

Magnetic Resonance-guided Focused Ultrasound (MRgFUS) Treatment of Uterine Fibroid

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Abstract

Magnetic resonance-guided focused ultrasound (MRgFUS) is a new treatment modality in treating uterine fibroid. It is noninvasive and can be done as out-patient procedure. It is the least invasive treatment option other than medical treatment. Early reports have demonstrated feasibility and safety. It is efficacious in symptom improve and fibroid volume reduction. This article reviews the principle, patient selection and treatment. Results from early trial and our center are summarized.

Keywords: Focused ultrasound, uterine fibroids, MRI.

INTRODUCTION

Leiomyoma (fibroid) of uterus are common benign tumor. Whereas most lesions are asymptomatic, some may cause symptoms including pelvic pain, pressure, menorrhagia, dysmenorrhea and urinary symptoms. Treatment is often required in 10 to 20% woman with fibroid. There are a number of options available other than the traditional mean of hysterectomy and myomectomy. Minimally invasive alternatives such as uterine artery embolization (UAE) and laparoscopic/hysteroscopic myomectomy are commonly used alternatives to open surgery. Ablative techniques such as cryomyolysis and myolysis have also been used for fibroid treatment. They are increasing popular due to the perceived advantage of minimize recovery time and associated morbidity. These methods are however still invasive requiring anesthesia and hospitalization.

Magnetic resonance-guided focused ultrasound (MRgFUS) on the other hand, represents a truly noninvasive alternative that can be performed without anesthesia, in an out-patient setting and appears to be both safe and effective. This article will review the principle and result of early trials using MRgFUS for fibroid treatment.

PRINCIPLE AND SYSTEM OVERVIEW

The capability of ultrasound (US) to thermally ablate biologic tissues has been known and studied for several decades.¹ Ultrasound wave generates heat due to absorption of the acoustic energy. Mechanical phenomena include cavitation, microstreaming, and radiation forces also contribute to heat generation. Focusing results in high intensities at a specific location and over only a small

volume. This focusing minimizes the potential for thermal damage to tissue located between the transducer and the focal point because the intensities are much lower outside the focal region. Coagulation necrosis occurs when the tissue temperature raise above 56°C during a 1 s or longer exposure. A single 2-s exposure results in an ellipsoidal lesion, typically 1.5 to 2 cm in length and 1.5 to 2 mm in diameter.

The MRgFUS is a hybrid technique using the heat-generating ability of US combined with magnetic resonance imaging (MRI). MRI provides exceptional anatomic detail for guidance, allows for real-time thermal monitoring during the treatment, and postprocedural assessment of the extent of treatment after the administration of a gadolinium contrast. The MRI treatment guidance and MR thermal monitoring distinguish MRgFUS from other implementations of FUS therapies such as high-intensity focused ultrasound (HIFU). Unlike MRgFUS, HIFU uses B-mode ultrasound for treatment guidance and monitoring.

The major advantage of using MR is that it enables real-time thermometry to be performed during delivery of an individual sound wave or sonication by measuring the change in proton resonance frequency of water in response to temperature change.² MR thermometry allows one to localize the sonication, measure temperature change so that we can evaluate the effectiveness of sonication.³ If the MR thermometry does not indicate that an appropriate thermal dose was delivered, the parameters of the sonication may be changed to improve effect (e.g., the power may be increased). It is the best imaging method currently available for real-time monitoring of thermal dose delivery and effect.

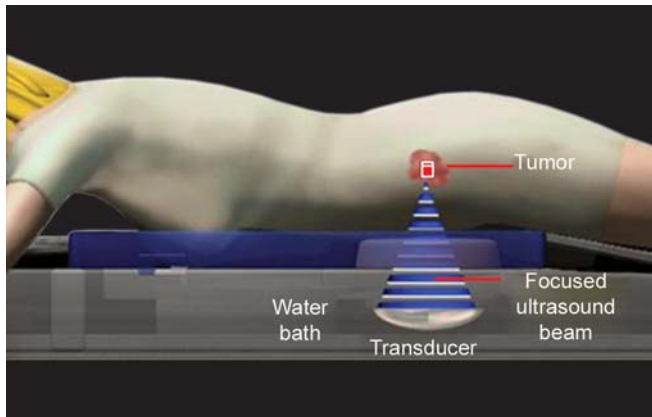


Fig. 1: The ExAblate table for treatment of uterine fibroid. Patient lied prone over the ultrasound transducer. Gel pad and water bath ensure good acoustic coupling (used with permission by InSightec Inc)

