

Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS) of Uterine Fibroids in Singapore

Nian-Lin R Han, ¹MD, PhD, Chiou Li Ong, ²MBBS, FRCR, FAMS

Abstract

Introduction: Uterine fibroids are the most common type of gynaecologic benign tumours, occurring in 25% to 50% of women during their reproductive lives. About half of the affected women have clinically significant symptoms, including abnormal bleeding, menstrual pain, frequent urination, constipation and abdominal distension. Magnetic resonance-guided focused ultrasound surgery (MRgFUS) has been used to treat patients with benign lesions and a variety of malignancies. The objective of this study is to evaluate symptom relief before and after MR-guided ultrasound ablation of fibroids. **Materials and Methods:** A total of 37 patients with symptomatic uterine fibroids were treated in this study. **Results:** MRgFUS treatment led to a significant, time-dependent decrease in not only Symptom Severity Scores (SSS), but also the mean fibroid volume. The average reductions in volume were 41.6% and 52.6% at 6 months and 12 months respectively ($P < 0.05$). The mean SSS of the 37 patients was 41.7 ± 2.8 before treatment whereas the average SSS was 26.9 ± 3.6 , 20.7 ± 3.4 , 18.5 ± 3.6 , 16.5 ± 7.1 , 9.8 ± 3.6 at 3 months, 6 months, 1 year, 2 years, and 3 to 4 years respectively. The decrease in scores was significant at all time points up to 3 to 4 years ($P < 0.05$ and $P < 0.001$). **Conclusion:** MRgFUS is a safe and effective non-invasive treatment for patients with symptomatic fibroids.

Ann Acad Med Singapore 2014;43:550-8

Key words: Non-invasive treatment, Symptom Severity Score

Introduction

Uterine leiomyomas, or fibroids, are the most common type of gynaecologic benign tumours, occurring in 25% to 50% of women during their reproductive lives. About half of the affected women have clinically significant symptoms, including abnormal bleeding, menstrual pain, frequent urination, constipation, and abdominal distension.^{1,2} The conventional treatment for symptomatic women who have completed their families is hysterectomy, or myomectomy in women who wish to preserve their uteri.²⁻⁴ Many of these are open surgical procedures associated with risks such as infection and blood loss. According to reports from the United States of America (USA),^{5,6} an estimate of over US\$2 billion is spent each year on hospitalisation for problems related to uterine fibroids, and more than US\$4600 is spent on the treatment of fibroids per woman per year.

Moreover, the cumulative rate of uterine fibroid recurrence at 12 and 24 months after abdominal myomectomy has been reported at 12.4% and 46.0%, respectively.⁷ Many women who wish to avoid surgical treatments or preserve the uterus increasingly seek less-invasive options. In order to reduce the cost, morbidity and lifestyle impact of surgery, several alternative approaches, for example, hormonal therapy, uterine artery embolisation (UAE) and focused ultrasound (FUS) surgery, have been used for the treatment of uterine fibroids.

FUS has been used to treat patients with benign lesions and a variety of malignancies. It uses FUS energy which is delivered to tissues deep within the body through intact skin. The high intensity of focused ultrasound energy is capable of producing thermal coagulative necrosis at a precise point. Magnetic resonance imaging (MRI) offers

¹Division of Clinical Support Services, KK Women's and Children's Hospital, Singapore

²Division of Clinical Support Services, Department of Diagnostic and Interventional Imaging, KK Women's and Children's Hospital, Singapore

Address for Correspondence: A/Prof Ong Chiou Li, Division of Clinical Support Services, Executive Office, Level 3, Children's Tower, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: Ong.Chiou.Li@kkh.com.sg

excellent soft tissue contrast and anatomic resolution needed during targeting, and temperature sensitivity for real-time treatment monitoring. The feasibility of an MR-guided focused ultrasound (MRgFUS) system was first described in 1995⁸ and this method has been tested extensively for the treatment of breast cancer, malignant bone tumour and liver cancer for more than 10 years.

The present study is the first report in Singapore of the use of MRgFUS to treat uterine fibroids. KK Women's and Children's Hospital (KKH) is the only centre in Singapore with a MRgFUS facility for the treatment of uterine fibroids. Many reports have shown that MRgFUS ablation is feasible and safe, with 6-month and 1-year follow-up demonstrating improvements in fibroid-related symptoms. Stewart et al⁹ had shown that 71% of women undergoing MRgFUS reached the targeted symptom reduction at 6 months, and 51% reached this at 12 months. A modest volume reduction similar in magnitude to the treated volume was seen. The same group also reported that their modified protocol achieved better outcomes; 91% of patients reached a targeted symptom reduction at 12 months while no serious adverse events were recorded.¹⁰ The recent study from Gorny et al¹¹ demonstrated that 86%, 93% and 88% of patients reported relief of symptoms at 3-month, 6-month and 12-month follow-up respectively. However, reports on long-term sustained symptom relief are few. In our study, we assess the effectiveness of MRgFUS ablation for uterine fibroids and show the post-treatment symptom relief at intervals of 6 months, 1 year, 2 years, and 3 to 4 years.

