Magnetic Resonance-Guided Focused Ultrasound Surgery

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ABSTRACT

Magnetic resonance guided focused ultrasound surgery (MRgFUS) is a non-invasive thermoablative therapy that was approved by the Food and Drug Administration in 2004 for the treatment of uterine fibroids (leiomyomas). Data on safety and long-term efficacy are accumulating to establish the unique usefulness of this therapy in targeting and treating leiomyomas through the integration of MR imaging. This article describes the established thermoablative therapies in the treatment of uterine fibroids, emphasizing their role in the genesis of MRgFUS. Treatment specifications are highlighted, and an overview of the procedure is given. Data from both clinical trials and commercial treatments are detailed for multiple efficacy outcomes, including symptom improvement, leiomyoma shrinkage, and use of alternative procedures. The concept of nonperfused volume as a surrogate marker for treatment success is discussed. Importantly, favorable pregnancy outcomes following MRgFUS have been reported. Applications of MRgFUS have recently expanded into the realm of adenomyosis treatment. MRgFUS has been deemed a safe and effective method of fibroid treatment and offers the advantages of no incisions or blood loss, speedy recovery, and a cost-effective means of treatment.

KEYWORDS: MRgFUS, leiomyomas, nonperfused volume (NPV), adenomyosis, pregnancy

For many diseases, from pituitary adenomas to renal calculi, definitive treatment has moved from major surgery to minimally invasive modalities. Uterine fibroids are now going through this therapeutic transition. Magnetic resonance-guided focused ultrasound (MRgFUS) is the first noninvasive surgical treatment and the newest thermoablative therapy for uterine fibroids. It uses the novel real-time guidance of an MRI system with thermal feedback to achieve fibroid destruction. Although medical and surgical treatments continue to be used, this minimally invasive procedure has paved the path for an intriguing new dimension in the treatment of uterine fibroids.

Uterine fibroids, also known as leiomyomas, are benign neoplasms of smooth muscle cells of the uterus. They are known to be the most common solid pelvic tumors in women, occurring in ~20 to 35% of all reproductive-age women.1 Studies have reported the cumulative lifetime incidence of fibroids to be 70% in white women and 80% in black women.2 This makes leiomyomas the leading indication for female pelvic surgery. It has been estimated that >$2 billion are spent

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every year on hospitalization due to uterine fibroids, and >$46000 per woman per year are spent on the treatment of fibroids.5,4

UTERINE FIBROID TREATMENTS
Traditionally, treatment options for uterine fibroids were limited to major surgery. Women with symptomatic fibroids who had completed childbearing had a hysterectomy. A myomectomy was offered to women interested in future pregnancy. These procedures, which were performed abdominally, incurred high costs, a longer hospital stay, and higher surgical morbidities such as infection and blood loss. Additionally, the rate of recurrence of uterine fibroids following myomectomy is 15 to 51% depending on the number of leiomyomas, which implies that more definitive as well as cost-effective methods need to be sought.5 Many patients may opt out of treatment altogether, especially after realizing the potential complications involved or simply due to personal anxiety. Hence patients may continue to suffer for years with the unrelenting symptoms of fibroids, including menorrhagia, pain, pelvic pressure, and bowel and urinary effects.

NOVEL AND MINIMALLY INVASIVE THERAPIES
In the 1980s, the emergence of laparoscopic techniques that used the morcellation of fibroids allowed patients to benefit from minimally invasive technologies while at the same time minimizing health-care costs. The introduction of endometrial ablation had a similar effect in the 1990s. In 1995, uterine artery embolization (UAE) was introduced, which eliminated the need for general anesthesia in the treatment of uterine fibroids, among having other favorable effects. The notion of combined patient care that involves both gynecologists and radiologists in the treatment of fibroids gradually became accepted.

