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MR-guided High Intensity Focused Ultrasound Treatment for Symptomatic Uterine Leiomyomata: Long-term Outcomes

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Abstract

PURPOSE—To evaluate the long-term clinical outcomes of MR-guided high intensity focused ultrasound (MR-g HIFU) treatments for symptomatic uterine leiomyomata.

MATERIAL AND METHODS—Patients were recruited for a prospective study for MR-g HIFU treatments of symptomatic leiomyomata, with up to three-year follow-up. The study was approved by the institutional review board and was HIPPA compliant. Clinical assessments were obtained at 3 months, 6 months, 1, 2 and 3 years after MR-g HIFU, as well as uterine fibroid symptom severity scores (SSS) and health-related quality of life questionnaires (UFS-QOL). MRI was performed at each follow-up to assess the efficacy of the treatment at 6 months, 1 year, 2 years and 3 years.

RESULTS—Fifty one leiomyomata in 40 patients were treated. All patients were treated within the FDA guidelines with leiomyomata localized on MR and treated with sonication. The mean baseline volume of treated leiomyomata was 336.9 cm³. The mean improvement scores for tSSS was 47.8 (p<.001) and for tUFS-QOL was 39.8 (p<.001) at 3 years. The mean volume decrease in treated leiomyomata was 32.0% (p<.001), and, in uterus, the volume decrease was 27.7% (p<.001) at three years. There were no long-term complications.

CONCLUSION—Long-term follow-up data from MR-g HIFU treatments show sustained symptomatic relief among enrolled patients. Although the results are preliminary, MR-g HIFU for the treatment of uterine leiomyomata may result in acceptable long-term outcomes at three years.

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INTRODUCTION

Uterine leiomyomata occur in approximately 20–50% of women of reproductive age (1, 2). Symptoms are found in less than 50% of women; however, uterine leiomyomata can cause significant morbidity in pre- and peri-menopausal women. Traditionally, gold standard therapy has been a hysterectomy. In the U.S. alone, hysterectomy is performed in over 600,000 women annually and uterine leiomyomata account for approximately 30–60% of all hysterectomies performed in middle-aged women (3). More than \$1.2 billion is spent each year associated with hysterectomies (4, 5). The cost is even greater when accounted for the loss of women's productivity during 6–8 weeks of recovery time after hysterectomy or myomectomy is considered.

Less invasive surgical techniques have been studied. Myomectomy is performed in 35,000–40,000 women for the treatment of uterine leiomyomata (6). Laparoscopic and hysteroscopic myomectomy have gained popularity as uterus-conserving surgeries (7). These less invasive techniques are restricted with regard to size and location of leiomyoma and still require general anesthesia. Laparoscopic thermoablative myolysis has shown significant variability in clinical efficacy (8, 9).

Uterine artery embolization (UAE) has gained popularity (10), and has become a “gold standard” in interventional radiology procedures for uterine leiomyomata through a large registry trial in the U.S. (11). However, a UAE may cause uncomfortable postoperative pain (12, 13) and postembolization syndrome (14). In addition, effects on ovarian function require further investigations (15, 16). Minimally invasive percutaneous treatments using thermal ablation techniques have also been proposed. Thermal ablation of uterine leiomyomata with RFA (17), cryoablation of uterine leiomyomata (18, 19) and laser treatments (20) have been reported.

MR-guided high intensity focused ultrasound (MR-g HIFU) is a novel technique for treating symptomatic uterine leiomyomata using heat generated by high focused ultrasound (21, 22). The short-term and two-year results (23, 24) suggest that focused ultrasound thermoablation can improve leiomyomata-related symptoms and may be a more cost effective treatment strategy for symptomatic uterine leiomyoma (25).

The purpose of this study was to establish the long-term safety of this novel technology, as well as the clinical efficacy of MR-guided HIFU for the treatment of uterine leiomyomata.

MATERIALS AND METHODS

Patients

The institutional review board (IRB) granted approval for this prospective study, and the study is HIPPA compliant.

