Clinical improvement and shrinkage of uterine fibroids after thermal ablation by magnetic resonance-guided focused ultrasound surgery

J. RABINOVICI*†, Y. INBAR†‡, A. REVEL§¶, Y. ZALEL*†, J. M. GOMORI¶**, Y. ITZCHAK†‡, E. SCHIFF* and S. YAGEL§¶

Departments of *Obstetrics and Gynecology and ‡Radiology, Sheba Medical Center, Ramat Gan, †Sackler Medical School, Tel-Aviv University, Tel Aviv and Departments of §Obstetrics and Gynecology and **Radiology, Hadassa Ein Kerem University Hospital and ¶Medical School, Hebrew University, Jerusalem, Israel

KEYWORDS: heat ablation; HIFUS; non-invasive surgery; therapeutic ultrasound; uterine myoma

ABSTRACT

Objective Hysterectomy or myomectomy are the accepted treatments for symptomatic uterine fibroids. Heat ablation of uterine fibroids has been shown to be an effective alternative treatment. The aim of this study was to determine the clinical efficacy of non-invasive thermal ablation by transcutaneous magnetic resonance-guided high-intensity focused ultrasound (MRgFUS) for the treatment of symptomatic uterine fibroids.

Methods In this prospective study, MRgFUS ablation of uterine fibroids was performed in 35 symptomatic women scheduled for hysterectomy. Clinical symptoms, patient satisfaction and uterine size were determined at 1 month and 6 months after the procedure.

Results This outpatient procedure was very well tolerated by all women. Sixty-nine percent (24/35) of the treated patients reported either significant or partial improvement in symptoms. Treated fibroids decreased in volume by 12% and 15% at 1 and 6 months, respectively. Minor transient side-effects were observed in two women. Six women underwent hysterectomy during the follow-up period.

Conclusion This study demonstrates the clinical efficacy of MRgFUS ablation of uterine fibroids. This novel, non-invasive surgical approach may offer an alternative therapy for women with uterine fibroids. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Uterine leiomyomas, or fibroids, are benign tumors that can occur in up to 50% of women and in about half of these cause clinically significant symptoms, including bleeding, pain, and pressure. The common treatment modalities for symptomatic women who have completed their families are hysterectomy or myomectomy. However, these surgical procedures are associated with morbidity in about 17 to 23% of cases, and involve at least several days of hospitalization as well as several weeks of convalescence. The high incidence of symptomatic uterine fibroids and the high cost of surgical interventions and their sequelae create a significant financial burden that has stimulated the search for alternative approaches. Uterine artery embolization (UAE) – a less invasive procedure – has been introduced in recent years via less invasive procedure – has been introduced in recent years, and it has been shown to decrease both the volume of the treated fibroids and the clinical symptoms. However, in many cases UAE requires hospitalization and can occasionally cause a number of major complications.

Application of heat to uterine fibroids can cause cellular necrosis, leading to decreases in both fibroid size and associated symptoms. Thermal ablation of uterine fibroid tissue has been performed by laparoscopic laser myolysis and by magnetic resonance imaging (MRI)-guided percutaneous laser ablation. Clinically significant decreases in fibroid size and symptoms have been reported following treatment with both modalities.

Focused ultrasound surgery (FUS) has been proposed in the past to treat soft tissue tumors deep in the body. When ultrasound propagates through human tissue, the resulting pressure wave causes molecular vibration, which heats tissue. During diagnostic ultrasound studies the wave is distributed over a wide area and temperature elevation is negligible. However the wave can be modified so that the

Correspondence to: Dr J. Rabinovici, Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Ramat Gan 52560, Israel (e-mail: yaronr@post.tau.ac.il)
Accepted: 31 May 2007
ultrasound energy is focused at a single spot, and a high temperature rise (60–90°C) that can induce irreversible cell damage can be generated within a few seconds at this focal point. But owing to the inherent inhomogeneity of patient anatomy (variability in the thickness of skin, fat, muscle, etc.) and the resulting effect on energy scatter, absorption, refraction, and reflection, researchers have been unable to focus precisely this wave onto a specific target, or accurately predict the size of the resulting lesion. This imprecision has led to markedly variable outcomes and to concerns over safety.

