The Role of MRI-Guided High-Intensity Focused Ultrasound (MRgFUS) in Cancer Therapy

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Outline

• Background of MR Guided High-Intensity Focused Ultrasound (MRgFUS)

• Currently available MRgFUS systems

• The potential of MRgFUS for cancer research and clinical applications
Diagnostic Ultrasound Vs Therapeutic Ultrasound

**Frequency**
- Diagnostic: 3-10 MHz (> 20MHz for skin scan)
- HIFU: 1-2 MHz

**Power output**
- Diagnostic: < 5mW/cm²
- HIFU: > 100 W/cm²
Background of MRgFUS

• High Intensity Focused Ultrasound (HIFU) first investigated in 1942
  (Lynn JG et al, biology. J Gen Physiol 1942;26:179-93)
  Many studies performed by groups of Dr ter Haar &
  of Dr Hynynen over the 3 decades

• Ultrasonic lesions seen on MR first reported in 1993
  (Cline HE et al MRM 1993;30:98-106)
HIFU lesions

Focal region: 3x15 mm
Defined on a beam profile (FWHM)

The water must be degassed
Mechanisms of Tissue Damage

• Primary mechanism of damage is thermal, i.e. “cooking” of the tissues (measured temperature >56 °C at focal zone)

• Another mechanism is cavitation
Advantages of the MRgFUS

- Completely non-invasive therapy
- Re-treatment possible
- Alternative therapy after RT and surgery
HIFU Lesions
Histology Findings in Liver (2 h after FUS)

treated  untreated
Factors affecting lesion formation

- Intensity
- Sonication duration
- Lesion separation
- Blood flow

Fig. 5.10 Examples of ultrasonically induced lesions in excised porcine liver. Lesions made with higher intensities are "carrot-shaped" (a) while lesions made at lower intensities are "cigar-shaped" (b).
Lesions produced in the liver with 261 W/cm², 3 mm focal depth, and 5 S exposure duration. 

a) 1 mm exposure separation 
b) 2 mm separation 
c) 3 mm exposure separation.

Chen et al 1997 UMB
Effect of Blood Flow

with reduced blood flow

with normal blood flow

Chen et al 1993 UMB
HIFU Surgery under MR Guidance

Lesions made in a rabbit brain (in vivo)

Chen et al 1999 JMRI
How to image HIFU lesions using MR?

- T2 shows cell death zone but not for real time monitoring due to time delay

*Figure 7. An example in one animal of time delay for bright ring to appear on T2-weighted MR images. The lesion between 26 and 35 minutes after FUS exposure.*

*Chen et al JMRI 10: 146-153 1999*
How to image FUS lesions using MR?

- Real-time MR thermometry can provide an indication of tissue damage if temperature thresholds/thermal Dose are known.

Graham, Chen and Leitch et al 1999 MRM
Temperature Measurement on MRI using Proton Resonant Frequency Shift Method

\[
\Delta T = \frac{\Phi - \Phi_0}{\gamma \alpha B \text{ TE}}
\]

- \(\Phi_0\) = the initial phase before heating
- \(\gamma\) = the gyromagnetic ratio
- \(\alpha\) = the coefficient of temperature change
  - \(0.01\) ppm/°C for aqueous tissues
- \(B\) = the magnetic field strength
- \(\text{TE}\) = the echo time
Temperature Maps

- *In vivo* laser ablation
- Color overlay where temp > 47°C

*Courtesy of Dr. K Butts*
Thermal Dose Calculation

$ (t_{43} = \text{equivalent time at } 43^\circ) $ 

\[ t_{43} = \int C^{43-T(t)} dt, \]

- $ C = 0.5 \quad \text{for } >43 \ ^\circ C $ 
- $ C = 0.25 \quad \text{for } < 43 \ ^\circ C $ 

non-linear behavior for tissue damage:

- at $ 43 \ ^\circ C$: 240 min; at $ 54 \ ^\circ C$: 3s; at $ 57 \ ^\circ C$: 1s;

FUS Equipments

Courtesy of Dr. J-F Aubry
Haifu Model JC Focused Ultrasound Tumour Therapeutic System

Operator Console

γ-motion Device

Amplifier

ψ-motion Device

3+1 D Motion Device

Treatment Bed

Courtesy of J. Kennedy, F. Wu

Oxford, UK & Chongqing, China

> 20,000 patients treated in China
ExAblate® 2000 Device (InSightec)

approved by FDA for treatment of uterine fibroids
ExAblate Main Components

Operator Console (operator room)

Equipment Cabinet (equipment room)

Patient Table (scanner room)
The phased array transducer is housed in a sealed bath and connected to a motion system.
What is MRgFUS?

