MR Guided Focused Ultrasound Treatment of Tumors in Bone and Soft Tissue

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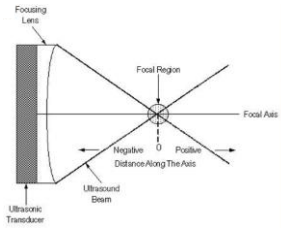
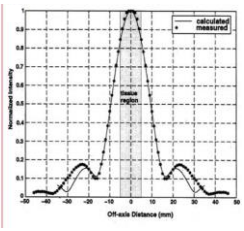
Physics in action

Painting by Giulio Parigi in 1600, via Wikimedia Commons

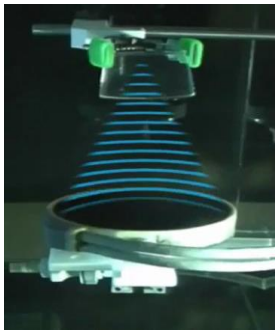
Focused ultrasound physics





What is focused ultrasound?

- large area ultrasound transducer array outside the body
- focused geometrically or electronically
- amplification
- high intensities deep within the body, lower intensities in intervening tissues

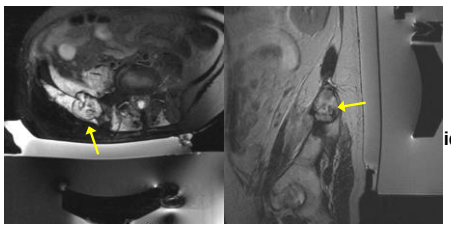


Why now?

Ultrasound was a therapeutic tool before it became a diagnostic modality
- physical therapy since 1930s
- focused US used clinically since 1950s
- rapid growth in past 10-15 years

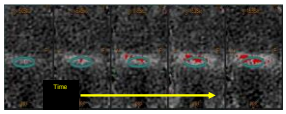
William Fry at the University of Illinois, Champaign, circa 1960, with a 4-beam high-intensity focused ultrasound applicator for neurosurgery.

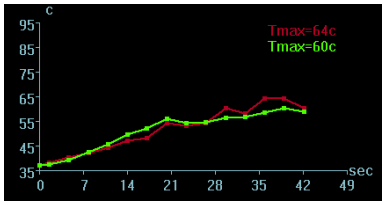
Advantages of MR guidance



Target identification

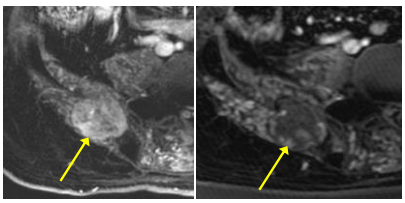
Advantages of MR guidance





Treatment verification during the procedure

Advantages of MR guidance



before MRgFUS **after MRgFUS**

Post-procedure target validation

Pain from bone metastases is often debilitating

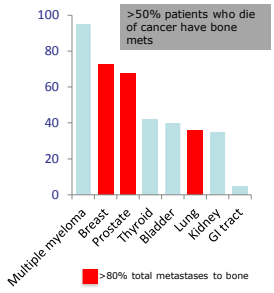
- 76% of patients with bone metastases report moderate to severe bone pain at some point in their disease
- Pain from bone metastases often becomes refractory to systemic therapies
- External beam radiation therapy (EBRT) is the current standard for refractory bone pain
- Up to 35% of patients do not experience any pain relief with EBRT and, in those that respond, pain recurs in up to 27%
- Patients not treated for bone metastases are at increased risk for skeletal complications which impact pain and quality of life (QoL)

Distribution of Skeletal Mets

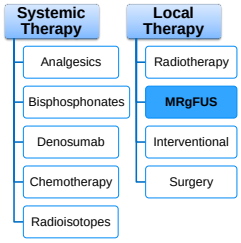
Sources: You et al., 2006; Hartsell et al, 2005.

Bone metastases are common in many cancers

% Patients Developing Bone Mets



Currently Available Palliation for Bone Metastases



Sources: Skeletal Care Academy; Coleman et al., 2006.

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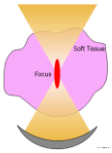
Focused ultrasound bone vs soft tissue treatment

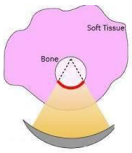
Treatment dictated by the properties of the target tissue

Focal Therapy in Soft Tissue



Ablates *only* at the focal point

Surface Therapy in Bone



Heats larger area of bone cortex

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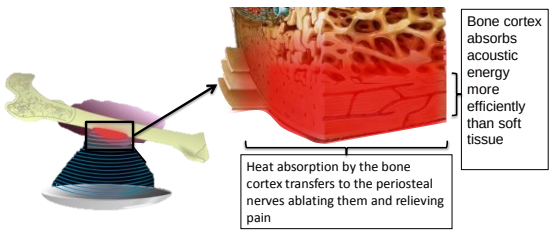
Mechanism of MRgFUS bone treatment

Thermal ablation of nerves within bone provides pain palliation



Bone cortex absorbs acoustic energy more efficiently than soft tissue

Heat absorption by the bone cortex transfers to the periosteal nerves ablating them and relieving pain

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MR guided focused ultrasound treatment

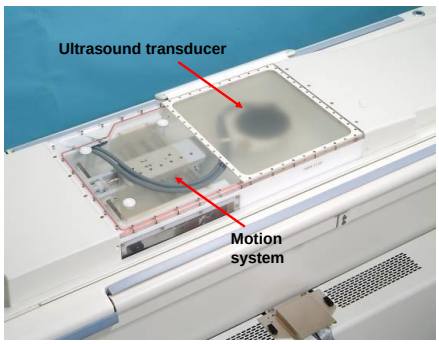
MR guided FUS

1. Patient Table
- Docks to 1.5T and 3T MR scanners
- Phased array transducer

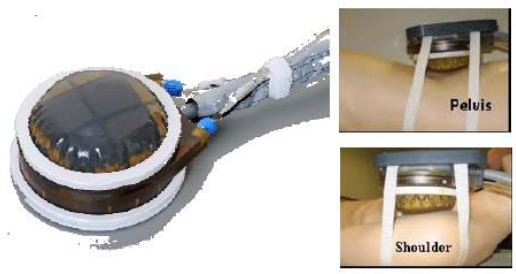
2. Operator Console
- Controls all treatment planning and operation
- Sits next to MR in console room