Materials and Methods

This prospective study was approved by the Ethics Committee of the Central Institutional Review Board of Singapore Health Services. Informed consent was obtained from each patient before every procedure. All MRgFUS procedures were performed using ExAblate[®] 2000 (InSightec, Haifa, Israel), which is integrated with a 1.5 Tesla MRI scanner (Signa HDxt; GE Healthcare, Waukesha, Wisconsin, USA).

Patients

From August 2006 to December 2009, 37 patients with symptomatic uterine fibroids were treated in this study. Most of the patients found out about this procedure through the Internet. Each patient was seen by a gynaecologist as well as the treating radiologist who obtained the patient's medical history, and assessed uterine fibroid symptoms according to the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL).¹² The UFS-QOL consists of 37 questions, of which the initial 8 related to menstrual flow and bulk problems were used to calculate the Symptom

Severity Scores (SSS). The inclusion criteria were as follows: (i) women in good general health, older than 21 years old, able to give independent consent, (ii) uterine fibroids assessed by MRI to be accessible to the focused ultrasound, and (iii) ability to communicate with nurse or physician during the procedure. Those with multiple fibroids (more than 3) were usually deemed unsuitable for this form of treatment. Exclusion criteria were derived from the ExAblate[®] commercial treatment guidelines. In general, patients were excluded if they had contraindications to MRI such as non-MRI compatible implanted metallic devices or extreme obesity. Pregnant women and patients with extensive abdominal scar, post-menopausal women, uterus size larger than 24 weeks gestation or other significant pathology (i.e. ovarian lesion, active pelvic infection) were also excluded from the treatment.

Pre-treatment MRI

All eligible patients underwent pre-treatment MRI with a standardised protocol. Assessment of fibroid number, size, volume, location and enhancement after administration of gadolinium was made. The scan was performed with the patient in the prone position, and 3 orthogonal T2-weighted images of the uterus were obtained followed by fat-suppressed T1-weighted images before and after gadolinium injection. The images were analysed to determine patient suitability for the procedure. The bulk of the fibroid mass should not be more than 12 cm away from the skin. This may be assessed during the screening MRI scan and measured from the skin surface to the centre of the fibroid. If it is over 12 cm, the likelihood of adequate sonication is diminished. Patients with bowel that could not be shifted from the potential beam path were excluded from the study, as gas or hard particles in the bowel may reflect or absorb the ultrasonic energy.

The fibroid volumes were calculated by a software programme in the MRI workstation using slice-by-slice area measurements, multiplied by the slice thickness. In cases where this was not possible, 3 orthogonal measurements of the fibroid were taken and calculated using the prolate ellipsoid formula. Patients who had total fibroid volume of 500 cm³ or more were pre-treated with a gonadotrophin-releasing hormone (GnRH) analogue for 3 months in an effort to reduce the size and vascularity of fibroids.

Magnetic Resonance-guided Focused Ultrasound Surgery

MRgFUS was performed under intravenous conscious sedation and analgesia in the form of midazolam and pethidine. Vital signs were monitored continuously and the patients were in direct visual and voice contact with the treating radiologist at all times. A switch was provided

to the patient at the beginning of the treatment to stop the sonication at any time she experienced excessive heating or abnormal sensations in her lower limbs or back. A nurse was assigned to monitor the patient in the MRI room at all times during the treatment. The patients were carefully positioned prone on the therapeutic system with the anterior abdominal wall in contact with a coupling medium placed over the ultrasound transducer used in the ablation. Pre-treatment T2-weighted MRI were acquired and used in drawing the regions for treatment. The equipment then mapped out the sonication spots in the regions drawn on the fibroids (Fig. 1A). The equipment can also display the ultrasound beam path, in 2 other orthogonal MRI views (sagittal or axial) of the target (Fig. 1B). The size and concentration of the spots may vary according to the type of fibroid. All treatments were performed by a single radiologist.

After approval of the treatment plan, a low-energy test power was aimed within the targeted fibroid to confirm the focus point before therapeutic levels of sonications were used. These verification sonications generate a very low non-ablative temperature rise at the focal point. Any discrepancy caused by the mechanical alignment of the system or movement in the location of the focal spot can be corrected at this point. Then a few higher power pulses were delivered at the target point until adequate temperature and thermal dose was reached. With rapid MRI (fast spoiled gradient-recalled echo sequences) to monitor the temperature and position of the focused ultrasound beams, the targets in each region were treated in turn. At each sonication, line graphs showing the temperature change in the target volume were recorded by the equipment (Fig. 2).

This process was repeated for each target until the planned treatment volume was achieved. The therapeutic energy and the sonication time were adjusted based on patient feedback and temperature map. Adverse events and the number of sonications were recorded. The patients were observed for about 2 hours following MRgFUS treatment and were discharged if there were no complications.

