Image Guided Therapy

“The New Frontier”

Asim Mian, M.D.
MRI has recently been applied to FUS thermal therapy

- Superior soft tissue contrast
- Imaging in multiple orientations
- Temperature Sensitivity
- Precise targeting
- Thermal quantification
- Post therapy imaging
- Repeatability
FUS initially used on breast lesions and fibroids

- Concept initially conceived in early 90’s
- Irreversible tissue damage found at >60 C with focused US beam
- MRI was ideal technology to localize and quantify energy deposition (temp. shifts) by acoustic energy (US)
Interventional radiologists provide less invasive alternatives to hysterectomy and myomectomy.

Radiology Treats Uterine Fibroids

By Beth W. Orenstein
Perpendicular to US beam direction

Tumor outline

Sonication Focus
MRI Guided Focused Ultrasound Surgery of Brain Lesions

A study to evaluate the safety and feasibility of transcranial MRI-guided Focused Ultrasound surgery in the treatment of brain lesions.
Goals and Objectives

- To evaluate safety of MRGFUS, using ExAblate 3000, through the intact human skull to the brain during procedure and follow up period of 3 months.

- To evaluate effect of thermal ablation on the target tumor with contrast MR imaging to identify viable tumor and non-viable thermally ablated tissue.

- To establish technical success as a basis for later studies that evaluate clinical efficacy.
Specific Aims

- Non-randomized feasibility using FUS under MRI guidance and thermometry through intact human skull to brain lesions in up to 10 subjects.

- After 3 patients, report will be sent to FDA and IRB prior to starting the other 7 patients.

- Subjects to be followed over 3 month period with contrast MRI and clinical exams.
Subject Selection

Inclusion criteria:

- Recurrent GBM grade 4 and recurrent mets for whom surgery is not an option
- Lesion located >1.5cm from dura
- Lesions clearly defined on pre-therapy enhanced MRI scans
- 3 or less lesions in brain none of which >2.5cm

Exclusion criteria:

- Lesion causing edema or mass effect with shift >5mm
- Lesion in brainstem or posterior fossa
- Recent hemorrhage
- Lesion has calcs
MRGFUS team

- Physicist
- Neurosurgeon
- Neuroradiologist
- Anesthesiologist
- Technical support staff (from Insightec)
- Radiation oncologist
Targeting by MR Guidance

Target delineation
MR guided Focused Ultrasound Technology

Why Focused Ultrasound?

- Generates heat required for tissue ablation
- Completely non-invasive
- **Can be safely applied time and again**
- Can be accurately focused at target tissue
- Has no heating affects outside the focal point
- Arbitrary target shape by multiple treatment spots
MR guided Focused Ultrasound Technology

Why MR guidance?

- 3D anatomic information for exact tumor targeting
- Beam path visualization for safe treatment
- Real time MR thermometry to monitor treatment and outcome
- Post Tx contrast imaging for evaluating treatment

Monitor treatment outcome in real time to achieve desired results
ExAblate 3000 Brain System

- Apply ExAblate technology for brain treatments through intact skull
- Obtain a completely non-invasive thermal ablation system of brain tissue
- *The interaction of ultrasound with bone presents technological difficulties*

Phase-1 FDA Approved Study: Feasibility and Safety Study
Skull De-focusing

Skull effect on the ultrasound beam path

- Variable thickness/density
- Variable incidence angles

Application software corrects de-focusing effects by extracting skull characteristics from CT data and generating an accurate skull acoustic model.
Skull Heating

Skull effect on the ultrasound energy

- Refraction => Decrease in efficiency
- Attenuation => Heating of the skull

Maximize beam path area on the skull to reduce local intensities
- Interface water is cooled to 15-18°C
- Application software displays estimated temperature on skull during treatment
- Real-Time MR thermometry continuous monitoring of Near Skull Temps changes
ExAblate 3000 Components

Scanner Room

Equipment Room

Control Room
Focused Ultrasound as a heat source

- Phased Array Transducer
- 512 channels to correct phase aberrations and focus
Transducer positioning

Transducer has 4 degrees of freedom (XYZ & Pitch)
Patient Interface

Accessories used to limit movements of the head during treatment:

- Personalized thermoplastic mask
- Immobilization mechanism
Treatment Flow

- Pre Treatment imaging & positioning
- Off line treatment simulation (optionally done as part of Tx session)
- Treatment Session
Treatment Planning

Planning includes:
- Target delineation
- Selection of transducer position
The Sonication Cycle

