



Magnetic Resonance-guided Focused Ultrasound Surgery

SUSAN B. A. HUDSON, MD
and ELIZABETH A. STEWART, MD

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, College of Medicine, Mayo Clinic, Rochester, Minnesota

Abstract: Uterine leiomyomas pose a significant health issue to reproductive-age women. Many women desire uterine conservation, and previously safe and efficacious therapies have been limited. Magnetic resonance-guided focused ultrasound surgery is a new noninvasive therapy that has been proven to be both safe and efficacious in the treatment of fibroids.

Key words: leiomyomas, MRgFUS

Introduction

Uterine leiomyomas, also referred to as myomas or fibroids, pose a significant health issue to reproductive-age women. It is estimated that 20% to 40% of women have diagnosed fibroids and many more have subclinical fibroids. These benign tumors may cause a variety of symptoms such as pain, menorrhagia, pelvic pres-

sure, and bowel and urinary tract complaints. In the United States, approximately 175,000 hysterectomies are performed annually as a result of fibroids. As a result, a significant amount of healthcare dollars are spent treating this condition.^{1–3}

To minimize healthcare costs, number of workdays missed, and complications associated with major abdominal surgery, physicians have been working for decades to develop less invasive means to treat symptomatic fibroids. Additionally, as the average age of childbearing rises, an increasing number of women have fibroids as a potential cause of infertility and pregnancy risk.

There are uterine-conserving medical and surgical options for the treatment of fibroids. Medical treatment has been limited to hormonal therapies such as oral contraceptive pills and gonadotropin-releasing hormone agonists. Surgical therapies have evolved with time and advancing technologies. Initially,

Correspondence: Susan B. A. Hudson, MD, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Mayo Clinic, 200 First St, SW, Rochester, MN 55901. E-mail: hudson.susan@mayo.edu

myomectomy was available only by laparotomy. The advancement of laparoscopic and hysteroscopic instruments, including the emerging robotic systems, has allowed for the removal of modest sized fibroids with minimally invasive techniques.

In 1995, uterine artery embolization was reported to have a favorable effect on the treatment of fibroids.⁴ This was a critical point in the treatment of myomas, allowing effective therapy for menorrhagia and pressure symptoms that did not require general anesthesia or the use of the traditional operating room. In this procedure, performed under conscious sedation, the femoral artery is catheterized under fluoroscopic guidance and microspheres are used to occlude the uterine artery. Though less invasive than traditional surgery, risks of the procedure include postembolization syndrome, vaginal expulsion of submucous fibroids, and increased incidence of ovarian failure.⁵

Thermo-ablation

For many years, scientists have been developing thermo-ablative techniques for the destruction of abnormal tissue, both in the uterus and throughout the body. Myolysis, the earliest of these techniques applied to uterine fibroids, was performed at the time of laparotomy or laparoscopy using laser, bipolar needles, or a freezing probe. However, because of the tedious nature of the procedure and concern over adhesion formation, this technique was never widely accepted.⁶

The key to develop a successful thermo-ablative technique is having an accurate and noninvasive method to monitor tissue temperature, to target the necessary tissue destruction, while ensuring safety to adjacent tissues. As fibroids vary in composition and density, tissue monitoring is of paramount importance. Several specific magnetic resonance imaging (MRI) parameters are able to gauge relative tempera-

ture, thus giving real time thermal feedback.⁷

MRI guidance was initially used in conjunction with cryomyolysis at the time of laparoscopy.⁸ However, because of the additional expense and impracticality of performing surgery without metal instruments, this regimen was never widely adopted. Percutaneous laser ablation under local anesthesia was later introduced, whereby laser fibers were passed to the fibroid through the skin.⁹ This outpatient therapy was limited to anterior fibroids.

MR-guided Focused Ultrasound Surgery

MR-guided Focused Ultrasound Surgery (MRgFUS) has been a treatment modality since 1942 and has been used for treating breast, brain, eye, prostate, bladder, renal, and liver tumors.¹⁰ MRgFUS uses ultrasound waves directed to tissue to elicit coagulative necrosis via thermal ablation. For MRgFUS to be successful, the tissue must be large enough to target, access, and absorb energy easily, without intervening bone or air. Therefore, fibroids are ideal for this technology. In addition, fibroids tend to have an excellent blood supply, which benefits treatment as heat is easily dissipated within the fibroid preventing injury to the adjacent tissue.