In 2004, the ExAblate 2000 (InSightec, Haifa, Israel) MRgFUS system was approved by the US FDA for the treatment of uterine fibroid. It consists of 3 major components: a modified MRI table (Fig. 1) containing embedded MRI-compatible phased array FUS transducer (MRgFUS table), FUS workstation, and the control personal computer. All 3 units are integrated with the MRI scanner (Signa; GE Medical Systems, Wisconsin, USA) in a closed-loop system. The FUS transducer (120 mm in diameter, 211 elements, 1.15 MHz principal frequency) and the motion system are enclosed in a tank filled with degassed water. The window above the FUS transducer is covered with a thin Mylar membrane. An integrated 2 part pelvic coil is used for MR imaging. Acoustic coupling between the transducer and a patient is enabled with a layer of degassed water mixed with US coupling gel spread on top of the Mylar membrane, and a gelatin patient pad is immersed in a small bath of degassed water formed inside a plastic patient drape tucked inside the opening in the anterior part of the coil. Patients are positioned prone on the MRgFUS table, and the table is subsequently advanced into the bore of the MRI scanner for imaging and treatment.

PATIENT SELECTION

Not all patients are suitable candidate for MRgFUS. Appropriate patient screening is very important factor in the successful application of MRgFUS in treatment of fibroids. The FDA has imposed strict selection criteria for research so that only 14% of women inquiring about minimally invasive image-guided treatments for fibroids were eligible for MRgFUS.⁴ It is anticipated that this percentage will increased when off research protocol (when most FDA restrictions were lifted) was used.

A screening MR examination is done for patients who are: at least 18 years of age, with no massive abdominal scarring in the treatment area, no contraindications to MRI, and no serious health complications.⁵ The screening MRI was done on the same treatment table with patient in prone position with the coupling gel pad in place in order to simulate condition during treatment. The imaging sequence includes T2-weighted images of pelvis in 3 orthogonal plane followed by T1-weighted images after IV gadolinium contrast injection. Images are evaluated for the number of fibroids, their size, and location. It is important to decide whether the fibroids that are amenable to MRgFUS are the likely cause of the patient's symptoms. The screening process also includes evaluation of any structure in the treatment path that would influence or prevent treatment.

Fibroids that are typically treated are usually more than 3 cm in size, have low signal intensity on T2-weighted images, are enhanced after IV gadolinium contrast, and are most commonly intramural in location. The efficacy of MRgFUS correlates with the signal intensity of fibroids on T2-weighted magnetic resonance images. Fibroids that have low or intermediate T2 signal intensity than myometrium are suitable candidates for MRgFUS whereas those with high signal intensity are not.⁶ The high signal of intensity in these fibroids may relate to increased vascularization, and this increase in blood flow may decrease heat deposition due to the dissipation of energy away from the tumor.

Multiple fibroids might require multiple treatment sessions. Patients with more than six symptomatic uterine fibroids may not be good candidates for MRgFUS, although they should be considered based on the accessibility of the fibroids and their presumed role in the patient's symptoms. Fibroids that are larger than 10 cm are less suitable for the treatment, as they may require a long treatment time. These fibroids might benefit from pre-treatment with GnRH agonist prior to MRgFUS which leads to fibroid shrinkage and improved treatment outcomes following MRgFUS.^{7,8}