3. Equipment Cabinet

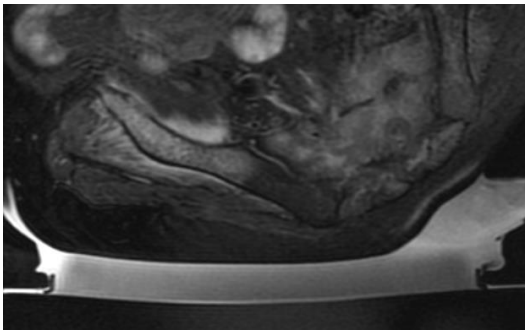
Patient table: patient cradle



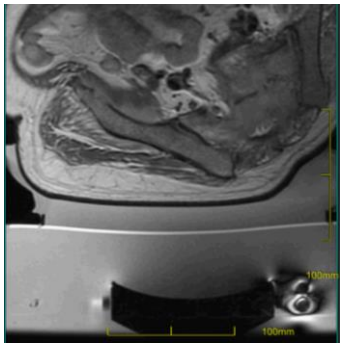
Conformal focused ultrasound probe



Pre-treatment imaging



Treatment planning



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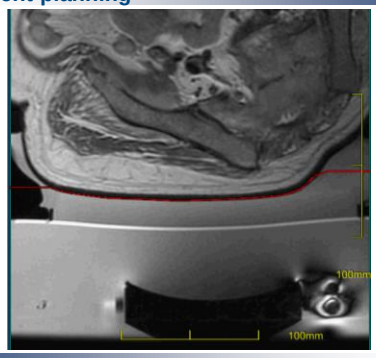

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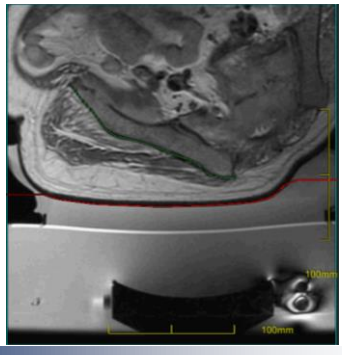

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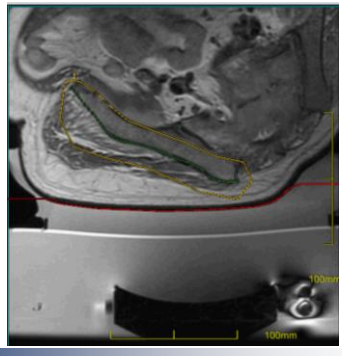

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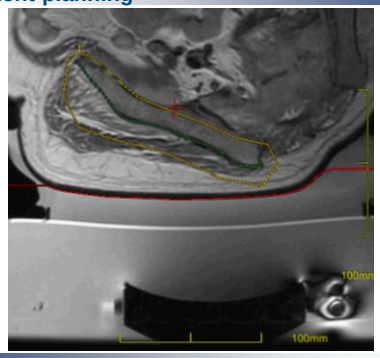
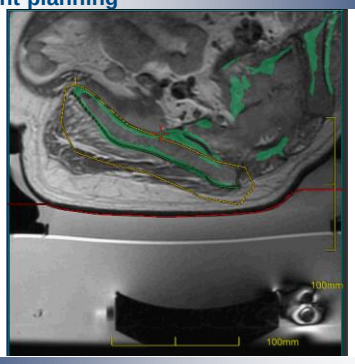


Treatment planning



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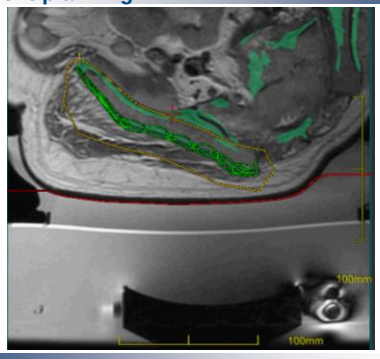

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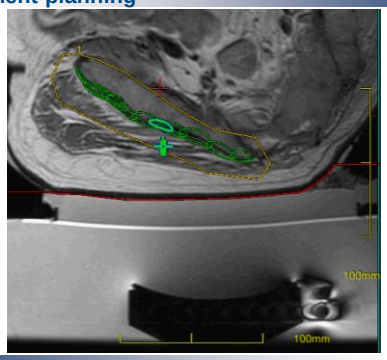

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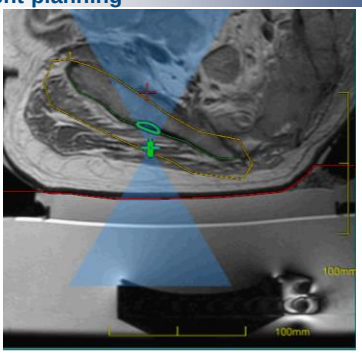

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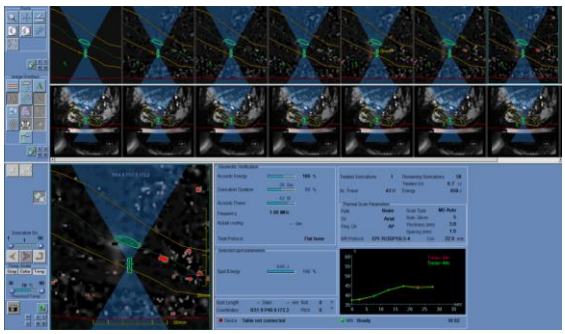
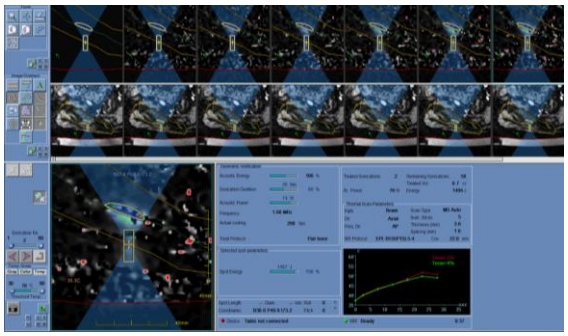