Procedure

The initial protocol approved by the Food and Drug Administration (FDA) was designed to evaluate safety and efficacy. After an initial gynecologic evaluation for symptomatic fibroids, the patient undergoes a screening MRI with intravenous gadolinium on a 1.5-T magnet in the prone position. This allows diagnostic confirmation, localization of all important structures relative to the fibroid

(bladder, bowel, pelvic nerves, spine), evaluation of fibroid size and volume, determination of enhancement (indicating vascularization of the fibroid), and the ability to exclude adenomyosis or lesions suspicious for malignancy. Both radiologists and gynecologists can collaborate on creating a treatment plan based on the patient's symptoms and the imaging.

The patient is asked to prepare by fasting overnight and shaving her lower abdominal wall to the pubic symphysis, as hair increases the risk of thermal injury to the skin. On the day of MRgFUS, a Foley catheter is placed to keep the bladder empty, as a distending bladder can cause complications due to changes in anatomic positioning, resulting in distortion of the ultrasound waves during therapy. Intravenous conscious sedation with midazolam and fentanyl allows adequate pain control with minimal patient motion, yet enables the patient to provide continuous feedback. A repeat MRI is performed to confirm the prior MRI findings using T2-weighted, fast spin echo images in 3 orthogonal planes. These images are used to develop the treatment plan. The volume of the fibroid to be targeted is then visualized in 2 planes. The software displays the path of the ultrasound waves. This display is evaluated to ensure that bladder and bowel are not in the pathway of ultrasound waves. Focal sonications are planned to encompass the entire target volume. These sonication positions are modified during the procedure as dictated by patient's discomfort, movement, and MRI thermometry. A low-energy test pulse is then aimed within the target to confirm location, and that temperature changes can be detected. Sonications are then performed in 20 to 40-second intervals with 80 to 90-second periods for cooling. Patients are given a "panic button," which they may press at any time to interrupt a treatment cycle, especially in the case of pain. After the completion of

the treatment plan, the patient then undergoes posttreatment imaging with and without gadolinium to determine the non-perfusion volume (NPV). The skin is then evaluated for possible thermal injury and the patient is allowed to recover from the sedation. The patient is then discharged to home with a friend or family member. Most women require no additional pain control other than a non-steroidal analgesic.¹¹

Evaluation of MRgFUS

As with any new therapeutic modality, it is of utmost importance to have a validated measure to determine if that modality is effective. In 2002, Spies et al¹² published 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). This questionnaire was developed to address menorrhagia, non-bleeding symptoms of fibroids, and to assess the quality of life impact of fibroids. Symptom issues addressed in the UFS-QOL include both frequency and severity of symptoms. Health-related quality of life issues evaluated included fatigue, self-image, psychologic distress, effect on daily activities, and sexual function. A recall interval of 3 months is used to minimize recall burden. The final questionnaire includes 8 symptom and 29 health-related quality of life items. A single subscale is used for symptom severity. The health-related subscale included concern, activities, energy/mood, control, self-consciousness, and sexual function. The UFS-QOL is able to identify mildly, moderately, and severely symptomatic women. Also, the test-retest reliability is high. 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.¹²

Feasibility

A phase I/II study was initially performed to determine the feasibility and safety of MRgFUS for the treatment of uterine leiomyomas.¹³ Technical feasibility was previously established by animal studies, and clinical feasibility has been demonstrated with breast tumors. Prospectively, premenopausal women over 18 years of age with symptomatic fibroids and uterine size less than 20 weeks, with no dominant fibroid greater than 10 cm in diameter, were selected for the study. Nine women were enrolled to undergo MRgFUS and subsequently undergo hysterectomy within 3 to 30 days. Posttreatment images were compared with pretreatment images. Six of 9 subjects received the fully planned thermal dose. Those who did not, included one with pain in an anterior abdominal scar due to increased absorption, thus increased temperature with no serious effects. One patient had multiple loops of bowel in the target zone, and in 1 patient the low-power sonications could not be visualized. The number of sonications in each patient ranged from 6 to 31, and was related to volume of tissue treated. In the 6 patients who received full focused ultrasound therapy, 98.5% of the sonications were visualized and all visualized sonications were analyzable for temperature. Room times for the procedure ranged from 3 hours 19 minutes to 4 hours 55 minutes, with treatment duration lasting 1 hour to 2 hours 32 minutes. All patients went home after a short observation period, and none reported clinically important issues at the 72-hour posttreatment visit. Minor skin burns were noted on 2 patients. After hysterectomy, 6 of 9 lesions (all of the fully treated subjects) demonstrated decreased contrast uptake, implying devascularization and necrosis as evidence of successful treatment. Five of these had histologic evidence of necrosis; the sixth did not undergo hysterectomy during the course of the study.¹⁰