Consecutive pre- or peri-menopausal women, 18-years of age or older, with symptomatic leiomyomata and interested in a prospective non-randomized study of MR-g HIFU were recruited from gynecology and interventional radiology clinic. Each patient gave written informed consent.

Our exclusion criteria included women who were pregnant at the time of the procedure and those who wanted to become pregnant after the treatment, as set forth by the FDA. Patients with a uterus larger than 24 weeks, or with skin scar in the area of the expected ultrasound beam path, were excluded. Patients with significant co-morbidities or those who could not tolerate MRI examinations were also excluded. Co-morbidities included significant conditions that would preclude prolonged MR examination or that would pose a moderate

sedation risk, such as cerebrovascular, cardiac and pulmonary conditions. Patients with leiomyomata positioned in the uterus such that they could not be accessed without being shielded by bowel or bone were also excluded.

Intraprocedurally, patients received IV midazolam (Bedford Labs, Bedford, OH) and fentanyl (Bedford Labs, Bedford, OH), titrated by a sedation nurse to moderate sedation per the hospital protocol.

After the treatment, the patients were monitored for 45 minutes per the hospital sedation protocol, and then discharged to home. No pain medication was given during the recovery period. Upon discharge, no medication was given. Specifically, no pain medication or antibiotics were given.

Patient demographics, clinical outcomes, and MRI findings were prospectively collected and analyzed.

MR-g HIFU Techniques

The MR-g HIFU technique was described in detail in earlier works (22–24). Briefly, all treatments were performed using a modified MR-guided Focused Ultrasound Surgery system (ExAblate 2000, InSightec, Haifa, Israel) coupled with a 1.5T MR system (General Electric Health Care, Milwaukee, WI). The patient was placed in the prone position on the table (Fig 1a). The table contained a 120 mm diameter ultrasound piezoelectric transducer array in the frequency of 1–1.5 MHz in a water tank. A 2–4 cm thick gel membrane (Parker Laboratories, Fairfield, NJ) with degassed water was placed between the patient and the transducer to improve acoustic coupling. To confirm the proper positioning of the patient with the MRI system, calibration was performed by aligning the transducer and skin line and setting the fiducials around the treatment zone.

Coronal, sagittal, and transverse T₂-weighted (T2WI) fast spin echo (FSE) images (TR/TE=5000/100ms; echo train length=12, slice thickness=4.0mm, 256×100, field of view=36×36cm) were obtained for treatment planning. During the planning, the HIFU beam path was projected onto the MR images. The treatment zone was outlined by a board-certified interventional radiologist, and the treatment path was modified to avoid passing through bowel, bladder, or nerves. To test the accuracy of targeting, a series of low-power focused ultrasound sonications were performed while the treatment effects were monitored by two orthogonal plane, phase shift MR images. After confirming the accuracy, treatment was performed by increasing the power to achieve 65–85°C at the target tissue. The duration of each sonication was about 30 seconds, followed by 60–90 seconds of a cooling period. Phase-sensitive MRI was performed to monitor the elevation and decline of the temperature in real time. Depending on the volume of the targeted leiomyomata and target treatment zone, a variable number of sonications was performed. All treatments were performed within the FDA guidelines that specified the following treatment parameters: Up to two leiomyomata were treated per patient. The treatments were limited up to 50% of all leiomyomata tissue, except submucosal leiomyomata which could be treated up to 33%, the maximum treatment volume of 150 cm³, and treatment time up to 180 minutes. Patients received up to two treatment sessions within 14 days.

MRI Parameters

The imaging protocol consisted of a series of T₂-weighted fast spin echo (FSE), T₁-weighted fast spoiled gradient recalled echo (FSPGR), spin phase shift gradient echo (GRE) and diffusion-weighted echo planar imaging (DW-EPI) sequences (TR/TE=5000/90ms, b=0,500–1000,128×128,28×28, ST=6mm) acquired before, during, and after the treatment. DW-EPI sequences were obtained as a correlative study. The multiplanar T₂WI FSE images