Treatment planning



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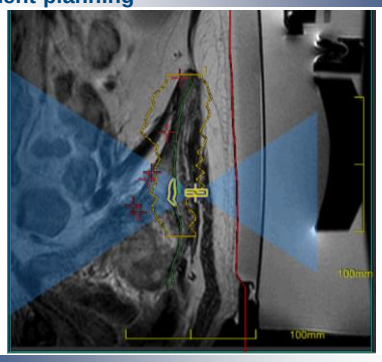

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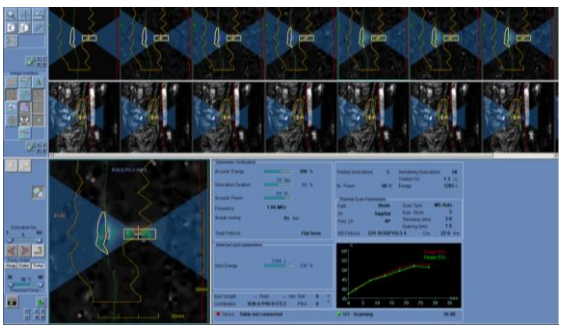

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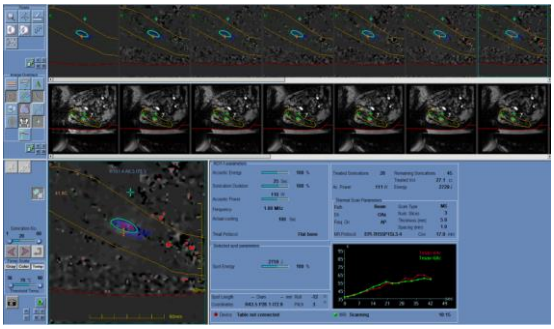
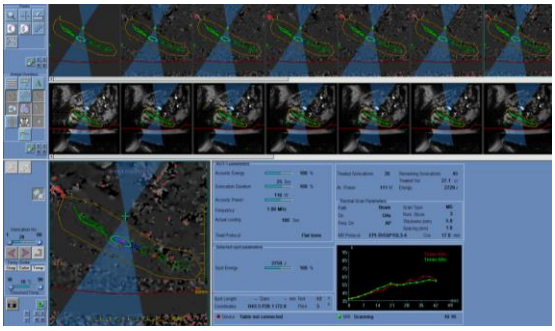
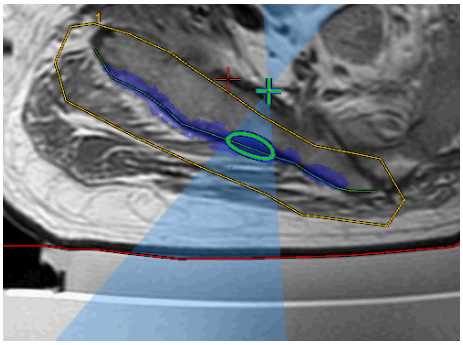


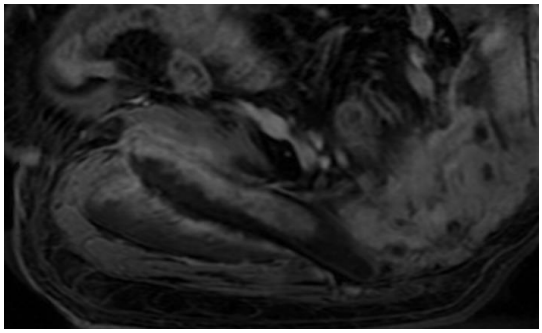
Treatment



Treatment

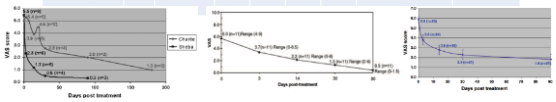


Post-treatment verification



Prospective clinical experience

Author	N	FU (m)	PR	CR	SD	PD	Pain	Sig AEs
Catane[1]	13	2	NR	NR	NR	NR	65%	0
Gianfelice[2]	11	3	54	45	0	0	92%	0
Liberman[3]	31	4	36	36	24	4	69%	0
Napoli[4]	18	3	3	13	0	2	84%	0



1. *Ann Oncol*, 2007 2. *Radiology*, 2008 3. *Ann Surg Onc*, 2009 4. *Invest Radiol*, 2013

Pivotal study of MRgFUS for bone metastases

- **Primary Efficacy Endpoints**

1. At least 50% of patients on treatment arm will achieve at least 2 point improvement in pain at 3 months without increase in medication.

2. The response rate in the treated group will be significantly greater than the response rate in the sham group.

Pivotal study of MRgFUS for bone metastases

- **Secondary Efficacy Endpoints**
  1. Numerical Rating Scale (NRS) score (0 – 10)
  2. Medication use quantified by 24 hour morphine equivalents
  3. Quality of life (QoL): BPI-QoL

- **Safety Endpoints**

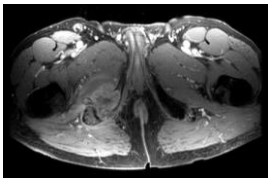
  Adverse Events (AE's) & Serious Adverse Events (SAE's)

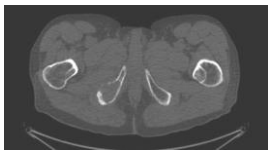
Inclusion and exclusion criteria

- ≥ 18 years of age with life expectancy ≥ 3 months
- Not candidates for RT
- Tumors were visible on MRI and device accessible
- Distinguishable pain at site of targeted tumor
- Tumors were ≥ 1 cm from skin or major nerves
- Low risk of fracture
- Excluded
  - significant comorbidities
  - if site needed surgical stabilization

Clinical case

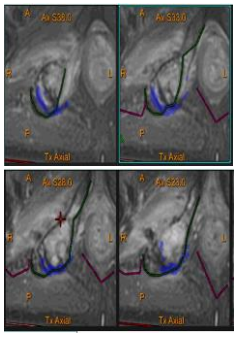
- 78 year old male
- Metastatic melanoma
- Painful osteolytic lesion in right ischium
- Treated with Cyberknife, with persistent pain

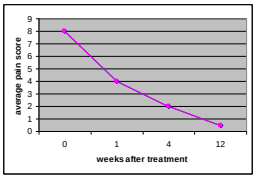




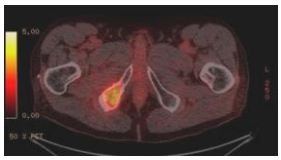
Clinical case

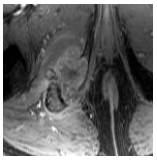
- 78 year old male with painful metastatic melanoma lesion in right ischium
- MRgFUS procedure required 19 sonications, up to 1900 J
- <60 min sonication time