Follow-up

Post-treatment MRI was performed immediately after completion of treatment to determine the changes in uterine fibroid perfusion. Gadolinium-enhanced MRI was used to measure the non-perfused volume (NPV). After discharge, the patients were followed up with a telephone interview over the next few days, and subsequently a week later at the outpatient clinic. Further follow-up assessments were carried out a month following treatment, and subsequently at 3 months and 6 months. Follow-up MRI studies were performed at 6 months and 1 year after MRgFUS. Information about possible side-effects as well their

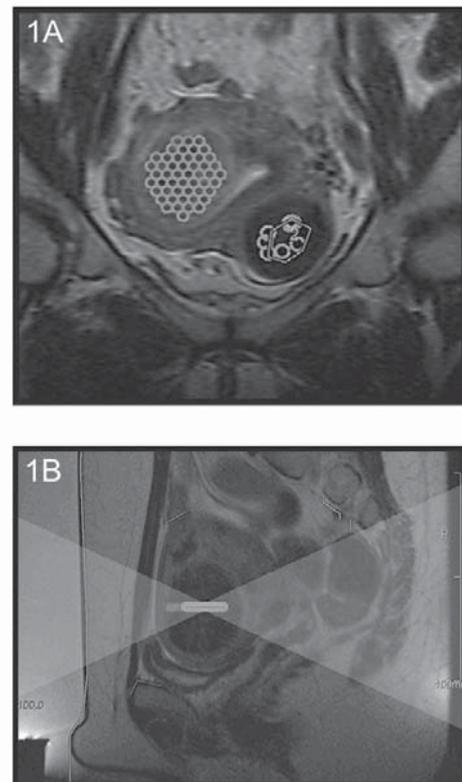


Fig. 1. (A) Coronal MRI showing the overlay of sonication targets in the fibroids. The regions indicated by an arrow are targets that cannot be treated due to various reasons such as overlying bowel or proximity to the spine (far-field bone). (B) Sagittal MRI showing the treatment target (small rectangle) in the fibroid and ultrasound beam path (triangles).

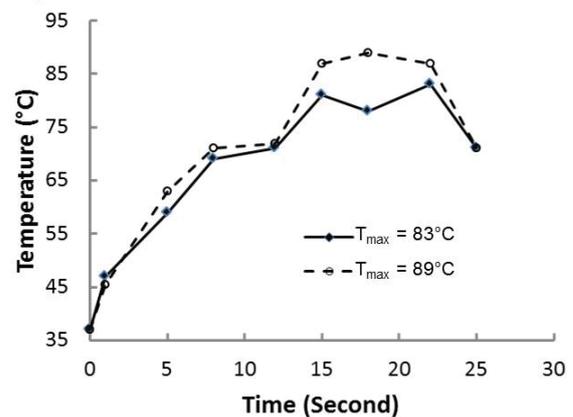


Fig. 2. Line graphs showing temperature rise within the sonicated tissue.

fibroid-related symptoms and their severity were recorded using SSS questionnaire at 3 months, 6 months, 1 year, 2 years and 3 to 4 years. A 10-point reduction in SSS score, which was validated earlier, was used as an indication of symptom improvement.

T2-weighted MRI was used to compare the fibroid size before and after MRgFUS. The NPV was defined as the fibroid coagulation volume in contrast-enhanced MRI. The NPV was taken as ablation volume as we excluded the fibroids from treatment that showed signs of degeneration or did not demonstrate enhancement. The fibroids showing heterogeneous enhancement were included if there were no large confluent areas of non-enhancement. The follow-up MRI was read independently by staff radiologists who may not be involved in the treatment. The signal intensities of the fibroids were assessed by the principal investigator in comparison to the native tissues in the patients, e.g. a fibroid was hyperintense, or had high signal intensity, when its signals were higher or similar to myometrium. A fibroid with low signals would have signals similar to that of skeletal muscles. Fibroids with intermediate signals were those with signals higher than skeletal muscles but lower than the myometrium. This classification has been used in other studies.^{13,14}

Statistical Analysis

The distribution of data was first identified by Kolmogorov–Smirnov test and Shapiro–Wilk test. For normal distribution data, the comparisons of means were assessed by paired t-test. For skewed distribution data, Wilcoxon signed-ranks test was used to evaluate the difference between before and after MRgFUS treatment. Data are reported as the median and 95% confidence interval (CI) for skewed distribution data, or mean \pm SD for normal distribution data.

The percentage change of fibroid volume is defined as the following:

$$\text{Percentage change of fibroid volume (\%)} = \frac{\text{Fibroid volume at 6 or 12 months} - \text{Fibroid volume before treatment}}{\text{Fibroid volume before treatment}} \times 100$$

Auto-regressive model for repeated measurement was used to measure the significance of the treatment effect. Linear regression analysis and Spearman correlation were used to evaluate for a correlation between SSS change and types of fibroids and treatment volume ratio. A significant difference was indicated by $P \leq 0.05$. IBM SPSS Version 19 software (New York, USA) was used for all data analysis.

Results

Characteristics of Patients

Thirty-seven patients with 50 fibroids were treated by MRgFUS in this prospective study. The average age of

the patients was 44.6 years old (range, 34 to 52 years old). Twenty-eight of 37 (75.7%) treated patients were evaluated by contrast-enhanced T1-weighted image at 6 months after MRgFUS treatment, while 11 (29.7%) patients were evaluated at 12 months. Using the SSS questionnaire, 22 of 37 (59.5%) treated patients were assessed at 3 months, 25 (67.6%) were assessed at 6 months, 10 (27.0%) were assessed at 1 year, 10 (27.0%) were assessed at 2 years and 8 (21.6%) were assessed at 3 to 4 years. A total of 10 patients (27.0%) underwent surgery (6 patients had hysterectomy, 4 patients had myomectomy) at 2 years follow-up.

