MR-guided Focused Ultrasound Surgery for Breast Cancer: Reliability and Effectiveness

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Introduction

Each year over one million women worldwide are diagnosed with breast cancer (BC), the second most common cancer in women. It is estimated there were 184,450 new BC cases and 40,930 deaths in 2008 in USA (1).

The impact of BC is life-threat and cosmetic damage of the breast. Especially in consideration of early BC treatment, secure pursuit of breast conservation becomes the most significant issue for the patients. Standard treatment of BC consists of local and systemic controls. Surgery is the major method and radiation therapy, adjuvant in local control. Systemic control is mainly pharmaceutical therapy. During the past decades, local treatment of BC has improved dynamically from aggressive resection of the entire breast with pectoral muscles with the fatty tissues embedding axillary lymph nodes, towards less invasive procedures such as muscle conserving and breast conserving surgeries. Recent standard local treatment of early and localized BC is lumpectomy (excision of the tumor with adjacent tissues) with or without radiation therapy. Although conventional surgical lumpectomy is not a major procedure, it is still invasive and is cosmetically undesirable for most women. It would be advantageous to develop a non-invasive ablative method for treating patients with smaller tumors. There may be less morbidity and less cosmetic deformity if local control of breast cancer could be achieved without a surgical resection.

In this lecture, a clinical study conducted to evaluate efficacy and safety of MRgFUS of BC in Japan is reported, and the current follow-up study and non-trial treatment are demonstrated.

A. MR-guided Focused Ultrasound Surgery (MRgFUS) System

Focused ultrasound (FUS) is a promising noninvasive technology for

thermal ablation. FUS is capable of concentrating ultrasonic pressure waves at a point inside a living tissue without a need for physical penetration (2, 3). Ultrasound waves are converted to heat when propagating through the tissue. The result is a clinically significant local heating (60–90 degrees C) at the ultrasonic focus, with only slight, insignificant heating along the ultrasonic beam path. In recent studies, MR guided Focused Ultrasound Surgery (MRgFUS) has been evaluated as a source of controlled thermal energy for the coagulation of benign and malignant tumors (4). One MRgFUS system gained FDA approval for the indication of treating uterine fibroids in October, 2004. Clinical trial in pain palliation of bone metastases are being conducted internationally currently. Future applications include prostate cancer, kidney tumors, thyroid tumors, bladder and lymph nodes, epilepsy and other central nervous system diseases, and a whole range of other illnesses.

The two main advantages of MRgFUS over the other minimally invasive ablation techniques are its noninvasiveness and its real-time, closed-loop MR feedback. MRgFUS can precisely deliver energy to a given point in soft tissue, accurate within 1 mm, without interrupting skin integrity (5). Furthermore, during MRgFUS surgery there is ongoing feedback detailing temperature changes at and around the treated region, which allows the operator to be fully in control of the induced thermal effect (6-8).

Thermal rise in treated tissue is monitored using an MR imaging technique that visualizes *in vivo* temperature changes, as well as the resulting thermal injury, in real time (9-11). Temperature alterations affect the T1 relaxation times of tissue in an inverse proportion, and these changes can be visualized on T1-weighted images. Temperature alterations also affect the proton magnetic resonance frequency, and these changes can be visualized in phase-shift images. It has been shown that using the phase-shift image to visualize the temperature-dependent changes in resonance frequency is more reliable than T1-weighted imaging (12).

B. MRgFUS of Early Breast Cancer (Fig. 1)

Overview

Among image-guided minimally invasive therapies such as ultrasound image-guided cryoablation, laser ablation, radiofrequency ablation, microwave ablation and high frequency focused ultrasound ablation, and MR-guided focused ultrasound surgery (MRgFUS), MRgFUS, a combination of MRI-guidance and focused ultrasound ablation, is expected to be most secure and accurate method for BC treatment. To establish safe and effective MRgFUS of breast tumors, benign and malignant, clinical studies have been taken place in the past decade in Germany, USA, Canada and Japan (13-18).