(TE/TR, 100/5000 ms; echo train length, 12; slice thickness, 4.0 mm; matrix size, 256 × 128; field of view, 36 × 36 cm) were acquired for calibration and treatment planning. For treatment monitoring, T₁ FSPGR images (TE/TR, 13/26 ms; flip angle, 30; matrix size, 256 × 128; field of view, 28 × 28 cm; slice thickness, 5.0 mm) were acquired before and during the focused ultrasound treatment to monitor the temperature using phase maps. The pre- and post-contrast T₁-weighted FSPGR images (TE/TR, 1.5/185 ms; matrix size, 256 × 128; field of view, 28 × 28 cm; slice thickness, 6.0 mm) were acquired to define the amount of ablated tissue using Gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, New Jersey, USA) at a dose of 0.01 mg/kg administered through the antecubital vein with a power injection device (Medrad, Pittsburgh, Pennsylvania, USA) five seconds after the start of image acquisition. The contrast agent bolus injection was followed by an injection of a 20 mL saline solution to flush the contrast agent (Fig 1b, c).

Study Endpoints

The primary study endpoint was the assessment of the long-term clinical effectiveness of MR-g HIFU treatment for symptomatic uterine leiomyomata. Clinical effectiveness of MR-g HIFU were defined by the changes in patient symptoms, and were quantitatively assessed through the symptom and health-related quality-of-life scores from the Uterine Fibroid Symptom and Quality of Life questionnaires. These questionnaires have been previously validated (26) and shown to be effective for assessing symptoms and quality of life status of patients with uterine leiomyomata. Eight leiomyoma-specific questionnaires and 29 overall health-related quality of life questions with six subscales were administered, and the responses were rated on a scale from 1 to 5. Raw scores were converted to a transformed score using the following formula: transformed score = (raw score – 8)/32 × 100. The transformed scores in the range of 0–100 were calculated and compared (26); lower scores indicated better relief of symptoms on the symptom severity scale (SSS), and higher scores on the health-related quality-of-life (QOL) scale indicated better quality of life. The questionnaires were given at three months, six months, one year, two years and three years, and the scores were compared between those at the baseline and those at the follow-up intervals.

The secondary study endpoint was the assessment of the outcomes of leiomyoma treatment based on the MRI findings. Uterine, leiomyomata and non-perfused volumes were analyzed longitudinally over three years (Fig 1d). The conventional method of estimating uterine and leiomyoma volumes as prolate ellipsoid shapes, using the formula (Volume = $\pi/6 \times$ longitudinal dimension × anterior-posterior dimension × transverse dimension), may under- or over-estimate the true volume due to deformations caused by leiomyoma within the uterus. To estimate an accurate volume for the uterus and leiomyomata, we used a 3D workstation with a Dextroscope (Bracco, Singapore) for all of our volume measurements using the T₁- and T₂-weighted images. The Dextroscope shows computer-generated stereoscopic images to an observer wearing liquid crystal display shutter glasses. The contours of a uterus or a leiomyoma on axial images were traced with a pencil-shaped sensor on the touch-screen. All contours of a uterus or a leiomyoma were drawn and added to form a computer-generated 3D image. The numbers of voxels within the uterus or leiomyoma were summed to calculate the volume.

The other secondary endpoints were long-term complications related to the MR-g HIFU treatment. Minor complications were defined as temporary and self-limiting symptoms that required no therapy, or nominal therapy with no clinical sequelae, and major complications were defined as those that required further intervention and/or hospitalization or those that resulted in permanent sequelae (27).

Statistical Analysis

Statistical analysis was performed using the Stata statistical package, version 10.0 (StataCorp, College Station, TX). We used random effects modeling for longitudinal data and to account for correlations of outcomes within individuals. We analyzed data from all individuals, including those who were lost to follow-up after 1 year. We tested the assumption of data was missing completely at random, and did not find evidence to reject this (28). We assessed statistical significance for differences from baseline and for mean estimates at the .05 level and report 95% confidence intervals. To estimate the time elapsed until alternative treatment, we used the Kaplan-Meier estimator, which adjusts for the presence of censored data. We estimated more than 90% power to detect the changes from baseline at three years of 35 points or more for tQOL and tSSS scores.