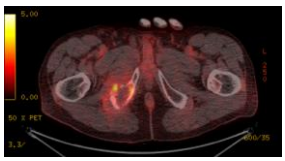


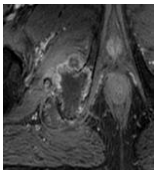


Clinical case









Magnetic Resonance–Guided Focused Ultrasound for Patients With Painful Bone Metastases: Phase III Trial Results

Mark D. Hurwitz, Pejman Ghanouni, Sergey V. Kanaev, Dmitri Iozeffi, David Gianfelice, Fiona Mary Fennessy, Abraham Kuten, Joshua E. Meyer, Suzanne D. LeBlang, Ann Roberts, Junsung Choi, James M. Larner, Alessandro Napoli, Vladimir G. Turkevich, Yael Inbar, Clare Mary C. Tempany, Raphael M. Pfeffer

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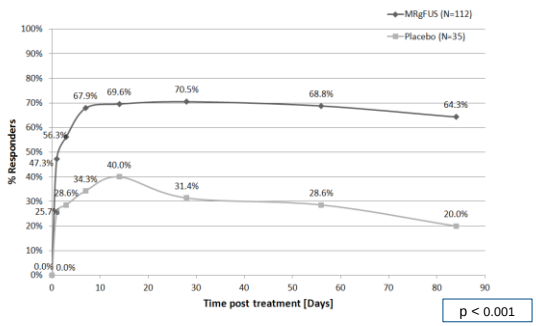
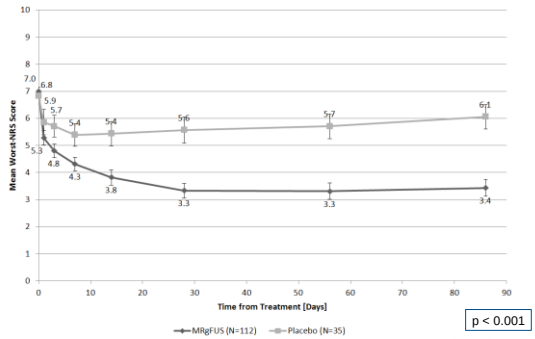
Responses by study arm



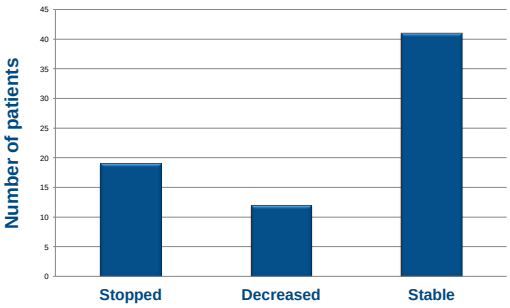
p < 0.001

NRS decrease durable to 3 months

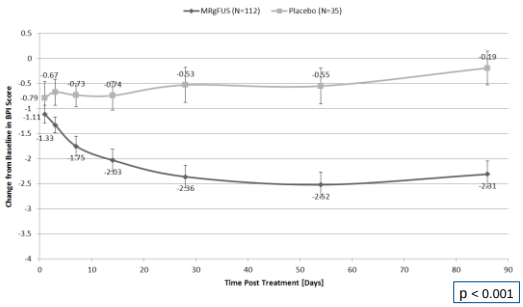


p < 0.001

Opioid use in responders at 3 months



Reduction in interference of pain with life



p < 0.001

Patient characteristics

Parameter		MRgFUS N=115 (76%)	Placebo N=37 (24%)
Primary Cancer Type [n (%)]	Breast	34 (30%)	19 (54%)
	Prostate	15 (13%)	2 (6%)
	Kidney	9 (8%)	2 (6%)
	Lung	17 (15%)	4 (11%)
	Other	35 (31%)	8 (23%)
Target Lesion Type [n (%)]	Osteoblastic	25 (22%)	6 (17%)
	Osteolytic	59 (53%)	21 (60%)
	Mixed	27 (24%)	8 (23%)

Patient characteristics

Parameter		MRgFUS N=115 (76%)	Placebo N=37 (24%)
Target Lesion Location [n (%)]	Pelvis	70 (63%)	19 (54%)
	Sacrum/Coccyx	12 (11%)	6 (17%)
	Rib/Sternum	16 (14%)	6 (17%)
	Extremities	7 (6%)	3 (9%)
	Scapula	7 (6%)	1 (3%)
Prior Radiation Therapy [n (%)]	Prior RT to lesion*	49 (44%)	9 (26%)
	Prior RT elsewhere	14 (13%)	2 (6%)
	No Prior RT	46 (41%)	24 (69%)
	Missing	3 (3%)	0 (0%)

Safety

47 AEs:

- 36 (32.1%) sonication pain
- 9 (8%) positional pain
- 5 patients stopped early

4 SAEs:

- Gr 3 skin burn
- Neuropathy (hip flexor weakness)
- 2 fractures in osteolytic bone lesions (1 away from treated site)

How does this compare to radiation?

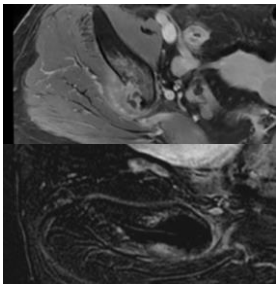
Comparison vs. first line treatment with radiation

	BM004 Study	RTOG 97-14*	
	MRgFUS (%)	8Gy x 1 (%)	3 Gy x 10 (%)
Complete Responders	23	15	18
Partial Responders	41	50	48
Non-Responders	36	35	34

Hartsell, WF, *J Natl Cancer Inst* 2005

Key to treatment success

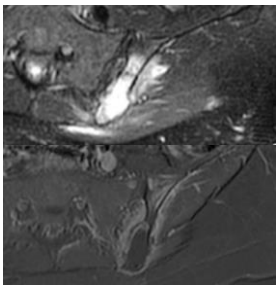
- "Only" 65% had treatment relief
- Hypothesized that some of the patients that didn't respond in the treatment group may not have had a technically successful treatment.
- Reviewed imaging for all the patients treated in the trial, looking for any imaging features that predict pain relief
  - Tumor location and size
  - Intact cortical bone
  - Lytic or sclerotic tumor
  - T2WSI
  - Enhancement
- Subcortical devascularization
- Presence correlates with pain relief