Clinical Outcomes

The data distribution for the fibroid volume before treatment, 6 months after treatment, 12 months after treatment and that of non-perfusion volume were analysed using the Kolmogorov–Smirnov test and Shapiro–Wilk test for the non-normal distribution, and were represented by their median values, whereas the percentage of NPV and percentage changes after the treatment showed normal distribution. The median fibroid volume was 105 cm³ (95% CI, 74.3 to 144 cm³) (Table 1). The MRgFUS resulted in a median NPV (indicative of successful ablation) of 46.9 cm³ (95% CI, 31.5 to 83.2) and the mean ratio of the NPV to the fibroid volume was 55.1 \pm 22.2% (range, 7.2% to 90.9%). Contrast-enhanced T1-weighted images 6 months after MRgFUS treatment showed more than 50% fibroid ablation in 10 patients, 30% to 49% in 11 patients, 10% to 29% in 6 patients and less than 10% in 3 patients. Figure 3 shows the sagittal view of T2-weighted MRI from a 48-year-old patient over time. The patient was diagnosed with fibroids for 10 years and had heavy menstruation, dysmenorrhea and gradually worsening pelvic pressure.

Table 1. Characteristics of Patients with Uterine Fibroids Treated with Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS)

Variable	Mean \pm SD*/Median†	Range
Age (years)*	44.6 \pm 4.2	34 – 52
Total number of fibroids treated	50	
Median volume of fibroids (cm ³)†	105.1	3.2 – 601.4
Median non-perfused volume‡ (cm ³)†	46.9	1.1 – 435.0
Average non-perfused volume percentage (%)*	54.0 \pm 22.6	7.2 – 90.9
Average number of sonications*	81.5 \pm 35.2	21 – 154

*Data are expressed as mean \pm SD.

†Data are expressed as median.

‡The non-perfused volume (NPV) is measured on the post-contrast images using a segmentation technique. The non-enhanced part of the treated fibroid is calculated as a percentage of the total fibroid volume obtained on the T2-weighted images.

Prior to treatment, she was treated with 11.25 mg leuprolide acetate 3-month depot (gonadotrophin agonist). The size of her fibroid on the day of the treatment was 210.4 cm³ and the treatment volume was 88.5 cm³ (42.1%). At the 6-month follow-up evaluation, her fibroid showed further reduction in size to 137.6 cm³ (34.6% reduction in volume). The patient experienced significant improvement in her symptoms, and her SSS score was reduced from 43.8 to 6.3 at 12 months. She did not have any treatment-related adverse events following the procedure.

Follow-up MRIs at 6 months were obtained in 30 patients with 33 fibroids. One patient underwent ultrasound instead of MRI. The rest of the 6 patients did not undergo the 6 months MRI due to following reasons: 1 patient underwent surgery, 2 are foreigners of which only 1 had MRI follow-up a year after treatment, 3 were lost to follow-up (did not turn up after treatment or after 6 months). The median fibroid volume of these 33 fibroids at 6 months after MRgFUS was 52 cm³ (95% CI, 39.5 to 78.4 cm³), which was significantly decreased by 41.6 ± 23.2% ($P < 0.001$) compared with those before treatment using Wilcoxon signed-ranks test (Fig. 4). However, in one patient, whose fibroid show 52.3% non-perfusion after treatment, there was an increase of 36.9% in volume at 6 months post-treatment. A second session of MRgFUS was performed at 7 months after the first session, and the fibroid volume still did not change 12 months later. This may be due to the very large fibroid volume (516.9 cm³) and the type of fibroid (intermediate type).

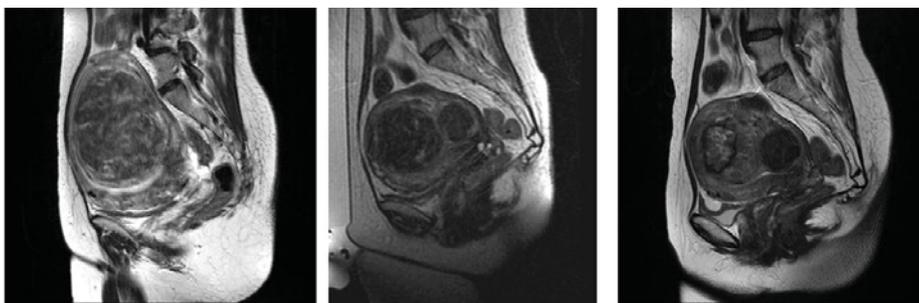
Follow-up MRI at 12 months was obtained in 12 patients with 15 fibroids. Eleven patients underwent ultrasound instead of MRI. Two patients underwent surgery, 1 patient became pregnant, 4 were lost to follow-up (did not turn up after 12 months). The median fibroid volume of these 15 fibroids at 12 months after MRgFUS was 34.4 cm³ (15.6 to 85.7 cm³, 95% CI), a significant reduction in volume by 52.6 ± 26.1% ($P < 0.005$, using Wilcoxon signed-ranks test) (Fig. 4).