MRI has excellent anatomic resolution, very high tumor sensitivity, and high thermal imaging sensitivity. Thus, the combination of MRI for planning, guiding, and control of the therapy, with FUS as a non-invasive thermal therapy device, overcomes many of the potential concerns related to FUS. The marriage of MRI and FUS enables safe and controlled non-invasive heat ablation of a wide range of benign and malignant conditions.

We have previously reported the ability of a new MR-guided FUS (MRgFUS) system (ExAblate 2000; Insightec Ltd, Haifa, Israel) to induce localized necrosis and ischemia in uterine fibroids. The aim of the present prospective study was to examine our initial experience and the clinical efficacy and safety of this procedure in symptomatic women who had been scheduled to undergo hysterectomy.

PATIENTS AND METHODS

Women in good general health, older than 35 years (Table 1), who had completed their families, and had clinically symptomatic uterine fibroids (irregular or excessive menstrual bleeding, pain, pressure, urinary or bowel problems) were included in this study, which was performed under an identical protocol at two centers: The Sheba Medical Center, Tel Hashomer, Israel and the Hadassa Ein Kerem University Hospital, Jerusalem, Israel. All patients had been scheduled by their physicians for hysterectomy. They agreed to undergo MRgFUS ablation of their uterine fibroids. The decision whether to ultimately proceed with a planned hysterectomy was postponed until at least 30 days after MRgFUS treatment. Ethics committee approval was obtained and MRgFUS ablation under conscious anesthesia was carried out as an outpatient procedure.

For inclusion in the study clinical uterine size had to be less than that at 20 weeks’ gestation and the dominant fibroid had to be less than 10 cm in diameter without areas of necrosis as judged by contrast MRI. Exclusion criteria included hematocrit under 25%, a positive pregnancy test, or a contraindication to MRI. Following informed consent and an initial clinical exam, all the women underwent a diagnostic MRI and were then scheduled for MRgFUS treatment.

One or two intramural fibroids were targeted for MRgFUS in each patient. The treatment aim of the current study was to ablate the central core of every targeted fibroid, including up to a third of its total volume. Treatment was planned with trajectories that avoided passage of the ultrasound beam through the bowel or urinary bladder. The ExAblate 2000 system is a high-intensity focused ultrasound system for thermal tissue coagulation that is fully integrated with the Signa 1.5 Tesla MRI scanner (GE Medical Systems, Milwaukee, WI), which provides real-time guidance and control. The system incorporates numerous phased-array elements with full electronic control of the acoustic beam to enable precise targeting, in spite of great variability between patients and tissue inhomogeneity within fibroids and throughout the beam-pass zone.

When ultrasound propagates through the body two related mechanisms are known to affect tissue: (1) the pressure wave causes molecular vibration, which results in tissue heating, and (2) mechanical phenomena involving non-thermal effects lead to cavitation of tiny bubbles in tissue and fluids. ExAblate 2000 is designed to maximize the thermal effects, while working at focal energy levels that are well below the energy threshold needed to induce cavitation. Using the geometric shape of the transducer and electrical (phased-array) focusing, the pressure wave can be directed to a tightly focused spot (∼2–10 mm in diameter) within the body. During these sonifications, energy concentration factors of several hundred are achieved in the focal spot, in comparison to the levels of energy deposited in tissue along the beam path. At the start of the treatment, multiplane T1- and/or T2-weighted MR images are used to define the target, plan treatment, and register the patient-, MRI-, and therapy-coordinate systems. MRI thermal imaging guides the treatment with real-time monitoring and control of energy delivery and tissue ablation.

Before treatment, the abdomen and pelvis are imaged in three orthogonal planes (i.e. axial, sagittal, and coronal) and the treatment volume of the uterine fibroid is defined on the acquired MR images. The ExAblate system computes the optimal sonication grid necessary to coagulate the targeted volume and positions the sonication foci in a sequential manner (as shown in Figure 1).