Key to treatment success

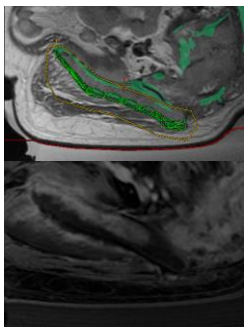
- *87 of 104* patients had the black band (84% technical success)
- *78 of 87* patients with successful treatment had pain relief (90%)
  - 71 had durable relief (82%)
- *12 of 17* patients without successful treatment had no pain relief (70%)

- OR of treatment resulting in pain relief: **7.2**
- OR of successful treatment resulting in pain relief: **14.4**

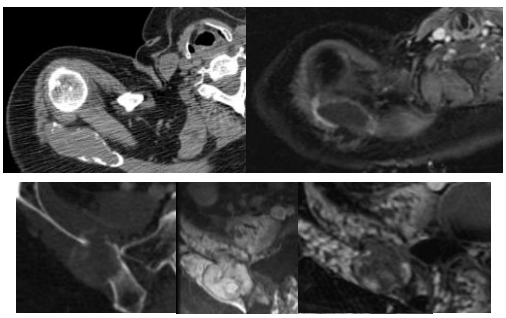


Key to treatment success

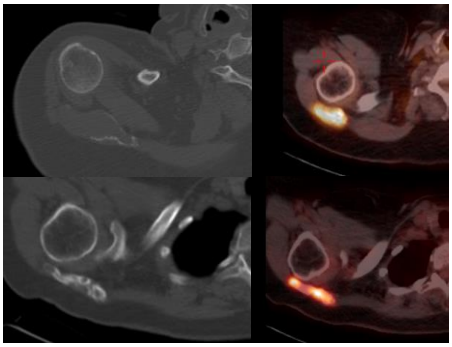
- Examined treatment parameters for correlation with technical success
  - Number of sonications
  - Sonication energy
  - Total energy delivered per treatment
  - Energy density on bone
- Black band correlates with %ROT covered during treatment, which correlates with response
  - CR – 93% coverage
  - PR – 90%
  - PR, but not durable – 62%
  - No response – 66%
  - No black band – 66%



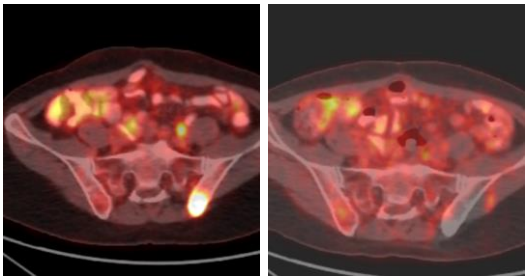
Tumor control – not necessary, but possible



Tumor control

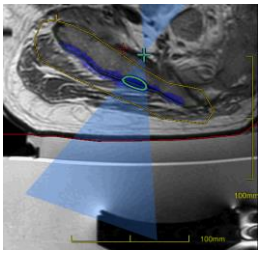


Tumor control



Treatment criteria

- Tumors must be in the following locations
  - pelvis and posterior lower lumbar spine
  - ribs and sternum
  - shoulders, arms, and legs
- Tumors must be visible on MRI
- Tumors must be accessible to the focused ultrasound beam
  - for example, tumors blocked by extensive scarring or bowel cannot be treated.
- The targeted bone must be at least 1 cm from the skin surface.

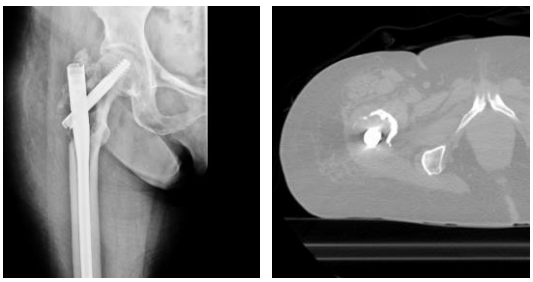


Contraindications to treatment

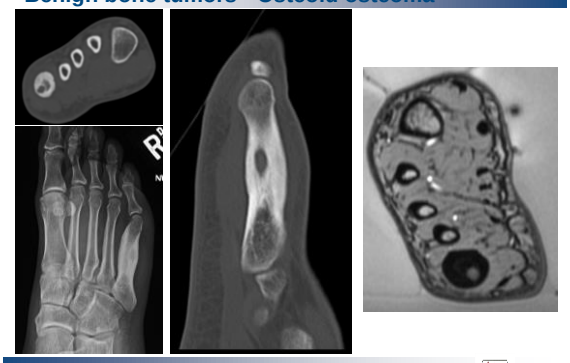
Not a good candidate for the treatment if:

- Cannot safely undergo MR imaging
- Have a bone that is fragile and may break or needs surgery to be stabilized, or has already been stabilized with surgical implants
- Have extensive skin scarring in the areas that would be treated.

Expanding applications



Benign bone tumors - Osteoid osteoma



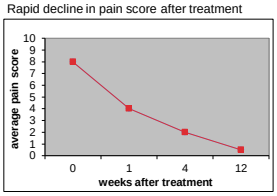
Risks of treatment

- Most common risk is pain or discomfort during treatment due to delivery of sonication energy
  - Relieved through anesthesia and intravenous medications
  - Dissipates shortly after each sonication ends
- Positional pain
- Nausea or vomiting as a side effect of the narcotic medications
- Blood in urine or urinary tract infection due to urinary catheter
- Low grade fever for a few days as a reaction to the ablated tissue
- Low risk of:
  - Skin burns, nerve injury, or bone fracture
  - Deep venous thrombosis because of the prolonged stationary position in the MR scanner

Benefits of treatment

- Non-invasive
- Single outpatient procedure
- Rapid reduction in pain
- Successful in patients that have not responded to radiation
- Favorable risk profile