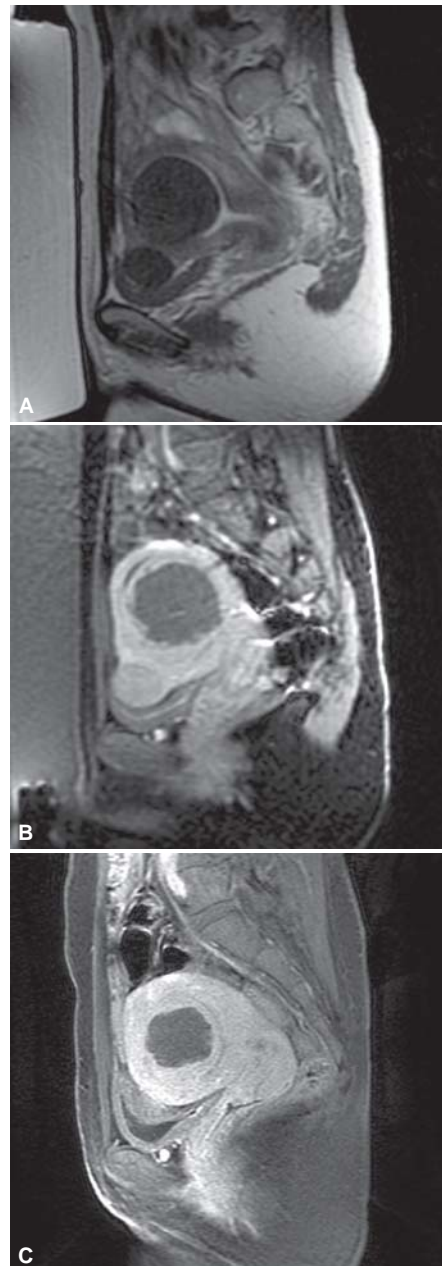
Evaluation of tissues anterior and posterior to the area of treatment is important in the MRI evaluation. Anterior to the uterus, it is important to assess for scars from prior surgeries. Scar tissue tends to absorb more of the ultrasound beam and can result in skin burns or pain at the site. Evaluation for the presence of bowel in the intended ultrasound beam path may result in a patient being excluded from treatment or aid in the preparation for the day of treatment. Treatments cannot be performed through bowel because bowel may contain air and may result in heat deposition in the bowel, causing injury.

In evaluating structures in the far field, the greatest concern is how close bony structures and pelvic nerves are from the planned treatment zone. An adequate distance is important to maximize patient safety and comfort. Bone absorbs ultrasound waves more readily than soft tissue, and low energies are sufficient to heat a bone surface to high temperatures. Nerves that are adjacent to a heated bone surface may be exposed to temperatures that can cause pain and, in extreme cases, may damage the nerve.⁹ Fibroids that are close to the lumbosacral plexus or to another bone surface should be considered carefully before the patient is deemed suitable for MRgFUS.

TREATMENT

Treatment can be done as an out-patient procedure. Preparation before treatment includes placement of peripheral IV line, urinary catheter and compression stockings. Patients are asked to shave their lower abdomen from the umbilicus to the pubic bone before arriving for treatment. Patients lie prone on the specialized MRI table. T2-weighted planning image are then obtained to assure proper positioning of the patient's fibroids for treatment. Images are then transferred to the ExAblate planning program, the target area is manually drawn and defined by the radiologist, and the target volume is analyzed with superimposed ultrasound beam paths in all three planes. This three-dimensional assessment is done to ensure that no beam passes through or near any bowel loops, bladder or major scar tissue, and no distal beam passes within 4 cm of the sciatic nerve or branches in front of the sacrum. During the procedure, the patient receives intravenous sedative, which allows her to remain fully conscious and comfortable and with little or no pain for the duration of procedure.

The procedure begins with the delivery of low-power sonication, with real-time thermometry acquired simultaneously. The operator then adjusts the focal spot according to the resulting thermal map. The power is gradually increases until the therapeutic dose is reached. When the therapeutic dose is achieved, the procedure continues with delivery of all planned sonications. With each sonication, the MR images illustrate the local heating, and the ExAblate screen shows the resultant temperature change. The treatment monitor displays the delivered sonications that have achieved the threshold dose of 60°C. One aims for a temperature of 65°C to 85°C, which ensures real tissue necrosis. Patient's blood pressure, heart rate, oxygenation, and comfort level are monitored throughout the treatment. Number of sonications depends on fibroid size, treatment session usually last 3 to 6 hours.



Figs 2A to C: MRgFUS treatment of uterine fibroid: (A) Pre-treatment T2W sagittal image of an intramural H₂ hypointense fibroid, (B) Post-treatment postcontrast T1W sagittal image demonstrating loss of contrast uptake in the treated region. 80.4% of fibroid was treated, (C) Follow-up postcontrast T1W sagittal image at 3 months demonstrating persistent nonenhancement of treated area. The fibroid shrink by 35%

Once treatment is finished, contrast MR is performed to assess treatment result. The treated tissue is no longer perfused and shows as nonenhancing area on contrast enhanced T1-weighted images (Figs 2A to C). The nonperfused volume (NPV) is measured as a measurement of the treated fibroid volume; the NPV ratio indicates the percentage of treated volume. The anterior abdominal wall

is examined for burns and the patient is observed for a short time prior to discharge home. Patient can resume normal activity the next day.