The UFS-QOL Symptom Severity Scores

The SSS score was able to discriminate between normal participants and women with fibroids.¹² Women with fibroids experienced significantly higher levels of symptom distress and lower health-related quality of life than normal controls. The average SSS for normal women is 22.5, whereas patients with fibroids had an average score of 44.0. In our study, the mean SSS for the 37 patients was 41.7 ± 2.8 before treatment, indicating significant uterine fibroid related symptoms. In the overall study population, 13 evaluable patients had a 10-point or greater symptom improvement at 3 months after treatment, 19 patients had a 10-point or greater reduction of SSS at 6 months after treatment. The symptom improvement was maintained throughout 2 years and 3 to 4 years in 6 patients. As shown in Figure 5, the average SSS was 26.9 ± 3.6, 20.7 ± 3.4, 18.5 ± 3.6, 16.5 ± 7.1, 9.8 ± 3.6 at 3 months, 6 months, 1 year, 2 years and 3 to 4 years respectively. The decrease in scores was significant at all time points up to 3 to 4 years ($P < 0.05$ and $P < 0.001$). The use of auto-regressive model for repeated measurement indicated the significance of treatment effect.

Type of Fibroids

Based on the T2-weighted image signal intensities, the fibroids were classified into 3 types: dark, intermediate and white. We compared fibroid volume changes among the different types of fibroids before and after treatment. The intermediate type of fibroids had the largest median volume (164.1 cm³, 95% CI, 104.6 to 231.6 cm³) before treatment, whereas the median volumes of dark and white type of fibroids were 59.4 cm³ (95% CI, 42.9 to 106.1 cm³) and 82.3 cm³ (95% CI, 36.3 to 140 cm³) respectively (Fig. 6). At 6 months after MRgFUS, the size of dark and intermediate types of fibroids significantly decreased (42.9 ± 20.1%) and (43.4 ± 21.2%) respectively (Fig. 6). At 12 months after treatment, the dark and intermediate



(A) Pre-treatment T2-weighted image of the uterine fibroid. (B) Sagittal T2-weighted image of uterus on treatment day. (C) Six months post-treatment T2-weighted image showing sustained reduction of fibroid size

Fig. 3. Sagittal view of T2-weighted contrast-enhanced MRI from a 48-year-old patient over time. The images (A, B and C) show a time-dependent decrease in size of the intramural fibroid.

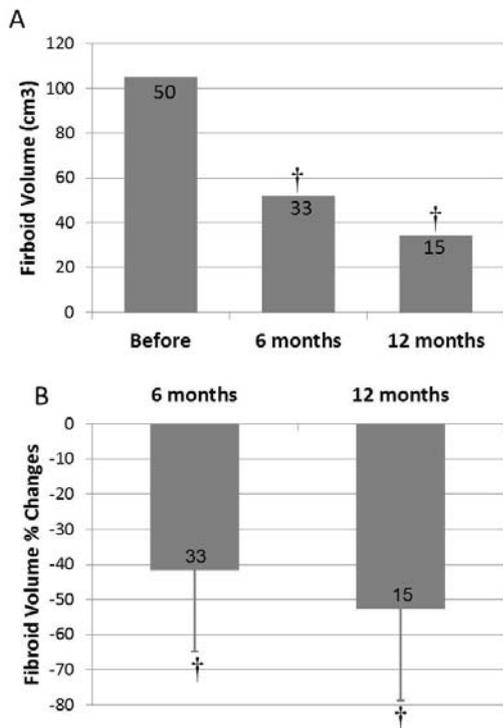


Fig. 4. Comparison of fibroid volume medians before and after treatment at 6 months and 12 months. (A) The fibroid volume medians comparison. Numbers inside the bars indicate number of fibroids. There was significant difference in fibroids volume between before and after treatments 6 months and 12 months. Bars in figure represent median volumes, † $P < 0.001$. (B) The percentage changes of fibroid volume. Numbers inside the bars indicate number of fibroids. There was significant difference in percentage changes of fibroid volume before and after treatment 6 months and 12 months. Bars in figure represent mean percentage change in volume \pm SD, † $P < 0.001$.

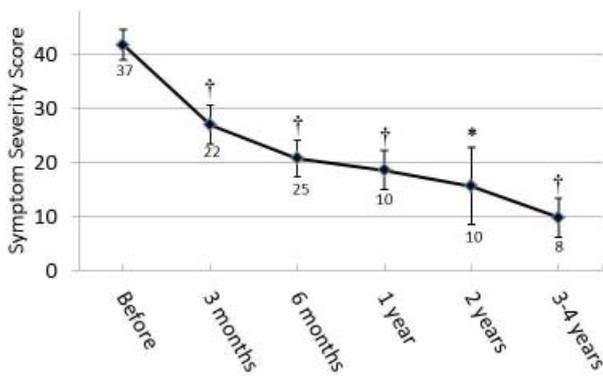


Fig. 5. Pair-wise comparison of UFS-QOL Symptom Severity Score (SSS) before and after treatment of 3, 6, 12 and 24 months. The numbers below the error bar are the number of patients. Auto-regression model for repeated measurement was used to measure the significance of treatment effect. † $P < 0.001$, * $P < 0.05$.

