

- Benign symptomatic tumors - Osteoid Osteoma - 9
- Locally Aggressive Tumors:
 - Desmoid tumor 4
- Refractory Malignant Soft Tissue/Bone tumors
 - Osteosarcoma 1
 - Rhabdomyosarcoma 1
 - Ewings Sarcoma 1
- Experience to date: 16 patients, 20 treatments



THANK YOU

Thermal Ablation

- Use of heat/cold to cause focal tissue destruction via coagulative necrosis
- Minimally invasive, image-guided thermal ablation modalities:
 Radiofrequency Ablation (RFA), cryoablation, microwave, laser, etc.
- These modalities have limitations:
 - Invasive probes and needles
 - Suboptimal treatment planning and monitoring
 - Inability to heat conformal (match treatment shape to lesion shape)
 - Inability to reach target temperature (convective heat loss & heat sink)
- MR-HIFU is a non-invasive alternative that can address these limitations