The main drawback to novel treatments for uterine fibroids including MRgFUS, however, is the lack of long-term data on their safety and efficacy. All treatments in which the uterus is left in situ are confounded by the growth of new fibroids in addition to preexisting smaller or undetected fibroids or inadequately treated myomas, increasing the need for additional therapy. To counsel patients appropriately regarding treatment, sound clinical evidence is a key factor. Hence progress in the development and evaluation of MRgFUS techniques continues to ensure optimal patient safety and treatment efficacy.

THERMOABLATIVE THERAPIES
Thermal therapies that employ heat, cold, or a combination of both to induce cell damage are known as thermoablative therapies. Although minimizing the need for highly technical surgical skills, high lethal tissue temperatures can be produced through the use of hot water, radiofrequency, and lasers in addition to high-intensity focused ultrasound (HIFU). Heat destruction of tissues can also be induced through electrical means, such as the use of diathermy and cautery.

Heat-based therapies produce tissue destruction by raising temperatures at the target to >55°C. The ablative effect is directly related to the temperature produced and the duration of treatment. The final effect on a cellular level is protein denaturation, cell death, and coagulation necrosis. Coagulative necrosis is immediate, in contrast to ischemic necrosis, which occurs following therapies such as UAE.5

Cryoablation, in contrast, involves the introduction of freezing temperatures to targeted tissue through cryogens. It is important to note that different cell types demonstrate different sensitivities to cold injury. For instance, prostate cancer cells have an increased susceptibility to freeze temperatures, which is related to the presence of androgen receptors. This knowledge helps streamline treatment strategies appropriately and efficiently.

MEDICAL APPLICATIONS OF THERMOABLATIVE THERAPIES
The number of clinical treatments available for tumor ablation in different organ systems is rising. These techniques have been implemented in the treatment of benign prostatic hypertrophy in addition to liver, kidney, and colorectal cancers. Furthermore, the treatment of several brain disorders and eye and cardiac conditions can be accomplished through cryoablation. The concept of tissue destruction as a minimally invasive interventional treatment modality is also illustrated in the management of biliary and renal calculi in the form of extracorporeal shock wave lithotripsy. The generation of high-energy shock waves or laser energy serves the purpose of stone fragmentation and destruction. In the field of breast surgery, noninvasive treatments including radiofrequency ablation, cryoablation, and FUS ablation have had a positive impact on the success of treatment of small breast cancers. Overall, fewer complications and a better cosmetic outcome can be accomplished in comparison with invasive therapies.

IMAGE-GUIDED THERMOABLATIVE FIBROID TREATMENTS
Myolysis, Cryomyolysis, and Percutaneous Laser Ablation
The use of heat energy in the form of microwave energy, which is similar in its effects to ultrasound energy, has been used in myolysis for the treatment of uterine...
fibroids. Myolysis was the earliest thermoablative fibroid treatment. Initially, it used laser fibers to destroy fibroids and later incorporated the use of bipolar needles. Other groups used cryoprobes, but all combined thermoablative therapy with laparoscopy. The tedious nature of myolysis decreased its popularity among physicians, likely due to the cumbersome nature of the placement of multiple probes to destroy even small fibroids. Concerns were also raised regarding the formation of adhesions as a result of myolysis.

The use of percutaneous laser ablation in the treatment of fibroids involved the insertion of laser fibers transabdominally under local anesthesia. Thus outpatient treatment was possible for anterior uterine fibroids without laparoscopy. MR guidance during the procedure allowed accurate temperature monitoring. This was the first therapy of its kind for which outcomes were reported at 1 year. Results were highly promising, showing a decrease in menstrual blood loss and effective fibroid shrinkage. A similar percutaneous approach was also used with cryotherapy probes.

**Focused Ultrasound**

Although ultrasound imaging is typically known as a diagnostic tool, it was first used as a therapeutic rather than a diagnostic modality. The use of ultrasound for medical ablative treatments has been recognized since the 1920s. HIFU, also known as focused ultrasound surgery (FUS), allows a concentrated amount of ultrasound energy to be delivered to deep tissue areas without incurring any thermal effects on the surrounding tissue. However, control of this ultrasound energy limited its early clinical usefulness.