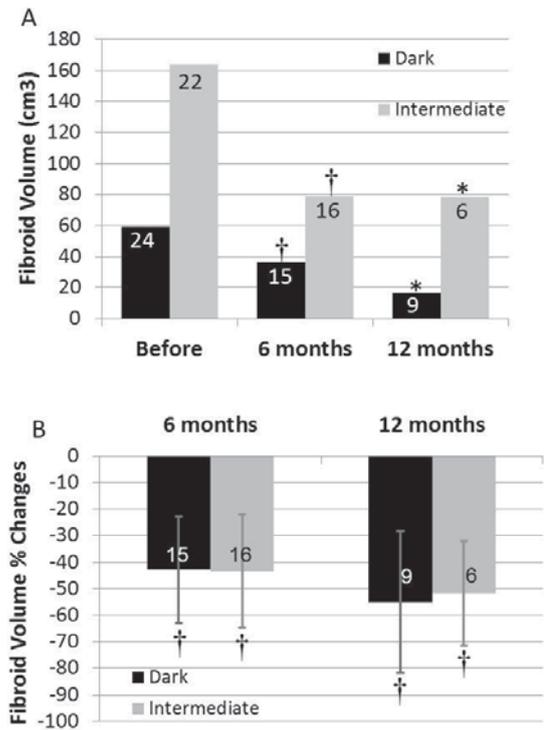


Fig. 6. Comparison of fibroid volume among different types of fibroids before and after treatment. (A) The fibroid volume medians comparison. Numbers inside the bars indicate number of fibroids. There was significant difference in fibroids volume between before and after treatments 6 months and 12 months. Bars in the figure represent median, † $P < 0.001$. (B) Volume changes percentage of different types of fibroids. Numbers inside the bars indicate number of fibroids. There was significant difference of fibroids volume changes between before (as 100%) and after treatments 6 months and 12 months. Bars in the figure represent mean \pm SD, * $P < 0.05$, † $P < 0.001$.

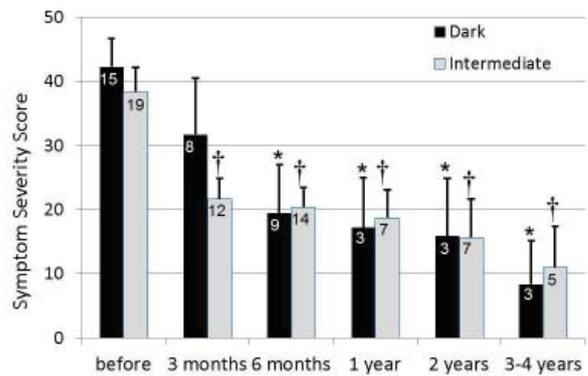


Fig. 7. Pair-wise comparison of Symptom Severity Score (SSS) changes of different types of fibroids before and after treatment. Numbers inside the bars are number of patients. Auto-regression model for repeated measurement was used to measure the significance of treatment effect. † $P < 0.001$, * $P < 0.05$.

fibroids demonstrated significant reduction in size by ($55.1 \pm 26.7\%$) and ($51.8 \pm 19.8\%$) respectively (Fig. 6). There was no patient with white type fibroids evaluated at 12 months in this study.

We also compared SSS score changes among different types of fibroids before and after MRgFUS. Interestingly, the patients with white type of fibroids showed highest SSS score (60.4 ± 4.5) before treatment, indicating they suffer the most severe clinical symptoms, such as dysmenorrhoea, heavy menstruation, and pressure symptoms. There was no significant difference between the SSS scores of patients with dark and intermediate type fibroids (42.3 ± 4.3 , 38.3 ± 3.9 , respectively, Fig. 7). Correlation analysis between the type of fibroid and NPV, type of fibroid and SSS score reduction showed that 3-month SSS reduction was correlated with types of fibroid, $r = 0.414$, $P = 0.031$. In addition, 3-month SSS reduction was also correlated with NPV ratio, $r = 0.569$, $P = 0.071$.

Adverse Events

All patients, except 1, went home after 2 to 3 hours of observation. The only patient who was hospitalised after treatment had requested for it, although she was fit for discharge. Nurses made phone calls to patients daily during the first 2 to 3 days after MRgFUS. There was 1 serious adverse event of bowel perforation and nerve injury, requiring re-admission to hospital a day after the treatment, and subsequent surgery to the bowel. She eventually recovered. Analysis showed operator error and there was no equipment failure. The patient had a large fibroid that changed in configuration and position during the treatment, but this was not immediately recognised, resulting in error in targeting of the sonication. The patient also breathed in too deeply during each sonication, which resulted in the change in uterine fundal position. The lesson learnt from this incident is that the uterine outline and the sonication beam path must be carefully checked during each image acquisition in the course of the treatment. In the presence of significant changes in the target organ, the region of treatment must be revised by acquiring new MRIs. Minor complications included first degree burns on the abdomen in 2 patients and 1 patient who had mild foot discomfort recovered fully after 3 months. Other minor complaints included mild lower abdominal pain or discomfort related to either position within the magnet or uterine discomfort due to sonications. Apart from the patient with bowel injury, the rest of the patients returned to their normal activities within a few days after the procedure.