An expanded study including 55 premenopausal and perimenopausal women from 3 sites was performed to further establish safety and efficacy. Women from 2 sites who were eligible for hysterectomy were treated expectantly and not compelled to undergo hysterectomy. This was referred to as the *observation protocol*. Adequate MRgFUS was performed on 76% of subjects, and 5% received no sonication due to bowel interference or equipment failure. Eighteen percent of patients received less energy than predicted for optimal therapy mostly owing to the inability to visualize the test pulse. This was mainly a result of surgical scars or muscle and fat deposition. A modest increase in pain and discomfort was noted with the procedure but the pain score immediately before discharge was not significantly different from prior treatment values. Discomfort remained significantly increased at the time of discharge. In patients who underwent hysterectomy, up to a 3-fold increase of necrosis was noted compared with the treatment volume. Importantly, this was confined to the margins of the myoma. All subjects were treated on an outpatient basis and none required readmission or further observation.

Within the first 72 hours of MRgFUS, 10% reported taking any analgesics for pain, the vast majority using acetaminophen or nonsteroidal anti-inflammatory drugs. The most common symptom reported at 72 hours was generalized discomfort in 25% (mild to moderate 92%), abdominal tenderness in 14%, and nausea or pain at the treatment site in 10%. Two individuals had first degree skin burns not noted immediately post-MRgFUS. Women who underwent hysterectomy did have a significant number of adverse events. Fever was the most common complication and was eliminated with initiation of prophylactic antibiotic at the time of MRgFUS. Two patients had a pelvic hematoma that required surgical

drainage, and 1 patient had significant incisional bleeding on the side opposite of where the sonication beam entered. Thermal injury to the normal myometrium was detected in 1 patient. Retrospectively, this was a result of anatomy change due to bladder filling.¹³

Long-term Outcomes

Not only do patients want to know the efficacy of MRgFUS, but many insurers currently limit payment for noninvasive technologies owing to lack of data on prolonged efficacy. Stewart et al¹⁴ published data on 2-year outcomes for MRgFUS. Outcomes and treatment were standardized using NPV, as later trials permitted increased treatment volumes and smaller margins. Subjects in all protocols were evaluated with MRI to assess fibroid size and NPV at 6, 12, and 24 months. A hematocrit was obtained at baseline and 6 months for those enrolled in the phase III trial. The NPV ratio was compared with the symptom severity score (SSS) measured by the UFS-QOL, number of subjects turning to alternative therapies after the treatment, shrinkage and change in hematocrit.¹⁴

The NPV groups were dichotomized into <30% and >30%. Both groups demonstrated significant improvement in the SSS at 3 months and beyond after treatment. At 12 and 24 months, an increased NPV ratio was significantly inversely related to the number of women undergoing alternative treatments. A difference was also noted between women who had >30% NPV, compared to less complete therapies. Fibroid shrinkage varied inversely with NPV ratios. However, with NPV ratios less than 10%, no shrinkage was seen. No significant difference was noted in hematocrit with the treated population as a whole, but in women with pretreatment anemia (hematocrit <35), a significant increase was

seen with an increasing NPV ratio after therapy.¹⁴

Other Factors

With the expansion of MRgFUS, studies are now being carried out to help improve outcomes and identify factors that may predict therapeutic success. Funaki et al¹⁵ evaluated the effect of signal intensity of the T2-weighted images on the therapeutic effect of MRgFUS on fibroids. In this study, 95 fibroids in 63 patients were treated with MRgFUS. No more than 4 fibroids could be treated in a single procedure, and the minimal treatment margin was 0.5 cm from the treated area to the edge of the uterus. Before treatment, fibroids were categorized on the basis of the signal intensity of the T2-weighted images. Type 1 was a very low density image (ie, skeletal muscle), type 2 was an image intensity lower than myometrium but higher than skeletal muscle, and type 3 was of intensity equal to or greater than myometrium. Usage of the “panic button” to stop therapy due to pain, was greatest in type 3 fibroids suggesting a need for higher energy. The treated area ratio was significantly greater in type 1 and 2 fibroids compared with type 3 fibroids. The mean percentage of area treated by target dose dropped from type 1 (31.3%) to type 2 (20.5%) to type 3 (16.5%). Highest shrinkage was noted in type 1 fibroids followed by type 2 fibroids. Also, marked decrease in fibroid size was noted only in type 1 or 2 fibroids. Some type 3 fibroids actually increased in size after treatment. The main concern of this study was that the intensity of type 3 fibroids represents vascularization, fluid-rich tissues, or degeneration—all factors that make adequate temperature elevation more difficult. Also, a high-intensity fibroid tends to have higher proliferative activity compared with a lower intensity fibroid. An additional concern is that leiomyosarcomas tend to be of higher

intensity and confirmation should be done before noninvasive therapy as to not wrongly treat an individual with cancer. Thus, caution should be used treating high intensity fibroids with noninvasive therapies owing to the risk of malignancy and possible decreased efficacy.¹⁵