- Treatment is performed by multiple sonication spots which are repeated until target is fully treated
- Single Sonication volume ~0.06cc (5mm ellipsoid)

Temperature based - closed loop feedback is essential to assure treatment outcome in real time and to provide essential safety features.
ExAblate 3000 Safety Features

- **Dynamic temperature graph display**
  - Unexpected heating effects of over heating
- **Thermal imaging with wide FOV**
  - Monitor heating on tissue adjacent to the skull
- **Anatomical fiducial**
  - Detect any patient motion
- **Patient Stop Sonication Button**
  - Conscious patient has full control over treatment progress
- **Physician Stop Sonication**
  - Located on Operator’s Console to immediately stop energy
ExAblate Brain Program

Animal Studies → Human Clinical Trial: Craniotomy → FDA Trans-Skull Studies → Brain Program Road Map
Delivery of chemotherapy agent (Doxil)

Fluorescent image showing targeted Doxil delivery to the rat brain
Treat LH et al. Int J Cancer 2007
Clinical Research: Patient treatment through open craniotomy

- Phase-I Study Protocol
- Study run in Israel
- 3 patients treated

*Used ExAblate 2000 body system*
Treatment Through Craniotomy

**Phase-I Study Protocol:** 3 patients treated

**Treatment Plan**

**Patient Table**

**Patient Immobilization**

Perpendicular to beam
Sonication Temperature Feedback

Energy 200W x 15s (3000 J)

Tmax 74°C
Tissue ablation with follow up MR imaging

- Single sonication plan matches MR measured thermal affect (1Wk follow up)
- Dark Lesion in T1+gad related to recovery of the BBB
- White ring around treated area related to edema
Brain Tumor Treatment Through Craniotomy

65 year old Patient with glioblastoma

(A) Accumulated thermal dose at end of treatment
(B) diffusion weighted image immediately post-treatment
(C) T1w contrast enhanced image immediately post-treatment

*Note*: Treated region matches accumulated dose
ExAblate Brain Program

- Animal Studies
- Human Clinical Trial: Craniotomy
- FDA Trans-Skull Studies
- Brain Program Road Map
Current FDA Study – Phase 1

- Transcranial MRI-Guided Focused Ultrasound Surgery in the Treatment of Brain Lesions
- IDE # G020182
Study Rationale

Safety of Transcranial MRgFUS thermal ablation of brain lesions using the ExAblate 3000 system

Collected data to establish the basis for later studies that will evaluate ExAblate 3000 Clinical efficacy
Study Hypotheses

FUS under MRI-guidance and MRI-based thermometry can be safely delivered through an intact human skull

- Low risk of transient short-term adverse effects as evaluated during 3 months of follow-up

A pre-defined target volume inside the brain lesion can be accurately ablated

- As shown on post-treatment MRI
Inclusion Criteria

- Subjects with only recurrent glioblastoma (grade IV astro) and recurrent metastatic cancer to the brain (as diagnosed by non-study associated physician)
- Lesion(s) to be treated are located in the cerebral hemispheres, ~> 1.5 cm from the cortex and the dura
- Lesion(s) ~> 3.0 cm from skull
- Lesion(s) are clearly defined on pre-therapy contrast enhanced MRI scans
- Three or less lesion(s) in the brain
Current Status of FDA Study

- Approval of 10 patients
  - Treat first 3 patients ➔ Submit Tx Report
  - Clearance to continue…..

- Treated 3 patients – June 2005

- Report Submitted to FDA – August 2005
Treatment Accuracy and Effectiveness

BT002-P002 – 03 June 2005
Sample sonication

Thermal Images Sequence

Sonication Dose Area

Target

Tissue above 52°C

Ablated tissue

Temperature Graph
Sonication induced thermal rise at the focus Vs. sonication power

Up to ~52°C Temps were reached at the focus ....

......Tissue Coagulation starts at ~54°C
Brain 220 KHz (1)

For accessibility to the entire brain

- Accessibility to the entire brain was expected
  Using theoretical analysis as well as acoustic Lab measurements

- First MRI full integration test indicates clearly that the 220KHz solution may be a huge breakthrough.
Images

Before

After

Pretreatment [T1+c]  

1D Post treatment [T1+c]
Summary

ExAblate treatments of the first 3 patients:

1. Good transcranial focusing using high resolution CT data

2. Transcranial ExAblate treatments of brain lesions show great level of safety

3. Overall treatment procedure well tolerated by the patients (managed by conscious sedation protocols)

4. InSightec system and treatment procedure training were effective
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