After approval of the treatment plan, the user begins a series of verification sonifications. Geometric verification is performed with very low energy, sublethal sonifications, to avoid damage to healthy tissue and address safety concerns. Verification sonifications generate a very low temperature rise at the focal point. The location of this

Table 1 Baseline characteristics of the 35 patients who underwent magnetic resonance-guided focused ultrasound surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.4 ± 4.7</td>
<td>47</td>
<td>35–55</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.4 ± 14.5</td>
<td>65</td>
<td>53–112</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 ± 8</td>
<td>160</td>
<td>147–178</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 5.5</td>
<td>24.2</td>
<td>19.5–36.4</td>
</tr>
<tr>
<td>Largest fibroid (mL)</td>
<td>250 ± 236</td>
<td>211</td>
<td>12–1194</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.

Thermal ablation of uterine fibroids by MRgFUS

The baseline characteristics of the first 35 women who underwent consecutive MRgFUS treatment in our centers are shown in Table 1. Irregular and/or excessive bleeding was the most common complaint of these patients, and occurred in 27 women (77.1%). Abdominal and pelvic pain (n = 15; 42.9%), pelvic pressure (n = 12; 34.3%) and urinary or bowel complaints (n = 8; 22.9%) were the other symptoms described by these patients. In 15 of the women (42.9%) two or more symptoms were present.

Forty-one fibroids were treated in these 35 women (Table 2). The mean volume of the treated fibroids was 216 ± 223 (range, 8–1093) mL. The mean volume of heat-ablated fibroid tissue, as measured by thermal maps using 240 min at 43°C as the ablation threshold, was

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroid volume (mL)</td>
<td>216 ± 223</td>
<td>8–1093</td>
</tr>
<tr>
<td>Volume ablated by MRgFUS (mL)</td>
<td>25 ± 21</td>
<td>2–78</td>
</tr>
<tr>
<td>Ablated volume (% of total fibroid volume)</td>
<td>18 ± 13.3</td>
<td>1–65</td>
</tr>
<tr>
<td>Non-perfused volume as seen by MRI contrast study (mL)</td>
<td>53 ± 94</td>
<td>1–554</td>
</tr>
<tr>
<td>Non-perfused volume (% of total fibroid volume)</td>
<td>31 ± 23</td>
<td>2–92</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging.
Figure 2 Sagittal view of the progression of heat deposition during a sonication. Images were taken every 3.4 s. The planned sonication spot size and location are indicated by the red rectangle.

25 ± 21 (range, 2–78) mL. Treated volumes represented a mean of 18 ± 13.3 (range, 1–65)% of the total pretreatment fibroid volumes. Immediately following treatment, perfusion of the fibroids was assessed by MR gadolinium-enhanced perfusion imaging. The duration of the procedure depended on the ablated ‘fibroid load’ and did not extend beyond 3 hours. The mean non-perfused volume was 53 ± 94 (range, 1–554) mL, which represented a mean of 31 ± 23 (range, 2–92)% of the pretreatment fibroid volumes. The correlation between the ablated and non-perfused volume of each leiomyoma was r = 0.59. No non-perfused tissue was visualized outside of the targeted fibroids in any patient.

Four women did not receive adequate ablation of fibroid tissue during MRgFUS owing to early cessation of treatment because of technical problems typical of the early stages of this therapy. Three of those women underwent hysterectomy; one patient chose to undergo surgery shortly after MRgFUS, the other two underwent hysterectomy at a later stage. Two patients judged to have received adequate ablation continued to experience significant complaints and chose to undergo hysterectomy. Thus, one patient underwent surgery shortly after the procedure and the others between 3 and 6 months after high-energy FUS (HIFUS). The 31 remaining patients chose to postpone their potential surgery after MRgFUS
and to await clinical changes. They were followed prospectively for at least 6 months after HIFUS.