**Evidence of Focused Ultrasound Surgery Efficacy in Fibroid Treatment**

HIFU was first shown to be clinically effective for uterine fibroids in a xenograft mouse model. An average reduction of tumor volume of 91% within 1 month of treatment was demonstrated with an ultrasound-guided device. Further studies in 2002 extended this model to Eker rats with spontaneously growing in situ uterine fibroids. HIFU was applied to these tumors and compared with sham treatment. It was found that the average tumor volume decreased to 69% overall, whereas uterine fibroids of the sham treated group continued to grow. This provided substantial evidence that HIFU can be an effective method in limiting fibroid growth.

**MRgFUS Treatment Logistics**

**Patient Selection**

There are differences in the contraindications to MRgFUS compared with surgical therapy. For instance, women with cardiac pacemakers or other metallic devices that are contraindications to MR imaging are not candidates for MRgFUS. Similarly, women with a high body mass index (BMI) can be excluded due to the difficulty in positioning within the bore of the MRI machine. Women with extensive scars or fibroids located in inaccessible areas in the uterus are excluded from MRgFUS. In addition, treatment of postmenopausal women is contraindicated. Initial studies restricted the use of MRgFUS to women who are not interested in childbearing to maximize safety due to the novel nature of the treatment. Additionally, experience from studies of UAE at the time were indicating both an age-related risk of ovarian failure and placentation problems, so caution with a new technique was justified.

Thus the MRgFUS procedure was initially FDA approved for premenopausal women with symptomatic fibroids who had no desire for future fertility. With expanded experience in the field of MRgFUS and especially knowledge of pregnancy outcomes (discussed later), the FDA changed the labeling of the device in 2009 to take into account desire for future pregnancy but not to have this as an absolute contraindication. In
Europe, patients who desire further fertility have been allowed to undergo MRgFUS since 2007 under the device’s CE Mark.

**Patient Screening**
Patients are screened with an MRI with gadolinium in the initial phase to establish the size, number, and location of fibroids and to exclude confounding diagnoses such as adenomyosis or other pelvic neoplasms. If a patient has multiple fibroids, then those fibroids that can be adequately targeted are selected for treatment. Fibroids that do not enhance with gadolinium do not benefit from MRgFUS treatment. Although initially there was a high screen failure rate following imaging, advanced treatment techniques have allowed the treatment of many more women. Clinical factors are also routinely taken into account by gynecologists and radiologists in selecting patients. The degree of abdominal scarring, presence and severity of adenomyosis, number, size, and location of fibroids, desire for future fertility, and patient symptoms all play a role.

**The Procedure**
The MRgFUS system is built into a table that docks with a standard MR scanner. The piezoelectric phased array transducer is located within the table and surrounded by a water tank. This encompasses the therapeutic ultrasound beam, which has a frequency between 1 and 1.5 MHz and delivers phased pulses of thermal energy.

The procedure is performed in the fasting state, under intravenous (IV) conscious sedation. Conscious sedation allows for continuous patient feedback during the procedure, and patient movement is reduced to a minimum. The patient is in the prone position, with the pelvis inside the bore of the MR machine and the anterior abdominal wall over the water tank. A Foley catheter is placed in the bladder to prevent movement of the fibroid as the bladder fills. Meticulous and ongoing confirmation of patient positioning is one of the main focuses of treatment. Fiducial markers are placed during treatment planning on key structures, including scars, bladder, bowel, and bone, which are monitored throughout the procedure.

Modifications are made throughout the treatment based on patient comfort, movement, and MRI thermometry. Ultimately, feedback from both the system and the patient is provided after each sonication. Typical treatment time is 2 to 3 hours.

**Posttreatment Phase**
Once treatment is complete, imaging is obtained following the administration of IV gadolinium to determine the volume of gadolinium nonenhancement or the non-perfused volume (NPV). An early study where treatment occurred before hysterectomy confirmed that the NPV was the best predictor of tissue necrosis following MRgFUS, and thus it has been a surrogate marker of treatment success.