3D anatomic information for exact tumor targeting

Beam path visualization for safe treatment

Real time MR thermometry to achieve planned outcome

close loop therapy
Correlation of MR Thermometry and Tissue Damage

Temperature map of a sonication

Temperature rise at center of sonication spot

Temperature rise at margin

Temperature rise in untreated area, 7mm from center

Thermal dose threshold (above 240 minutes at 43°C)

Pathology of same sonication
Potential Applications for Cancer Treatment

- Brain tumor
- Breast cancer
- Bone metastases (palliative pain relieve)
- GI (liver, pancreas)
- Prostate cancer, Kidney
- GYN
Breast cancer - excisionless study

- **Objectives:**
  Evaluate long term local recurrence of up to 1.5 cm MRgFUS treated breast carcinoma and evaluate safety of the procedure

- **Design:**
  Only patients with MR identified single focal lesion (up to 1.5 cm) of T1/T2, N0, M0 disease will be treated

- **Location:**
  Breastopia Namba Hospital, Miyazaki, Japan

Pre treatment T1w+CE MIP image  2 weeks post treatment T1w CE MIP image
Breast Cancer: before and after MRgFUS treatment

Brain Tumor Study

**Objective:**
- Safely treat brain tumors through intact skull

**Results:**
- 3 patients treated (recurrent glioblastoma or metastatic cancer)
- No skull heating
- Reported to FDA; FDA approved continuation based on safety

Targeting the brain: ExAblate4000 (InSightec)

*For investigational use in the US and in Zurich*

- Helmet shaped transducer
- Set up
- Test in MR

**Boston system**

Phase 1 trial on 3 patients to test the safety (500 transducers)

New system: 1024 transducers (trials to come)
Brain Tumor Study

Results (continued):

2 patients are still alive (27 and 30 months later), 3rd patient survived 10 months after treatment (Paper submitted for publication)

Accumulated thermal dose at end of treatment

Diffusion weighted image immediately post-treatment

T1w contrast enhanced image immediately post-treatment

Courtesy of Sheba Medical Center, Tel Aviv, Israel
Liver Tumor Study

Objective:
• Demonstrate capability of treating liver tumors safely with respiratory gating

Results:
• Treatment synchronized with respiration enables consistent target position during sonifications for entire procedure
• High quality MR thermal imaging

Treated dose following FUS treatment shown on T1w MR
Contrast enhanced T1w subtraction image showing the lesion.
Pathology after 4 days
Microscopy pathology
MRgFUS for Palliation of Bone Metastasis

Treatment principles

- Bone heating is used to ablate the adjacent periosteum
- Palliation achieved by the ablation of the bone periosteum, which is the sensory origin of the pain
MRgFUS for Palliation of Bone Metastasis
(FCCC’s experience)

- metastatic breast cancer
- previous radiation to left shoulder
- OxyContin 100 mg bid
- Oxycodone 30 mg q 4 h prn pain; on average, 3 to 4 doses per day
- Lidoderm 5% patches daily
- pain 8 of 10
Results (from FCCC)
CT before Tx

Figure 2

CT 3 months after Tx

Figure 5

Figure 3. Average visual analog scale score of 13 treated patients (15 treatments) during follow-up.


Prostate Cancer- Endorectal System

- Endorectal phased array probe
- Steerable beam for focal spot size control (2 x 7mm to 10 x 30mm) for fast treatment and to prevent complications related to nerve bundle
- Combined pelvic and endorectal imaging coil for high resolution target definition
Animal Studies

- Correlation between thermal dose, non-perfused volume (NPV) and gross pathology

*Courtesy of Sheba Hospital, Tel-Aviv, Israel*
MR guided Pulsed FUS for Enhancement of Local Gene/Drug delivery

- Enhancement of drug delivery to tumors with MRgFUS demonstrated in animals modes
  

- Mechanism: non-thermal effect (stable cavitation)
  → increase vascular, cell membrane permeability
  → concentrate macromolecular pharmaceutical agents to the treatment target without permanently damaging the tissue

- Applications of pulsed HIFU to enhance the delivery for cancer treatment in chemotherapeutic and gene therapy
Enhanced Drug Delivery

- Radioactive tritiated docetaxel used to determine the uptake in prostate tumor

Chen et al. at FCCC
Conclusions

- MRgFUS is a noninvasive, alternative therapeutic tool for cancer treatment

- Need large volume of published clinical data from multiple centers to support early experience

- Technological advances should help overcome some of the comparative limitations