The majority of the treated women experienced clinical improvement at 6 months after treatment. Of the 31 women who completed a full MRgFUS treatment, 13 (41.9%; 37.1% of all 35 patients) reported a significant improvement, and another 11 (35.5%; 31.4% of all 35 patients) reported a partial improvement in their complaints.

Twenty-four women treated at the Sheba Medical Center underwent an MRI examination at 1 month after treatment and 29 underwent an MRI examination at 6 months after treatment. At 1 month, the mean leiomyoma volume was reduced by 12 ± 16 (range, −30 to 47)% compared to the volume on the day of treatment (P < 0.05); one patient experienced a marked increase in fibroid volume at this juncture. At 6 months after MRgFUS treatment the mean leiomyoma size was reduced by 15 ± 27 (range, −70 to 77)% versus size at the day of treatment in the 35 patients treated in both centers (P < 0.05); one patient experienced a marked increase in fibroid size at 6 months correlated more strongly with the ablated volume (r = 0.51) than with the non-perfused volume (r = 0.32) immediately after MRgFUS treatment.

Twenty-nine women (82.9%) chose not to undergo hysterectomy during the following period owing to abatement of symptoms following MRgFUS, while six women (17.1%) required hysterectomy within 6 months because they did not experience satisfactory improvement in their symptoms. Two of the six women did not receive adequate treatment owing to inability to deposit energy in the target, which appeared on T2-weighted MRI as brighter than the uterine myometrium. We have since developed treatment strategies that are effective in this type of fibroid as well. Two other women among the six had uterine adenomyosis rather than leiomyoma, as confirmed by histology. One additional patient had eight fibroids, out of which only two were treated with MRgFUS. While the treated fibroids did shrink, the other six untreated fibroids increased in size. All the operations were completed without significant complications.

None of the treated patients experienced any major short-term or long-term side effects. One patient suffered a small abdominal skin burn that subsided within 2 weeks of treatment, and another patient complained of sciatic pains that started a few days after therapy and subsided after a week. All patients were able to return to their daily routine after cessation of the effects of the conscious anesthesia. Several women complained of minor lower abdominal pain that subsided shortly after the procedure.

Figures 3 and 4 present two illustrative cases. A 49-year-old patient was scheduled for hysterectomy because of dysmenorrhea, bowel complaints, and gradually worsening pelvic pressure. She underwent MRgFUS of her fibroid, which measured 576 mL on the day of treatment (Figure 3). At the 6-month follow-up evaluation, the fibroid had shrunk to 355 mL, a 38.4% reduction in volume. The patient experienced a major improvement in her symptoms, and she did not experience any treatment-related adverse events following the procedure. Figure 3a shows a sagittal view of the uterus, with the fibroid clearly visualized. Figure 3b shows a T1-weighted, contrast-enhanced view immediately following treatment. The
Figure 4 T1-weighted contrast magnetic resonance image showing pelvic anatomy of the same patient over time. The images show a time-dependent decrease in size of the intramural fibroid before (a), immediately after (b) and 6 months after (c) magnetic resonance-guided focused ultrasound surgery. Note the temporal changes in uterine fundal height in relation to the lumbar vertebrae. A, anterior; P, posterior.

DISCUSSION

The results of this prospective study demonstrate that non-invasive, targeted heat ablation by MRgFUS leads to an improvement in fibroid-related clinical symptoms in the majority of treated women. More than two thirds of all included patients described either a marked (13/35, 37.1%) or a partial (11/35, 31.4%) improvement in their clinical symptomatology over time after MRgFUS. These clinical changes as well as the significant changes in mean fibroid volume were observed although we incorporated in this study all MRgFUS treatments performed, including the very first treatments where only relatively small volumes of the fibroids were coagulated. Of the 31 women who completed a full MRgFUS treatment, the percentages reporting a significant improvement and a partial improvement in their complaints were 41.9 and 35.5%, respectively. It should be borne in mind that these primary results were achieved in the first series of women who underwent this new treatment. Owing to safety considerations only a part of the fibroid was treated in this study. Future treatments with larger areas of coagulation of fibroid tissue and longer follow-up periods will determine the ability to achieve even higher levels of improvement.