Rapid decline in pain score after treatment

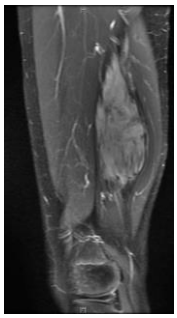


Conclusions

- Relief from painful bone metastases is a significant clinical need
- MRgFUS intervention
  - Targeted
  - Effective
    - 80-90% of those with successful treatment had pain relief
  - Minimally invasive
  - Nontoxic
- MR image guidance and intervention
  - MR thermometry provides safety and treatment verification
- Future directions
  - Tumor control

Clinical Background for Soft Tissue Tumors of the Extremities

- Heterogeneous group of tumors arising from connective tissues
- Natural history
  - Benign
  - Benign, but locally aggressive
  - Malignant

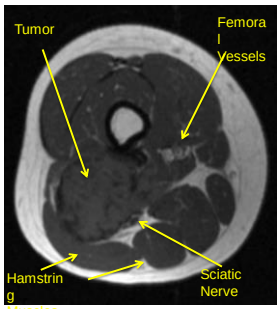


Treatment of soft tissue tumors

- Desmoid tumor:
  - Observation
    - Useful to differentiate aggressive vs slow-growing tumor
  - Surgery and/or radiation therapy
  - Medical approaches include: anti-estrogens, NSAIDs, chemotherapy, targeted therapies
  - Cryoablation
- Vascular malformation
  - Surgical resection
  - Image-guided percutaneous sclerotherapy
  - Image-guided ablation – radiofrequency, laser or cryoablation
- Soft tissue sarcoma:
  - Surgery alone or in combination with radiation or chemotherapy
    - Potentially curative
    - Significant adverse events and impact on quality of life

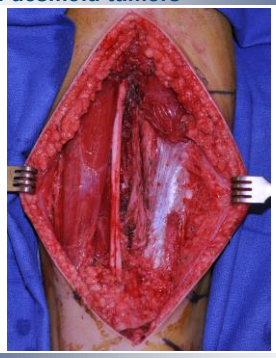
Treatment of desmoid tumors

- Surgery
  - Infiltrative tumor, so large resection needed to achieve negative margins
- Radiation used to:
  - Reduce the rate of local recurrence
  - Treat unresectable tumors
  - Palliate pain
- Conservative approach now aims to preserve function
  - Recurrence depends not only on positive margin as well as behavior of tumor

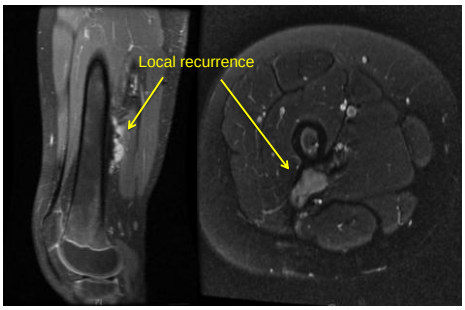


Treatment of desmoid tumors

Treatment of desmoid tumors



Treatment of desmoid tumors



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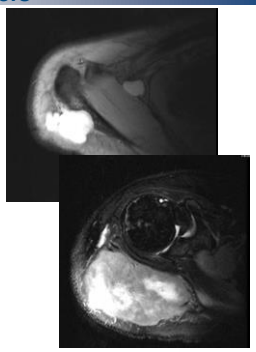
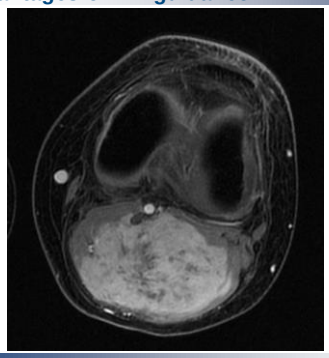


Clinical background for soft tissue tumors

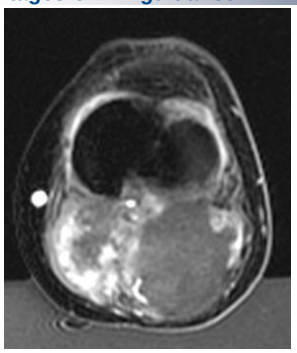
- Treatment
  - Surgical resection
  - Radiation therapy
  - Chemotherapy
  - Novel systemic treatments (targeted therapies)
- Side effects
  - Surgical morbidity
  - Radiation burns, secondary malignancy, fibrosis, chronic edema
  - Chemotherapy toxicity
- Clinical need
  - Decrease morbidity associated with treating soft tissue tumors
  - Primary, recurrent, or palliative treatment