Discussion

MRgFUS has been approved for treatment of uterine

fibroids by the United States Food and Drug Administration (USFDA) in 2004. KKH was among one of the first worldwide to install the ExAblate 2000[®] system and currently is the only treatment centre in Singapore to perform this procedure. Since the first treatment in our centre in June 2006, almost all of the patients who have undergone this procedure were treated and discharged on the same day. With increasing numbers of patients seeking treatment options that allow them the least amount of disruption to their daily routine, the demand of minimally invasive or non-invasive treatment is clear and growing. Many studies have demonstrated that MRgFUS provided an effective, non-invasive and safe treatment option for uterine fibroids.^{9-11,15,16} However, there is a lack of long-term (up to 4 years) follow-up data after MRgFUS treatment. Based on a PubMed search on 30 July 2013, we are the second to report on long-term observation up to 3 to 4 years. Kim et al¹⁷ first reported the 3-year outcomes and showed sustained symptomatic relief among enrolled patients and there was no long-term complication.

In our present study, 76% (19 out of 25) of evaluated patients had a 10-point or greater improvement in their clinical symptoms at 6 months after treatment. The symptom improvement was maintained in 7 patients throughout 1 and 2 years, and in 6 patients over 3 to 4 years' duration. Our results are comparable with previous reports by Fennessy et al¹⁰ who demonstrated 10-points reduction in 74% of included patients at 6 months and in 73% of patients at 12 months. Using modified protocol that utilised larger ablation volume, the authors showed 10-points reduction in 88% of included patients at 6 months and in 91% patients at 12 months.

These clinical changes as well as the significant changes in the fibroid volume were observed although we included in this study all MRgFUS treatments performed. It should be borne in mind that these results were summarised from the first series of women who underwent this new treatment and the treated volume (NPV) was relatively smaller due to safety considerations. The later treatment with larger treated volume of fibroid tissues showed higher levels of improvement as some results indicated that the reduction in size might depend on the ablated volume.^{18,19} Steward et al²⁰ even developed a model indicating that probability of additional leiomyoma treatment was correlated with non-perfusion volume ratio. Fennessy et al¹⁰ compared the symptom relief between 2 protocols in which the averaged treatment fibroid volume ratio in original protocol was 16.7% whereas that in modified protocol was 25.8%. Better symptom relief was found in patients with modified protocol. Zhang et al¹⁹ showed there was no major adverse effect with the average treated fibroid volume ratio up to 75%. In our present study, the average treated fibroid volume (NPV) ratio was 54% and the 3-month SSS reduction was greatly correlated with NPV ($r = 0.569$, $P = 0.071$).

MRgFUS treatment led to a significant, time-dependent decrease in not only SSS, but also the mean fibroid volume. The average reductions in volume were 41.6% and 52.6% at 6 months and 12 months respectively ($P < 0.05$) which is comparable with other reports. Funaki et al²¹ demonstrated that mean decrease in fibroid size was 36.5% at 6 month and 39.5% at 24 month.

Most of the studies on MRgFUS conduct follow-up of the patients' symptoms at a regular time interval, i.e. 3 months, 6 month, 1 year, 2 years and so on. However, there is a lack of consensus on the appropriate time of follow-up for assessment of fibroid by MRI. Several reasons may contribute to this: (i) the cost of MRI is partly or fully borne by patients in Singapore, whereas it may be covered in other countries with more comprehensive medical insurance, (ii) although symptom improvement occurs as early as 3 months, it may not be consistent with the reduction of fibroid volumes. Further research needs to be done to address the optimal time point for evaluation of effectiveness of MRgFUS treatment.

An interesting finding in our study was that different types of fibroids were associated with different levels of severity of clinical symptoms. We classified the types of fibroids based on T2-weighted contrast-enhanced MRI. The highest pre-treatment SSS score was found in 4 patients with white type of fibroid whereas the lowest was found in the intermediate type. There was no significant difference between dark and intermediate type fibroids before treatment. Interestingly, the intermediate type of fibroid is the most responsive group in terms of volume reduction compared to other studies although this type of fibroids had the highest pre-treatment fibroid volume. Correlation analysis between the type of fibroid and NPV, type of fibroid and symptom severity reduction showed that 3-month SSS reduction was correlated with types of fibroid ($r = 0.414$, $P = 0.031$). Our results indicate that the classification of type of fibroid would help us to optimise the treatment protocol and predict treatment outcomes.

Recent findings from Zhao et al¹⁴ are in agreement with our results. The authors speculate that the white type of fibroids is predominantly cellular, while the intermediate type and dark type of fibroids that may contain tissue degeneration are less cellular and more fibrous.^{13,22}

In our study, 10 out of 37 (27%) patients underwent surgery at 2 years follow-up. All of them still had heavy and irregular menstruation at 6 months after MRgFUS treatment. Out of these 10 patients, 8 patients had large intermediate type of fibroids ($>200 \text{ cm}^3$), one patient had small white type of fibroid (56 cm^3) and one patient had small dark type of fibroid (70 cm^3) in the posterior wall. Out of 37 patients in our study, 3 patients underwent second

MRgFUS treatments. One patient had very large fibroid (517 cm^3) and after 6 months of first treatment, her fibroid enlarged to 700 cm^3 . After 6 months of second MRgFUS treatment, the volume her fibroid remained unchanged. She eventually went for hysterectomy after 2.5 years. Another patient had a hyperintense fibroid that also increased in size, and was found to have an endometrial stromal sarcoma. The third patient had an intermediate fibroid, but had sustained symptom improvement at 2 years.