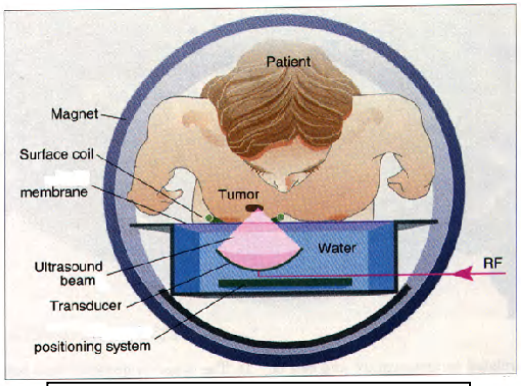

Fig.1 Scheme of MRgFUS of breast tumor.

Lumpectomy and MRgFUS

The localized 3D extent of BC is confirmed only by meticulous microscopic pathological study of thin sliced surgical specimens, and consists of masses, infiltration to the adjacent fatty tissue, and intraductal growth of BC cells which is minimal in size and changes. Failure in controlling the extension of BC cell growth inside the mammary ducts is the most common cause of local recurrence. Among all current imaging modalities, contrast MRI plays the best role in providing accurate 3D images for surgical designing leading to complete excision of BC tissue. Major problems of MRI are a small portion of BC lesions are not correctly depicted and difference in patients' positions, supine in surgery and prone in MRI. Unstable movement of soft tissues by maneuvering during surgery is another serious issue leading to inaccurate excision of the entire BC tissue. In MRgFUS, treatment can be operated in the same prone position and in monitoring the MR

images, temperatures and all other data in almost real-time. As far as the effect of ablation of BC tissue by focused ultrasound has been proven to result in complete cancer necrosis without undesirable adverse effects, it can be considered to be equivalent to surgical lumpectomy.

C. BC003: Clinical study to estimate the efficacy and safety of FUS ablation of BC tumors (19).

Patients

Patients enrolled in this protocol received standard clinical care for their condition. The study was conducted in accordance with ICH-GCP requirements, and was monitored routinely. Each patient signed an informed consent form prior to inclusion in the study.

Among 48 patients recruited, thirty women with biopsy-proven breast cancer with well-demarcated masses (smaller than 3.5cm in diameter) underwent MRgFUS treatment. Gadolinium-enhanced MR images were used for treatment planning and posttreatment imaging assessment of treated tissue, and temperature-sensitive MR images provided real-time treatment monitoring. Following MRgFUS all 30 women underwent segmental tumor resection or mastectomy. The effect and extent of thermal ablation was assessed by comparing all MR images taken for the treatment and pathological study of thin-sliced surgical specimens.

Materials

All treatments were performed at Breastopia Namba Hospital (Miyazaki, Japan), between April 2004 and February 2005. MRgFUS was performed using the ExAblate 2000 system (InSightec, Haifa, Israel) integrated into a 1.5T MRI scanner, (GE Healthcare, Milwaukee, WI). MRI provides planning and real-time thermal monitoring, thus creating a closed-loop procedure. The surface ring-shaped coil used was especially designed for the ExAblate breast treatments (USA Instruments, Aurora, OH).

Screening MRI for Selecting Patients

All patients were screened on T1-weighted contrast-enhanced MR imaging prior to the MRgFUS surgery to evaluate tumor size and location. See Fig.4(left).

MRgFUS Treatment

1. Positioning and Pre-treatment (Fig.2)
   The patient was placed in a prone position on the treatment table with the targeted breast positioned in the center of MRgFUS breast surface coilafter receiving a local anesthesia by injection of 2% mepivacain. The gap between the breast and the MRgFUS table was filled with degassed water to ensure acoustic coupling. The temperature of the degassed water was kept at 20°C using the active cooling capability of the MRgFUS device.