RESULTS

Fifty-one leiomyomata in 40 patients (mean age 45.98 years $\pm$ 4.52) were treated with sonications. At three years after the treatments, 29 patients had completed the follow-up. Despite repeated attempts (approved by the IRB), eleven patients could not be located. These eleven patients had total of fourteen leiomyomata treated.

The mean baseline tSSS was 64.8 (95% CI: 60.8, 68.8). Mean reduction of tSSS at the three-year follow-up was 47.8, and the mean tSSS at three-year follow-up was 17.0 (95% CI: 8.9, 25.1) (Table 1). The mean baseline tQOL was 44.1 (95% CI: 37.7, 50.6). Mean improvement in tQOL at the three-year follow-up was 39.8, and the mean tQOL at the three-year follow-up was 83.9 (95% CI: 74.5, 93.3) (Table 1). Significant symptom and life quality improvements were sustained during the three-year follow-up period (Table 1). Similar significant and sustained improvements were seen among all six subscales of the UFS-QOL (Table 2).

The mean baseline volume of the treated leiomyomata was 336.9 cm³ (95% CI: 295.2, 378.6) and that of the uterus was 978.7 cm³ (95% CI: 925.1, 1032.3). The mean reduction in treated leiomyoma volume was 108.5 cm³ or 32.0% at three years, and the mean volume of the treated leiomyoma at three years was 228.4 cm³ (95% CI: 171.9, 284.8). The mean reduction in uterus volume was 271.4 cm³ or 27.7% at three years, and the mean volume of the uterus at three years was 707.3 cm³ (95% CI: 622.2, 792.4). The most significant volume reduction of the treated leiomyoma and uterus occurred at six months after treatment, and was sustained for the follow-up period of three years (Table 3) (Fig 2a). Non-perfused volume within the treated leiomyoma at baseline was 7.1 cm³ (95% CI: -11.6, 25.8). The increase in the non-perfused volume was the most significant immediately after MR-g HIFU, at 108.1 cm³ (95% CI: 87.5, 128.7), and gradually decreased to 30.5 cm³ (95% CI: -7.0, 68.0) at three years (Table 3) (Fig 2b).

Within three years after the MR-g HIFU treatments, nine patients received alternative treatments for failed symptom control or recurred symptoms; two patients had hysterectomies, two patients had myomectomies, and five patients had uterine artery embolizations. The alternative treatments were elective, and no emergent procedures were performed after MR-g HIFU. Kaplan-Meier analysis estimated the time elapsed until the alternative treatment after the initial MR-g HIFU (Fig 3). The curve also demonstrates the proportion of patients who did not receive alternative treatments. At approximately 2.5 years, the analysis demonstrates that about 69% of patients had no necessity for alternative treatments.

There were no long-term minor or major complications related to the MR-g HIFU. Specifically, no chronic skin burns or tissue changes along the path of the ultrasound

treatment, or chronic back or chronic leg pain attributed to nerve damage along the ultrasound treatment path were described by patients during follow-up sessions. No patients attempted pregnancy.

DISCUSSION

In this study, we demonstrate long-term clinical results after non-invasive MR-g HIFU treatment for symptomatic uterine leiomyomata. At three years, the patients enrolled in the study demonstrated a mean SSS (47.8) and UFS-QOL (39.8) improvement. These mean scores of symptomology represent significant improvements in every follow-up period. Stewart et al, showed short-and mid-term clinical outcomes after MR-g HIFU (23, 24). Our study shows that the clinical outcomes in the patients who completed the 3 year study are sustained after MR-g HIFU in long-term, as 69% of patients did not look for alternative treatments in long-term. Furthermore, our study shows no long-term ill effects or treatment associated complications at 3 years.

Our results from early stage of HIFU treatments for uterine leiomyomata are encouraging, and compare similarly to the previous long-term UAE studies. Goodwin et al. reported the mean SSS and UFS-QOL improvement scores of 41.4 and 41.5 respectively at three years after UAE from the Fibroid Registry study (29). Long-term UAE studies have shown 25–26% repeat intervention rates after UAE at 3–5 years (30, 31). Such repeat intervention rates are similar to our study population, where 31% of patients who completed MR-g HUFU study elected alternative treatments within three years.