So et al¹⁶ evaluated whether the phase of the menstrual cycle affected MRgFUS. It had been noted previously that myometrial signal intensity was lower in the proliferative phase compared with the secretory phase owing to transient changes in blood volume, which changes the water content of the myometrium. In this study of 58 patients, 28 were treated in the proliferative phase, and 30 treated during the secretory phase. The SSS at baseline and in 6 months between the 2 groups showed no statistically significant difference.¹⁶

Methodologic Improvements

Now that a method for MRgFUS has been approved for use by the FDA, showing efficacy and safety, researchers have been working to refine the procedure to improve patient response and minimize side effects. As part of a phase III, multicenter clinical trial, and extension of the pivotal trial, subjects before April 30, 2004 were treated under the aforementioned original study guidelines, and those treated subsequently were treated with a modified protocol (Table 1). The goal of the modified treatment protocol was to safely sonicate a larger fibroid area to lead to a larger area of nonperfusion. The SSS of the UFS-QOL was used as a

primary end point. Adverse effects were also documented and classified as serious/nonserious, important/nonimportant, and mild/moderate/severe. Patients in both studies were evaluated at 1 week, 3, 6, and 12-month intervals. One hundred and sixty patients were enrolled, 96 in the original treatment protocol and 64 in the modified treatment protocol. Twenty-three subjects in the original group sought alternative treatment by 12 months and 7 sought alternative therapy with the modified protocol. The modified protocol did permit a second MRgFUS during the first 14 days after initial treatment. Twenty-four patients used this option. The original population demonstrated a 10-point improvement in SSS (considered significant) in 73.9% at 6 months and 72.7% at 12 months. Those under the modified protocol noted a 10-point improvement in 87.5% at 6 months and 90.5% at 12 months. Under both protocols, maximal rate of improvement was noted at 3 months after treatment. The NPV in the original group was calculated to be $59.4 \pm 65.1 \text{ cm}^3$ ($16.65\% \pm 16.1\%$) and $131.6 \pm 138.1 \text{ cm}^3$ ($25.79\% \pm 21.8\%$) with the modified protocol. Two hundred and ninety adverse effects were reported, most of which were nonserious, nonimportant, relating to positioning or uterine discomfort. No serious adverse effects were reported and no important adverse effects were reported under the modified guidelines. Under the original guidelines, 2 important side effects were noted: intravenous cannula-induced paresthesia, which resolved in 6 weeks and mild sonication-related leg pain which resolved in 2 days.⁷

TABLE 1. Comparison Between 2 Treatment Protocols

Treatment volume	< 33%	< 50%, submucosal 33%
Maximum treatment time (min)	120	180
Distance (sonication to endometrium)	1.5 cm	Unlimited
Distance (sonication to serosa)	1.5 cm	1.5 cm
Second treatment	None	Within 14 d

Patient Selection

The initial patient population selection for the FDA clinical trials was focused on a group of relatively healthy women with moderate sized fibroids. The candidates were required to be premenopausal, over 18 years of age, with no future plans for childbearing. The uterus could not exceed 20 weeks' size and the largest fibroid could not exceed 10 cm in diameter. Women with a history of other pelvic disease or other uncontrolled systemic disease were excluded from the study. Women with specific contraindications to MRI, that is cardiac pacemakers or exceeded the size limitation of the MRI machine, were excluded. As abdominal scarring can focus the ultrasound beam and lead to thermal skin injury, women with extensive lower abdominal scarring were also initially excluded. A negative pregnancy test was necessary for participation in the procedure.¹⁰ With experience, a majority of these contraindications are deemed as relative contraindications rather than absolute. Absolute contraindications mainly encompass those specifically in reference to the MRI, such as having metal implants, or not fitting into the machine. As the clinical trials are focusing on safety and efficacy, many of these restrictions are made to protect the participants from potential harm. In reference to age restrictions, postmenopausal women with growing, symptomatic fibroids are at an increased risk for malignancy compared to their premenopausal counterparts. Future fertility effects from MRgFUS are unknown.

The Future

MRgFUS has provided a safe and effective therapy option for women with symptomatic fibroids who desire preservation of their uterus. Although current applications remain limited to premenopausal women without a desire for future child-

bearing, this therapy has the potential to reduce healthcare spending by minimizing the number of hysterectomies performed for fibroids. This treatment has a relatively rapid therapeutic effect, thereby improving quality of life of these affected women in a timely manner. Future studies on MRgFUS are likely to focus on maximizing effectiveness, minimizing adverse effects, and expanding those eligible for treatment.

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