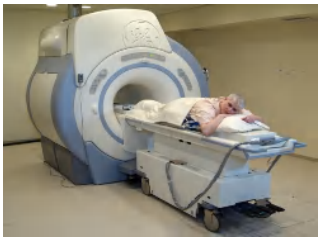

Fig.2 Patient Table

·Docks to MR scanner
·Consists of electronics and transducer in water bath

2. Planning and Designing
   Prior to starting the MRgFUS procedure, contrast-enhanced MR images along the three main MR axes were acquired. Images were automatically transferred to the ExAblate 2000 system, where they were used for treatment planning. The system operator drew the targeted volume on one or more of the coronal planning images showing the tumor. The outline of this volume should have included at least a 5 mm safety margin of normal tissue surrounding the tumor in all directions. ExAblate 2000 software generated the required acoustic parameters for the complete ablation of the targeted volume.
3. Test Sonication
   The center of the lesion was initially sonicated with a sublethal dose (20-60W) of energy to test the accuracy of lesion targeting in the patient.
4. Treatment by Multiple Sonication under Real-time MRI Monitoring ‘(Fig.3)
   Sonication at therapeutic power levels was then successively performed on multiple overlapping tissue points until ablation of the whole targeted volume was completed. Each treatment point was visualized using MR imaging phase maps that depicted temperature-dependent changes in resonance frequency.

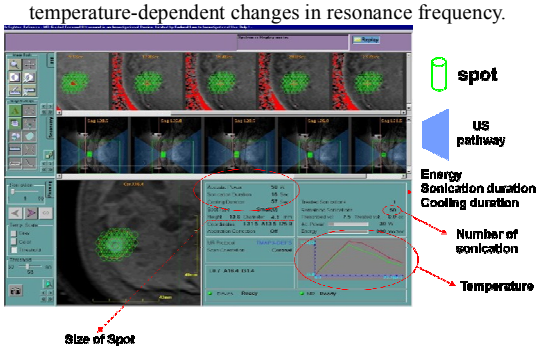

Fig.3 All the parameters are continuously displayed every 3 seconds during the treatment.

5. Pain Relief and Sedation
   During the procedure, starting from several minutes before the first sonication and as needed during treatment, the patients were given analgesic (fentanyl citrate, 1 mg per dose) and sedative agents (midazolam, 10 mg) intravenously to reduce or alleviate pain, and to reduce patient motion, anxiety, and claustrophobia. The number of analgesic and sedative agent doses was determined by assessment of each patient’s need. During the entire course of the treatment, the patient’s blood pressure, heart rate, and partial pressure of oxygen were monitored by using standard MR compatible pulse oxymeter (Invivo-Intermagnetics, Orlando FL).

Post-treatment EvaluatiFon by Contrast MRI

Immediately following the treatment another set of MR images was taken to evaluate the result of the treatment. See Figure 4 (right). The patient went through her planned excision surgery after the FUS. All the pathological material was prepared by the site pathologist and sent to a central core lab for analysis.

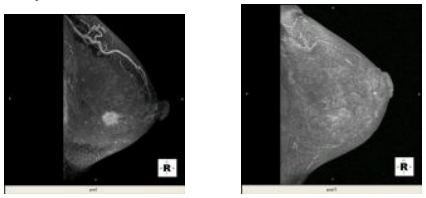

Fig.4 (left) : Pre-treatment 3D MRI
Fig.4 (right) : Post-treatment 3D MRI

Surgerical Procedure

Patients underwent routine segmental tumor resection or mastectomy after MRgFUS treatment, which included resection of wide margins around the treated area. If indicated according to the standards of care at the investigational site, intraoperative ultrasound localization or wire localization was employed. After tumor resection, routine patient care was rendered according to standard practice guidelines at the site.

Data Data Analysis

Efficacy data was analyzed on 28 of the 30 recruited patients. Two patients were excluded for the following reasons:

1. One patient (7202) could not tolerate the treatment, and it was stopped in a very early phase
2. One patient (7204) was only partially treated, according to plan. This was a violation of the study protocol.

Three-dimensional macroscopic and microscopic histopathological analysis of the 5mm-thick sliced specimen was preformed after surgery to determine the efficacy level of MRgFUS treatment. Pathologic evaluation of the hematoxylin-eosin stained slides provided the tumor diameters, the diameters of the treated zone and the diameters of the necrosis zone (Fig. 5).

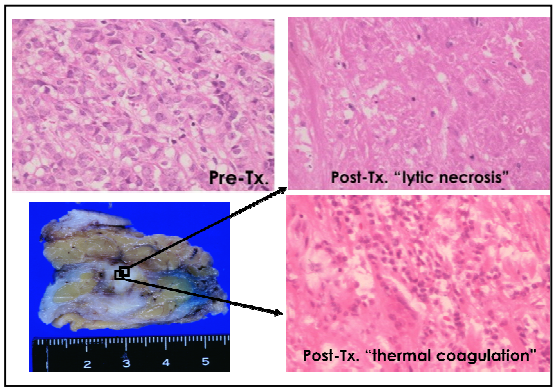

Fig.5 Pathological study reveals cancer necrosis.