MRgFUS treatment led to a significant, time-dependent decrease in the mean volume of the uterine fibroids. At 1 and 6 months after treatment we observed a mean decline of 12% and 15% of pretreatment leiomyoma volume ($P < 0.05$). Since the reduction in size might depend on the ablated volume, we expect that larger declines in leiomyoma size will be seen in the future as we ablate larger volumes within the tumors.

The results of this study indicate that MRgFUS can deliver ultrasound energy transcutaneously to ablate tissue in a discrete area within uterine leiomyomas. This energy coagulates tissue, and causes cell death in a precise and well-defined zone within the tumor. This coagulative necrosis is different from the ischemic necrosis achieved by UAE. Heat ablation by MRgFUS results in a gradual, time-dependent decrease in leiomyoma size, and improvement in leiomyoma-related symptoms. The integrated MRI-based thermal mapping, and the ability to adjust the delivered ultrasound energy, ensure a good correlation between the planned and the coagulated volume. We used MRI guidance not only to target the fibroid but also because currently no other imaging technology has similar thermal imaging sensitivities.

At the end of treatment the non-perfused, ischemic areas of the leiomyoma as determined by gadolinium-enhanced perfusion imaging exceeded the coagulated area in most cases, but were always confined to the fibroid capsule. Based on previous histologic studies in patients who underwent MRgFUS a short time before hysterectomy we know that coagulation leads to localized necrosis surrounded by a reactive local vasoconstriction in the adjacent area. The correlation between the ablated volume measured on the thermal MR image and the decrease in leiomyoma size at 4 to 6 months later was stronger than that between the non-perfused volume on gadolinium-enhanced images and leiomyoma size decrease ($r = 0.51$ vs. $r = 0.32$, respectively). Thus, measurements of the non-perfused area surrounding the coagulated tissue do not appear to reliably predict longer-term leiomyoma shrinkage or symptom abatement as well as do measurements of the actual ablated volume. In addition, it should be noted that in this study neither the coagulated nor the non-perfused tissue border ever extended beyond the edges of the targeted leiomyoma. Based on MRI and perfusion studies the surrounding healthy myometrium was not damaged in any patient in this study. The combination of MRI and FUS enabled
us to target the tissue and to determine immediately the temperature changes of the tissue and the resulting tissue damage. To our knowledge other imaging techniques are not able to provide similar information.

All the patients returned to their homes following treatment, and were able to return to their routine daily activities that same day, or the next day. Only two patients experienced short-term side effects that subsided quickly: one patient developed a first-degree skin burn and another patient complained of transient sciatic pain along her left leg. The skin burn occurred because of trapped air bubbles in the ultrasound gel that resulted in inadequate ultrasound coupling and heat generation at the level of the skin. Since that occurrence we have instructed all patients to shave their pubic hair (above the pubic bone) and to avoid the use of skin creams and lotions before treatment. The low rate of side effects observed in our study and the quick return to routine activity are in contrast to the relatively high morbidity and need for variable time of hospitalization associated with the currently used surgical procedures for uterine leiomyomas or with uterine artery embolization. If our results are corroborated by future studies, MRgFUS could provide a therapeutic solution for women who want to maintain their uterus for future fertility. However, we find it encouraging that despite the limited ablation of the fibroids performed in this study — up to a third of the volume — a significant proportion of women experienced symptomatic improvement. Comparative studies with other treatment regimens (hysterectomy, UAE) will determine the role and relative advantages of MRgFUS.

In conclusion, the results of this study demonstrate that heat energy generated by MRgFUS and deposited in uterine fibroids can achieve clinical improvement and shrinkage of the fibroids without significant side effects. MRgFUS is able to coagulate distinct sections of the leiomyoma without damage to the adjacent healthy myometrium as judged by MRI and perfusion studies. Future studies will have to address the clinical efficacy of MRgFUS after ablation of larger areas of the fibroid. Our present encouraging results might suggest that this novel non-invasive surgical technique could also be used in future for the treatment of other solid tumors.

REFERENCES