Advantages of MR guidance



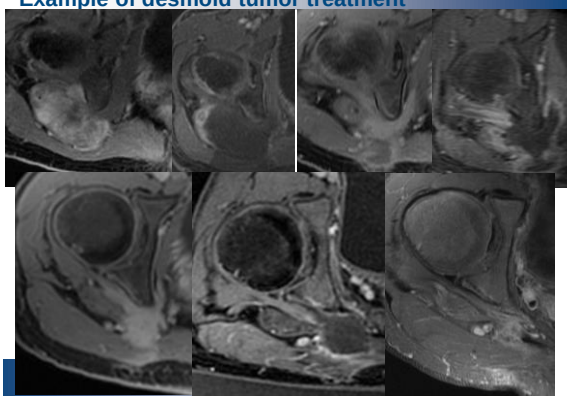
Targeting and safety

Advantages of MR guidance

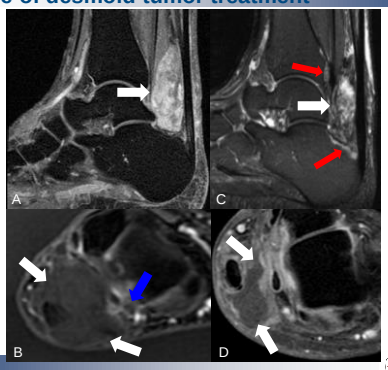


Post-procedure validation

Example of desmoid tumor treatment



Example of desmoid tumor treatment



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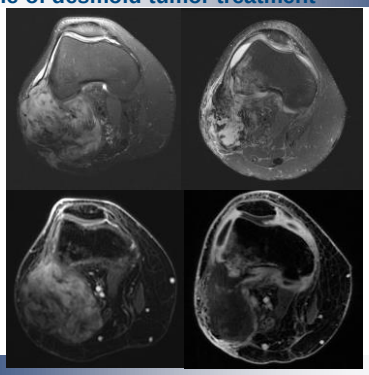
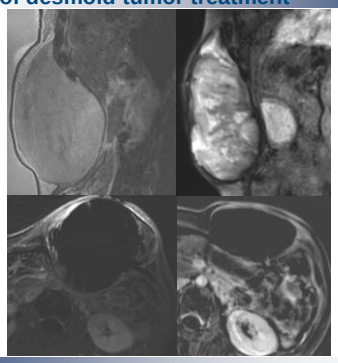
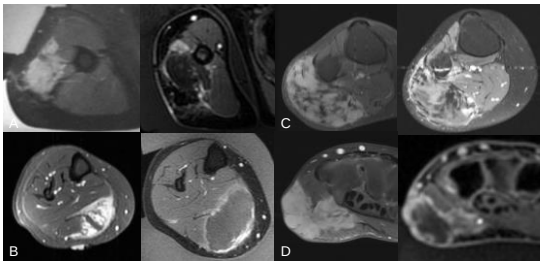
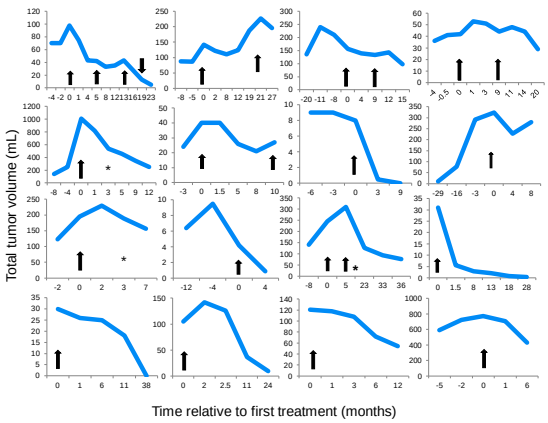


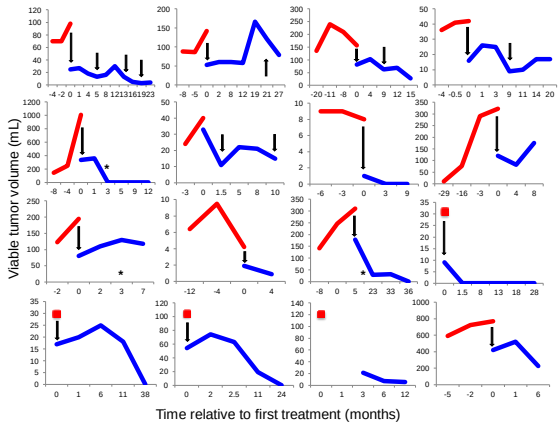
Example of desmoid tumor treatment



Other treatment sites





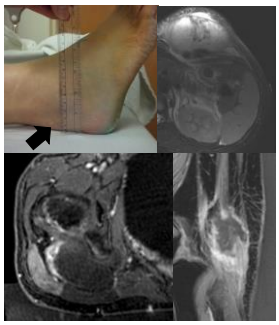


Treatment summary

- Four sites, 15 patients, 26 treatments
- Average follow-up: 17.5 months (4 – 38 months)
- Patient age: 28 years (7 – 66 years)
- Anesthesia: GA, regional, regional + GA, local + conscious sedation
- Sonications per treatment: 90 ± 47 (17 – 235)
- Treatment time: 3.5 hours (0.8 – 8 hours)
- Spot energies: 1428J (419 – 2867J)
- Spot temperature: 58 ± 5° C
- Median total tumor volume: 212 mL (4 – 1010 mL)
- Average NPVR: 69% (95% CI: 61-77%)
- Pain relief:
  - Max: 7.5 ±1.9 → 2.7 ± 2.6 ($p < 0.0002$)
  - Avg: 6 ± 2.3 → 1.3 ± 2 ($p < 0.003$)

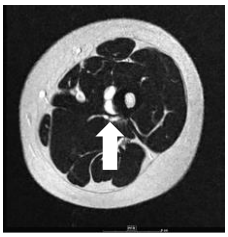
Adverse events

- 1st or 2nd degree skin burn
  - 8 of 26 treatments
- Non-target ablation
  - 3 of 26 treatments
- Nerve injury
  - 3 of 26 treatments



Clinical Background for Vascular Malformations

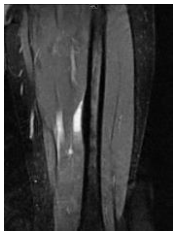
- Heterogeneous group of tumors arising all over the body
  - Most common cause of pediatric soft tissue tumors
- Vascular malformations are classified based on flow dynamics
  - High flow – AVM or AVF
  - Low flow – venous, lymphatic capillary, or mixed
- Grow proportionally with the patient
  - Exacerbated by hormonal changes during puberty or pregnancy, or by trauma or infection



Soft Tissue Vascular Malformations

Venous malformations

- Most common vascular malformation
- Location
  - Head and neck (40%)
  - Trunk (20%)
  - Extremities (40%)
- Composition
  - Large dysplastic thin walled vascular channels with sparse smooth muscle and abnormal stroma, and thrombi and phleboliths
  - Connect with adjacent physiologic veins
  - Invade across adjacent tissues
- Presentation
  - Congenital, but symptomatic in late childhood or early adulthood
  - Symptoms vary with depth of lesion
    - Pain
    - Impaired mobility
    - Skeletal deformity



Soft Tissue Vascular Malformations

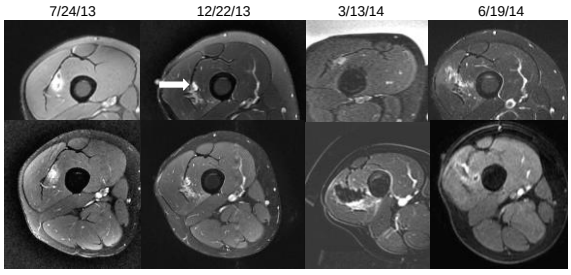
Standard treatment for slow flow lesions

- Surgical resection – 90% success
- Image-guided percutaneous sclerotherapy – 65-90% success
- Image-guided percutaneous radiofrequency, laser or cryoablation

Treatment summary

Patient age	44 years	18 – 66 years
Anesthesia	General a/o regional	
Follow up	5.5 months	3 – 12 months
Sonication number	53	14 – 92
Treatment time	2.5 hours	1 – 4 hours
Sonication energies	1700 J	650 – 2500 J
Power	187 W	97 – 253 W
Sonication duration	9.7 s	7.6 – 13.2 s
Spot temperature	50°C (avg)	56°C (max)
Total tumor volume	17.6 mL	0.4 – 61 mL
Maximal tumor diameter	5 cm	1.4 – 11.4 cm
NPV	21.7 mL	
NPVR	6.1	1.05 - 13