All MR images, MRgFUS procedure files, and pathology data were analyzed. Tumor size as well as the tumor's distance from the skin and ribs was measured on the pretreatment MR images. The procedure parameters were gathered, and the planned treatment dimensions and safety margins were measured. Treatment effect was assessed by measuring the dimensions of the non-contrasted area on the immediate post-treatment images.

Safety results were measured by the adverse event reports that were captured by the treating physicians.

Results:

1. Patient age ranged from 41-to-79 years (mean 56.9 years).
2. The planned focal point volume of a single sonication varied between 0.16 and 0.67 cc.
3. The average number of sonications that were required to cover the lesions was 48 (range 26-75 sonications) resulting in an average treatment time of 2:20 hours, (range 1:16-3:51 hours).
4. The average treated tumor size was 13 mm (range between 5–25 mm), with average distance from skin of 16.6 mm (range 5-34 mm) and average distance from the ribs of 24.7 mm (range 3-9 mm).
5. On pathological examination,
   a. Mean necrosis of the targeted breast tumors was 96.9% ± 4% (median 100%, range 78% to 100%) of tumor volume.
   b. Fifteen (53.5%) of 28 evaluable patients had 100% necrosis of the ablated tumor, while only three patients (10.7%) had less than 95% necrosis.
   c. In 28 (93.3%) patients, 100% of the malignancy was within the treatment field, while 98% and 95% of tumor lay within the treatment field on two remaining patients.
   d. Retrospective analysis in two patients with residual tumor showed treatment was not delivered to the full recommended area, reaffirming the need for precise localization and the value of contrast-enhanced images for treatment planning.

Safety

Only one severe and five minor adverse events were reported. This severe event was a third-degree skin burn, which was discovered at the end of the treatment. Following detailed analyses of this particular treatment, it was found that the cause of this adverse event was related to using high-energy sonications in close proximity to the skin. No other significant device-related adverse events were reported.

Conclusion

MRgFUS has a great potential to become a viable noninvasive replacement to lumpectomy. Further studies with a larger population by several different institutions as well as follow-up studies focusing on evaluation based on post-treatment images are needed.

D. Current and Future Aspects

ACRIN Study

Based on the results of BC002 and BC003, ACRIN (American College of Radiology Network, http://www.acrin.org/) has listed Protocol 6674, "MRI Evaluation After Focused Ultrasound Ablation of Breast Cancer". Protocol document is currently in development. After the protocol is approved by the Cancer Therapy Evaluation Program (CTEP), international clinical study which will be similar to BC003 is expected to start for US FDA approval.

BC004: Non-surgical Follow-up Study of MRgFUS of Early Breast Cancer

In Japan, non-surgical follow-up study (BC004) has been conducted since April, 2005. This is a phase two study to evaluate the safety and effectiveness of MRgFUS in the ablation of early breast tumors, without surgical procedures. The goal of the study is to demonstrate low rate of local recurrence after MRgFUS treatment followed by radiation therapy and on MRI-based follow-up. Eligible patients with early stage single tumor of less than 1.5 cm size will be treated with MRgFUS as replacement for lumpectomy. Patients will be closely followed-up for 5 years. Currently, among nearly 40 patients, there have been no local recurrences, no distant metastases, and no severe adverse effects

Non-study MRgFUS of Early Breast Cancer (20)

Nearly 50 patients whose BC is smaller than 2cm and satisfies all indications of BC004 but do not intend to enter the clinical study to avoid radiation therapy and for other private reasons have been treated by MRgFUS solely or adjuvant radiation therapy. There have been 4 local recurrences. One case was mucinous carcinoma in which insufficient rise of temperature was observed within mucinous lake occupying almost the entire mass. After this experience, mucinous carcinoma has been excluded from indications. Strict selection of the patients seemed to be essential to avoid local recurrence.

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