Since the first clinical trial of MRgFUS treatment for uterine fibroids in 2003,¹⁵ the selection criteria have been broadened. For patients with bowel obstruction, simple measures such as rectal and bladder filling can effectively clear bowel away from the sonication beam path allowing for increased treatment ability. Recent development on the new generation of ExAblate[®] 2100 system has seen the implementation of several technical modifications and improvements. The transducer can be elevated close to the abdominal wall allowing for reduced energy density in the near and far field. Together with better energy dispersion, the maximum sonication spot size has been enlarged to 70 mm to facilitate treatment of larger fibroid volumes. Pre-treatment of large fibroids with a GnRH analog helps to reduce fibroid volume and increase fibroid tissue susceptibility to the treatment, which may improve MRgFUS outcomes.

Our study has several limitations. First, our patient population was relatively small. In addition, only a small number of patients returned their completed SSS questionnaires at 12 months and later. Evaluation of significance in treatment response over the longer durations is thus limited to the small group of patients. The questionnaires are valuable in assessing treatment response, and continue to be used routinely for all patients undergoing treatment, including those on long-term follow-up. Second, it was a single treatment arm trial. However, with emerging evidence on the outcomes of MRgFUS treatment, the selection criteria have evolved to make this procedure more broadly available to women who may benefit from it. Meanwhile, the treatment protocol has been optimised and redefined over the time. More patients will definitely benefit from this non-invasive, safe and effective treatment. Recent data on fertility after MRgFUS are promising and MRgFUS has potential to become the preconception treatment for uterine fibroids in asymptomatic women desiring to preserve their fertility.

Acknowledgements

The authors would like to thank Ms Pamela Teo for her assistance as nurse clinician, and Mr Gu Qing Long for his technical support.

REFERENCES

1. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol* 1997;90:967-73.
2. Stewart EA. Uterine fibroids. *Lancet* 2001;357:293-8.
3. Lumsden MA. Embolization versus myomectomy versus hysterectomy: which is best, when? *Hum Reprod* 2002;17:253-9.
4. Vollenhoven BJ, Lawrence AS, Healy DL. Uterine fibroids: a clinical review. *Br J Obstet Gynaecol* 1990;97:285-98.
5. Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. *Am J Obstet Gynecol* 2006;195:955-64.
6. Hartmann KE, Birnbaum H, Ben-Hamadi R, Wu EQ, Farrell MH, Spalding J, et al. Annual costs associated with diagnosis of uterine leiomyomata. *Obstet Gynecol* 2006;108:930-7.
7. Nishiyama S, Saito M, Sato K, Kurishita M, Itasaka T, Shioda K. High recurrence rate of uterine fibroids on transvaginal ultrasound after abdominal myomectomy in Japanese women. *Gynecol Obstet Invest* 2006;61:155-9.
8. Cline HE, Hynynen K, Watkins RD, Adams WJ, Schenck JF, Ettinger RH, et al. Focused US system for MR imaging-guided tumor ablation. *Radiology* 1995;194:731-7.
9. Stewart EA, Rabinovici J, Tempany CM, Inbar Y, Regan L, Gostout B, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. *Fertil Steril* 2006;85:22-9.
10. Fennessy FM, Tempany CM, McDannold NJ, So MJ, Hesley G, Gostout B, et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--results of different treatment protocols. *Radiology* 2007;243:885-93.
11. Gorny KR, Woodrum DA, Brown DL, Henrichsen TL, Weaver AL, Amrami KK, et al. Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. *J Vasc Interv Radiol* 2011;22:857-64.
12. Spies JB, Coyne K, Guaou G, Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol* 2002;99:290-300.
13. Funaki K, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. *Am J Obstet Gynecol* 2007;196:184 e1-6.
14. Zhao WP, Chen JY, Zhang L, Li Q, Qin J, Peng S, et al. Feasibility of ultrasound-guided high intensity focused ultrasound ablation of uterine fibroids with hyperintense on T2-weighted MR imaging. *Eur J Radiol* 2013;82:e43-9.
15. Tempany CM, Stewart EA, McDannold N, Quade BJ, Jolesz FA, Hynynen K. MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. *Radiology* 2003;226:897-905.
16. Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynynen K, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. *AJR Am J Roentgenol* 2004;183:1713-9.
17. Kim HS, Baik JH, Pham LD, Jacobs MA. MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata: long-term outcomes. *Acad Radiol* 2011;18:970-6.
18. Kopelman D, Inbar Y, Hanannel A, Freundlich D, Vitek S, Schmidt R, et al. Magnetic resonance-guided focused ultrasound surgery using an enhanced sonication technique in a pig muscle model. *Eur J Radiol* 2006;59:190-7.
19. Zhang L, Chen WZ, Liu YJ, Hu X, Zhou K, Chen L, et al. Feasibility of magnetic resonance imaging-guided high intensity focused ultrasound therapy for ablating uterine fibroids in patients with bowel lies anterior to uterus. *Eur J Radiol* 2010;73:396-403.
20. Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, Tempany CM. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. *Obstet Gynecol* 2007;110: 279-87.
21. Funaki K, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. *Ultrasound Obstet Gynecol* 2009;34:584-9.
22. Lenard ZM, McDannold NJ, Fennessy FM, Stewart EA, Jolesz FA, Hynynen K, et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--imaging predictors of success. *Radiology* 2008;249:187-94.