Patient #1



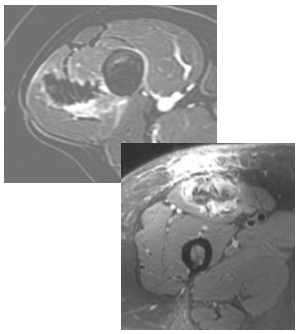
Pre-surgery
Pain = 7

Post-surgery
Pain = 8

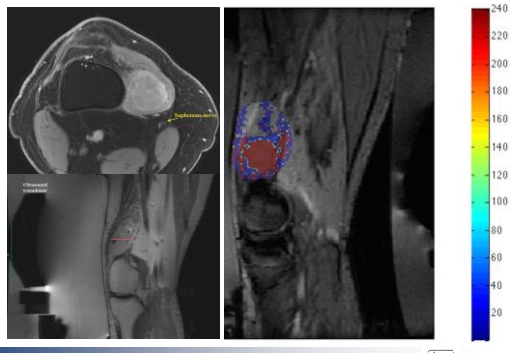
Post-MRgFUS
Pain = 0

Adverse events

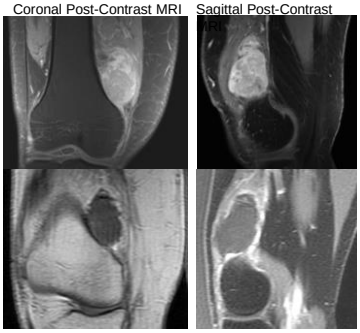
- No skin burn or nerve injury
- Non-target ablation
  - Fascia
  - Bone
  - Fat



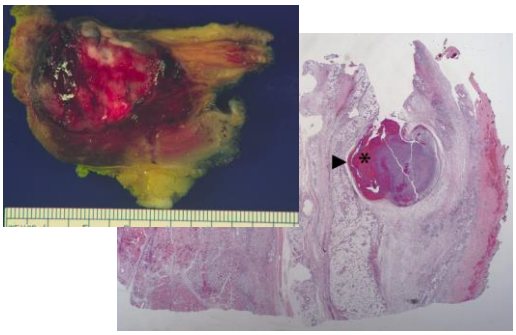
Soft tissue sarcoma treatment



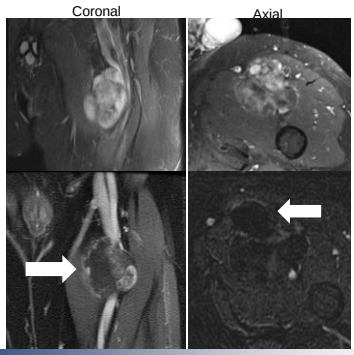
Soft tissue sarcoma treatment



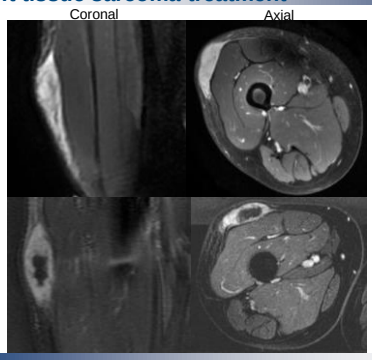
Soft tissue sarcoma treatment



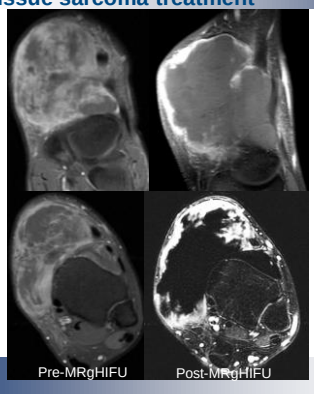
Soft tissue sarcoma treatment



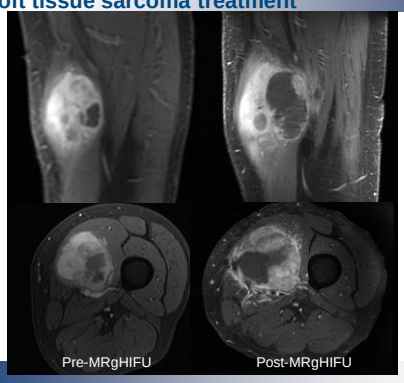
Soft tissue sarcoma treatment



Soft tissue sarcoma treatment



Soft tissue sarcoma treatment

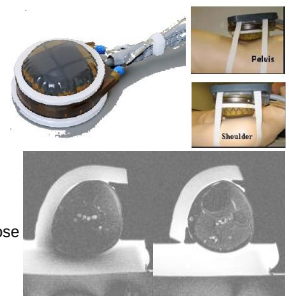


Sarcoma treatment summary

- 5 patients
- Patient age: 54 years (28– 70 years)
- Anesthesia: regional
- Sonications per treatment: 57 (34 – 81)
- Treatment time: 2 hours (1 – 3 hours)
- Spot energies: 1506 J (679 – 2985 J)
- Spot temperature: 56 ± 4˚ C (avg); 67 ± 10˚ C (max)
- Median total tumor volume: 104 mL (31 – 205 mL)
- Median NPV: 35 mL (7 – 101 mL)
- Average NPVR, total volume: 47% (14 – 97%)
- Average NPVR, planned volume: 818% (0.72 – 36.1)

Challenges

- Positioning
  - Coupling to transducer
  - Anesthesia
- Higher frequency transducer
- MRI artifacts
- Side effects from far-field
  - Cooling mechanism
- More accurate thermometry
  - Volumetric, with cumulative dose
  - Temperature in fat
- More conformal treatment planning



Conclusions

- Histologic feedback from sarcoma treatments will improve our ability to plan treatments, perhaps allowing us to treat recurrences or to avoid surgery
- Preliminary experience suggests that MRgFUS can be used to achieve durable local control of desmoid tumors
- Early experience suggests that MRgFUS can be used to achieve durable local control of ***small slow-flow*** vascular malformations
- So far, good safety profile, but need larger number of patients

Conclusions