In our study, the most significant uterine and treated leiomyoma volume reduction occurred within the six months. Subsequently, gradual decline ensued, although volume reduction at each follow-up was statistically significant when compared to the volume at baseline. The mean volume reductions of uterus and treated leiomyoma are somewhat less than those reported from UAE studies (32, 33). Our study was limited to the treatment guidelines by the FDA for the initial safety concerns and may improve with greater flexibility in treatment parameters.

Since, for this study, partial ablation of leiomyomata tissue was all that was allowed under FDA guidelines, incomplete nonperfused volume after MR-g HIFU (mean of 32.1% of the treated leiomyoma) was to be expected. The study also shows that there were rather sharp decline in the nonperfused volume during the six months after MR-g HIFU and the gradual decline over the remaining three-year follow-up. Such treatment related outcomes has also been reported in UAE studies. Pelage et al. suggested that incomplete devascularization after UAE may lead to regrowth of uninfarcted leiomyoma and symptom recurrence in long-term (34). Fennessy et al. reported a modified HIFU treatment protocol with increased ablation treatments beyond the FDA guidelines resulted in greater treatment effectiveness at 1 year. Stewart et al. showed an association between improved clinical outcomes and increased nonperfused volume in the treated leiomyomata after MR-g HIFU (23). Thus, it may be possible with optimization of the treatment protocols and techniques of MR-g HIFU to improve ablation volume and outcomes. Future efforts should be directed toward improving MR-g HIFU treatment protocols to increase the thermal coagulation necrosis volume, which may lead to further improvements in clinical outcomes. Such improved technique may also improve leiomyomata volume reduction after MR-g HIFU.

There are limitations of the present study, and include that this is a small single-center prospective non-randomized study which followed FDA recommendations; there is no control group, and whatever biases which may have existed in the patient selection. None

the less, the results are quite encouraging and further evaluation with different protocols is definitely warranted.

CONCLUSION

We have demonstrated that long-term follow-up data from MR-g HIFU treatments show sustained symptomatic relief of symptoms among enrolled patients. Although the results are preliminary, MR-g HIFU in the treatment of uterine leiomyomata may result in acceptable long-term outcomes at three years.

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Figure 1.

Figure 1a. Baseline T₂-weighed sagittal MR image showing a dominant leiomyoma (closed arrow) with the patient in a prone position. Note the top of uterus at the level of upper end plate of L5 vertebral body (open arrow).

Figure 1b. Baseline T₁-weighted axial MR image after Gd contrast with the patient in a prone position showing homogeneous enhancement (arrow) in the leiomyoma.

Figure 1c. T₁-weighted axial MR image, with the patient in a prone position, immediately after MR-g HIFU treatment demonstrates non-enhancing region (closed arrow) that corresponds to the treatment-effect area. Note the thick gel membrane (open arrow) with degassed water under the patient.

Figure 1d. T₂-weighted MR image, with the patient in a supine position three years after MR-g HIFU treatment. Note significant decrease in the dominant leiomyoma volume (open arrow). Note a closed arrow at the level of upper end plate of L5 vertebral body as a reference to compare to pre-MR-g HIFU treatment uterus and fibroid volumes.

Figure 2.

Figure 2a. Treated leiomyoma volume changes and uterus volume changes over the three years after MR-g HIFU.

Figure 2b. Non-perfused volume changes over the three years after MR-g HIFU.

Figure 3. Kaplan-Meier estimates of the time elapsed until the alternative treatments after the initial MR-g HIFU.