Because MRgFUS is a fibroid-specific treatment modality, in contrast to UAE where the entire uterus is treated at once, assessing the adequacy of treatment of all fibroids is important. The NPV ratio allows comparison between treatments, especially when some fibroids in a uterus are treated and others are not. The NPV ratio is calculated as the ratio of the sum of the NPV of all treated leiomyomas divided by the volume of all the uterine leiomyomas (treated and untreated).

**MEASURES OF MRgFUS EFFICACY**

**Rapid Return to Work**
More than 4000 women have undergone MRgFUS to date. Patients typically return to work within 24 hours of the procedure, a major improvement over most fibroid techniques.

**Symptom Improvement**
The Uterine Fibroid Symptoms Quality of Life (UFS-QOL) questionnaire was first described by Spies et al in 2002. This is a disease-specific questionnaire that has been used to evaluate the efficacy of fibroid therapy as a score reflecting patients’ quality of life. This was first used in the evaluation of UAE and was the primary efficacy end point in initial clinical trials of MRgFUS. UFS-QOL questions address both the frequency and severity of specific symptoms common to uterine fibroids.

Suitable symptomatic patients for early clinical trials were chosen using an eight-item symptoms severity score (SSS) of the UFS-QOL. To enroll in the trial, women had to have at least 40 points on the 100-point scale, and in most studies the mean level of symptoms exceeded 60 points. The usefulness of this assessment tool is clearly demonstrated in an early study of treatment outcomes, in which patients completed the questionnaire before treatment and at 3 and 6 months with a primary end point of an improvement of 10 points in 50% of patients. MRgFUS resulted in improvement in symptoms at 6- and 12-months for most women. Subsequent studies indicated that as treatment guidelines were expanded, statistically significant reductions in symptoms could be obtained.

Outcomes of MRgFUS over a 24-month follow-up period emphasized the durability of treatment results. This study demonstrated a significant reduction in SSS starting at 3 months and extending to 24 months.
for all subjects. However, patients with a NPV ratio greater than the mean had a statistically significant improvement that was maintained over time compared with patients with a lower NPV ratio for 24 months following treatment.19 Fibroid shrinkage clearly varied inversely with the NPV ratios. However, when the NPV ratio approached 10%, there was no shrinkage observed. Additional studies demonstrate a consistent decrease in symptoms following MRgFUS, first manifest by 3 months in multiple patient populations.23–26

Volume Reduction
Volume reduction also appears to be directly related to the adequacy of treatment of the myomatous uterus. Initial studies were disappointing in the amount of volume reduction achieved. In the pivotal clinical trial, the mean reduction in volume was 13.5 ± 32.0%; however, treatments in this study targeted an average of 10% myoma volume.21 It was shown that the larger the NPV after treatment, the greater the effective volume reduction in fibroid volume by 12 months, although mean shrinkage was ~20% in this series.19 In addition, an inverse relationship between the residual NPV and fibroid shrinkage at 6 and 12 months has been determined, which implies that absorption and breakdown of tissue occurs over time.19 More recently published series of women treated in commercial treatments appear to achieve shrinkage in the range of 30% 6 months following treatment.24,25

Use of Alternative Treatments
In general, there is a high rate of leiomyoma recurrence following all surgical interventions in that up to a third of women have an additional procedure over a short follow-up period. The data for MRgFUS are further confounded by the fact that initial treatments targeted only a limited amount of the fibroid disease. Initial reports demonstrate that by 12 months, 28% of patients underwent an alternative treatment.27 At 24 months, alternative treatment rates were related to the extent of treatment.19 Treatments achieving <10% NPV ratio saw 48% of women seeking additional treatment and where NPV >40%, the treatment rate was 17%.28 However, newer series from outside the United States that achieve mean NPV ratios of ~60% have demonstrated additional treatment in only 8 to 10% of women at 12 months.24,25