POST-TREATMENT ASSESSMENT AND RESULT

Treatment efficacy is assessed by symptomatic improvement and MR imaging. Improvement in symptoms is measured by the symptom severity score (SSS) using a validated health and symptom-related quality of life questionnaire specific for fibroids known as the Uterine Fibroid Symptom and Quality of Life (UFS-QOL).¹⁰ The SSS assesses menorrhagia and bulk-related symptoms on a single 100-point scale, with higher scores indicating worse symptoms. A 10-points improvement from baseline signifies significant symptom improvement. This testing modality has been one of the primary measures researchers have used in determining the efficacy of MRgFUS and may be used in the clinical setting.

Early studies reported feasibility and safety of phase I and II trials.^{11,12} Initial report from phase III trial described the treatment of 109 patients with FUS.⁹ 79.3% of the patients had significant improvement in their fibroid symptoms 6 months after their FUS treatment despite only approximately 25% of the fibroid volume was treated because of FDA regulatory restrictions. Follow-up report of the 12-month from the same study found 51% of the 82 patients had sustained relief of their fibroid symptoms at 12 months.¹³

Patients with larger treatment volumes have a higher degree of symptom improvement. In a report comparing two protocol differing in treatment volume, 73% had significant improvement in their fibroid symptoms under the original more limited protocol compared with 91% of the patients when larger treatment volume was allowed. At 12 months, 37% of the patients in the original protocol required an alternative treatment because of their continued symptoms compared to only 28% of patients in the modified protocol.¹⁴ A recently published article reviewed the treatment of 359 women with 24 months of follow-up from 4 research protocols.¹⁵ Patients were divided into 2 groups: one group had 20% or less of their fibroid volume treated and the other group had more than 20% fibroid volume treated. Patients with larger treatment volumes had a higher degree of symptom improvement initially and at 6, 12, and 24 months and required fewer alternative treatments. Hematocrits were also increased more in anemic women with increasing volumes of fibroid treatment.

Fibroids decreased in size over time after treatment. Early studies showed a 13.5% decrease in the mean volume of the treated fibroids 6 months after treatment.⁸ More recent studies reported an approximately 25% decrease in the size

of ablated fibroids 12 months after treatment.¹⁵ Both studies were conducted under FDA guidelines that had multiple restrictions which limited the amount of volume that could be targeted for treatment. Patients are now treated with off-research protocol; larger treatment volume is being targeted for therapy. Fibroid volume reduction is expected to be more than earlier studies.

Focused ultrasound has a good safety profile for the treatment of fibroids. No mortality has been reported. Sciatic nerve injury was noted in one patient who recovered with conservative management.⁹ There was only one reported side effect in the literature that required surgical intervention. This was a full thickness abdominal skin burn¹⁶ that required excision and direct closure 2 weeks after the treatment. Overall, 5% of patients suffered skin burns reported as being localized to areas of abdominal wall for which hair removal was incomplete. No urgent surgical interventions or bowel injuries have been reported, and febrile episodes were only noted in 6%, mostly associated with urinary tract infections. There were no blood transfusions or rehospitalizations categorized as being directly related to the FUS treatment.

MRgFUS AT HONG KONG SANATORIUM AND HOSPITAL

The ExAblate 2000 system was installed at our hospital in 2007. The selection criterion and treatment strategy is outlined above. We targeted larger fibroid volume since the FDA imposed research restrictions are not applicable. 17 patients successfully complete treatments without complications. The mean nonperfused volume ratio measures 67%, the mean treatment time 3.4 hours (2-5 hours). We routinely do follow-up MR examination at 6 and 12 months. Interim follow-up MR was done for 6 patients at 3 month. The fibroid shrinks by $25 \pm 12\%$. The mean SSS reduced significantly from 37.5 to 25.6 at 3 months.

CONCLUSION

Magnetic resonance-guided focused ultrasound is a promising option in treatment of uterine fibroid. It is a safe and noninvasive procedure with minimal morbidity. It has proven efficacy in symptom improvement and fibroid size reduction. Proper patient selection is important to ensure the best result. It is anticipated that larger treatment volume will enhance the efficacy.

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