Table 1

Clinical Assessment: Transformed SSS and transformed QOL

Time	tSSS		tQOL	
	Mean Value (95%CI)	Mean Change (95% CI)	Mean Value (95%CI)	Mean Change (95% CI)
baseline	64.8 (59.1, 70.6)		44.1 (37.7, 50.6)	
3 month	35.3 (29.3, 41.3)	−29.5 (−37.8, −21.3)	68.8 (62.1, 75.6)	24.6 (15.4, 34.1)
6 month	32.2 (26.3, 38.2)	−32.6 (−40.9, −24.3)	68.6 (61.9, 75.4)	24.5 (15.2, 33.9)
1 year	40.5 (32.5, 48.7)	−24.3 (−34.2, −14.3)	68.7 (59.6, 77.9)	24.6 (13.4, 35.8)
2 year	18.0 (8.0, 28.1)	−46.8 (−58.4, −35.2)	86.1 (74.8, 97.5)	42.0 (28.9, 51.2)
3 year	17.0 (8.9, 25.1)	−47.8 (−57.7, −37.9)	83.9 (74.5, 93.3)	39.8 (28.3, 51.2)

Table 2

Subgroup analysis of UFS-QOL.

	Mean Concern	Mean Activities	Mean Energy	Mean Control	Mean Consciousness	Mean Sexual Function
baseline	47.8 (39.6, 56.0)	44.0 (36.3, 51.7)	45.4 (38.0, 52.8)	45.1 (36.9, 53.3)	29.2 (20.2, 38.2)	51.1 (42.3, 59.8)
3 month	69.4 (60.9, 78.0)	68.1 (60.1, 76.1)	69.9 (62.2, 77.6)	71.8 (63.3, 80.4)	59.7 (50.4, 69.1)	72.3 (63.2, 81.3)
6 month	72.2 (63.6, 80.6)	71.0 (63.1, 79.0)	71.2 (63.5, 78.9)	72.2 (63.6, 80.7)	60.1 (50.8, 69.5)	75.7 (66.7, 84.8)
1 year	71.3 (59.7, 82.8)	68.2 (57.4, 79.1)	72.5 (62.1, 82.9)	73.8 (62.1, 85.4)	48.8 (36.1, 61.5)	68.1 (55.7, 80.5)
2 year	90.8 (76.4, 105.1)	82.3 (75.9, 102.7)	89.6 (76.7, 102.5)	86.5 (72.1, 100.9)	62.8 (47.0, 78.6)	85.6 (70.2, 100.9)
3 year	87.4 (75.5, 99.2)	82.9 (71.8, 94.0)	85.3 (74.6, 96.1)	87.4 (75.5, 99.3)	69.3 (56.2, 82.4)	86.8 (74.1, 99.5)

Table 3
Volume changes in Leiomyomata, Uterus and Non-perfused area within the treatment zone.

Time	Leiomyoma Volume (in cm ³)	Mean Change (95% CI), % change	Uterine Volume (in cm ³)	Mean Change (95% CI), % change	Non-perfused Leiomyoma Volume (in cm ³)	Mean Change (95% CI), % change
baseline	Mean Value (95%CI) 336.9 (295.2, 378.6)		Mean Value (95%CI) 978.7 (925.1, 1032.3)		Mean Value (95%CI) 7.1 (-11.6, 25.8), 2.1%	
Immediate post-treatment					108.1 (87.5, 128.7), 32.1%	101.0 (76.6, 125.5), 1422.5%
6 month	273.6 (229.3, 318.0)	-63.3 (-96.5, -30.0), -18.7%	875.0 (819.2, 930.8)	-103.7 (-159.4, -47.9), -10.5%	45.0 (25.2, 64.9), 16.5%	40.0 (14.1, 61.9), 563.4%
1 year	249.7 (207.7, 291.7)	-87.2 (-127.7, -46.7), -25.8%	835.9 (782.4, 889.5)	-142.7 (-209.8, -75.7), -14.5%	39.4 (14.9, 63.8), 15.8%	32.3 (3.9, 60.7), 454.9%
2 year	243.1 (192.2, 293.9)	-93.9 (-142.5, -45.2), -27.6%	762.9 (687.9, 837.9)	-215.7 (-296.4, -135.1), -22.0%	26.6 (-4.2, 57.5), 10.9%	19.6 (-15.2, 54.4), 276.1%
3 year	228.4 (171.9, 284.8)	-108.5 (165.5, -51.4), -32.0%	707.3 (622.2, 792.4)	-271.4 (-365.1, -177.7), -27.7%	30.5 (-7.0, 68.0), 13.4%	23.4 (-17.5, 64.3), 329.6%