Limitations to Treatment
A survey conducted during the inaugural Focused Ultrasound World Congress in October 2008 queried clinicians regarding contraindications to MRgFUS treatment.29 Respondents were surveyed before and after the symposium. Factors such as severe adenomyosis, gadolinium nonenhancement, and postmenopausal status were noted to be limiting factors in recommending treatment. On the contrary, mild adenomyosis, heavy bleeding, bulk complaints, and pelvic pain were the least likely factors to be a concern regarding treatment.29

Following the symposium, more respondents considered having five or more fibroids >3 cm as a contraindication to treatment. Overall, it was shown that only a third of patients screened are actually potential candidates for MRgFUS.29

Treatment Expansion
Using pretreatment with gonadotropin-releasing hormone (GnRH) agonists to reduce fibroid volume has contributed to improved outcomes following MRgFUS.30 GnRH agonists cause a reduction in fibroid size when given in a continuous fashion and may also intensify tissue response to FUS treatment due to decreased vascularity of tissue. A case series from the United Kingdom demonstrated that in women with fibroids >10 cm in diameter, pretreatment with GnRH agonists resulted in significant improvement in symptoms at 24 months following MRgFUS in 83% of patients.30

MRgFUS SAFETY
MR guidance provides two key safety functions. The first is to provide continuous real-time imaging of the abdomen and pelvis just as vision does with laparoscopy. Second, MR guidance allows accurate temperature control though monitoring of proton resonance frequency shift. This function provides ongoing temperature feedback that allows the operator to alter tissue coagulation intensity with each sonication. Overall, this protects adjacent tissue from thermal damage and enhances patient comfort.

The most common complication following MRgFUS is skin burns confined to the area of the abdominal wall. Most have been minor; however, one case where treatment took place through an abdominal scar was reported to require a skin graft.31 In addition to avoidance of abdominal scars, providing good acoustic coupling to the abdominal wall with complete hair removal and avoidance of creams, lotions, or waxes has decreased the incidence and severity of this problem. Other repeated complications include pelvic neuropathies, injury of bowel and bladder, and deep venous thrombosis following treatment; these complications are rare based on reports to the Manufacturer and User Facility Device Experience Database (MAUDE) and expert report at the World Congress.29,32

One device-related adverse event was noted in 109 patients in an FDA-approved early study.27 The most serious complication was noted to be sciatic nerve
palsy as a consequence of energy absorption by distant bony structures in the treatment of a posterior fibroid. This manifested as lower limb weakness and numbness immediately after treatment. Symptoms resolved within 12 months. Neurography and electromyography did not show any intrinsic damage; however, review of the MR studies showed that the sciatic nerve was present in the field of sonication. This led to technical changes in device operation and an alteration in the required distance between sonication beams and nerve bundles in addition to other important structures.

There were no deaths or life-threatening events including no urgent surgical procedures or bowel injuries. Postembolization syndrome, a typical finding following UAE, is generally not experienced after MRgFUS. The rehospitalization rate was 7%, and transfusion risk was 3%. This was attributed to the underlying condition rather than procedure complications.

COST EFFECTIVENESS OF MRgFUS

A study comparing the cost effectiveness of MRgFUS with UAE, myomectomy, and hysterectomy was undertaken in the United Kingdom in 2007. Using a Markov model, it was determined that the total direct medical costs of treatment of 1000 women at age 39 (followed until menopause) was £3,101,644 compared with £3,396,913 for 1000 women treated with other available procedures. An average cost saving of £295 was incurred in addition to a marginal gain in the quality-adjusted life years (QALY). In this study, the NPV relative to the total fibroid volume and the rate of alternative treatments were used as study end points.

In the United States, costs of MRgFUS treatment were obtained from a large administrative database and secondary sources. UAE was found to be associated with the most QALYs followed by MRgFUS, myomectomy, hysterectomy, and finally medical therapy. MRgFUS was estimated to cost $27,300; UAE cost $28,000, and myomectomy cost $35,000. Cost per QALY gained was found to be most significant for hysterectomy ($21,800) followed by MRgFUS ($27,300), then UAE. Myomectomy was found to be the most costly and least effective treatment modality. Hence MRgFUS fulfills acceptable criteria for optimal cost effectiveness in the treatment of leiomyomas.

PREGNANCY OUTCOMES FOLLOWING MRgFUS

Uterine fibroids are prevalent in up to 10 to 20% of pregnant women, with a higher prevalence noted in women with advancing maternal age. Myomectomy, both hysteroscopic and abdominal, has been the gold standard treatment for women who require fibroid treatment and desire fertility. Rabinovici et al recently reported on all pregnancies that occurred after MRgFUS at all sites worldwide. There were 54 reported pregnancies in 51 women. The mean time to conception was 8 months. Mean patient age at the time of delivery was 37.7 ± 4.5 years. The live birthrate was 41% with a significant number of ongoing. The term delivery rate was 93% in the delivered pregnancies, and there was one preterm birth at 36 weeks of gestation. Fifty-seven percent of pregnancies had no maternal or neonatal peripartum complications.

The most serious complication during pregnancy following MRgFUS occurred when a myomectomy was performed at cesarean delivery and complicated by uterine atony, hemorrhage, and disseminated intravascular coagulopathy. However, this patient subsequently had a second-term delivery without complication.

Other pregnancy complications did not appear to differ from commonly experienced pregnancy complications such as unexplained vaginal bleeding and gestational diabetes. The rate of placental previa was reported to be 9% overall. Unlike case reports following UAE, both women had prior uterine surgery, a risk factor for placenta previa. Based on the good outcomes following pregnancy, a multicenter trial is now ongoing randomizing women with unexplained infertility and distortion of the endometrial cavity to myomectomy or MRgFUS (NCT00730886, clinical trials.gov).

TREATMENT OF ADENOMYOSIS

The use of MRgFUS in other conditions such as adenomyosis, in which benign endometrium appears to invade the myometrium of adjacent smooth muscle, has been reported. The underlying process is smooth muscle hyperplasia, which makes FUS treatment ideal in targeting such lesions. The effectiveness of MRgFUS in reducing fibroid volume and improving symptoms has allowed its application to the treatment of adenomyosis in which dysmenorrhea, menorrhagia, and abnormal uterine bleeding are common symptoms. The clinical distinction between fibroids and adenomyosis is made through MR imaging showing typical diffuse or focal thickening of the junctional zone of the uterus in the presence of adenomyosis.

The first case report to describe a patient treated with MRgFUS for symptomatic adenomyosis at 1 year following treatment showed promising results. The patient completed treatment without complications and had clinical improvement with shrinkage of both the uterus and the adenomyomatous mass. Early study results have supported this conclusion and indicated the safety and efficacy of MRgFUS in adenomyosis with symptom improvement at 6 months and a 12.7% reduction in mean uterine volume and SSS.

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CONCLUSION
Treatments of leiomyomas have evolved over time. There has been an upward trend toward the use of thermoablative therapies with and without image guidance; results have been variable, however. MRgFUS has been recently proven to be a successful noninvasive therapy targeted for a particular population of women: those seeking later childbearing and a minimum treatment recovery time. The novel addition of real-time MR imaging and thermal mapping have been key factors in its success and popularity among gynecologists and radiologists. Its rapid therapeutic effects and sustained symptomatic relief have been persistently demonstrated in the literature without any negative implications on the rate of adverse events. Long-term studies have clearly illustrated that to ensure treatment success of any novel medical procedure, continued investigation and development are of paramount importance. The applications of MRgFUS are gradually expanding and its treatment cohort is broadening. Emerging evidence of successful outcomes in patients desiring pregnancy has made this therapy a unique noninvasive treatment modality that caters to the needs of an even larger group of patients than initially intended. Further treatment modification and optimization remain essential components in ensuring continued success.

REFERENCES