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Patient suitability for magnetic resonance guided focused ultrasound surgery of uterine fibroids

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ABSTRACT

Objective: To assess selection criteria used to determine eligibility for magnetic resonance-guided focused ultrasound surgery (MRgFUS) for the treatment of symptomatic uterine fibroids; to assess the percentage of patients suitable for MRgFUS.
Study design: A retrospective analysis of 144 patients seeking minimally invasive treatment options for symptomatic uterine fibroids at a single treatment center. Clinical eligibility for MRgFUS was assessed at a gynecology clinic by a Gynecology research fellow trained in the procedure and suitability was assessed by magnetic resonance imaging. Several techniques were used to mitigate against factors that are contra-indications for MRgFUS.
Results: 100% of patients interested in MRgFUS were deemed clinically eligible for the procedure and 74% were deemed technically suitable to proceed with treatment.
Conclusions: Mitigation techniques allow for less restrictive MRgFUS selection criteria for treatment for symptomatic uterine fibroids. These less restrictive criteria are expected to expand the pool of patients for whom MRgFUS is a viable treatment option for uterine fibroid symptoms.

1. Introduction

Uterine fibroids (myomas) are benign smooth muscle tumors of the uterus that are found in at least 25–35% of women over the age of 35 years. Although some of these tumors are asymptomatic, up to 50% cause symptoms severe enough to warrant therapy, and surgery is the conventional treatment of choice. As a result, uterine fibroids account for 30–70% of the approximately 600,000 hysterectomies performed in the United States each year [1,2]. Symptomatic myomas also account for approximately 35,000 abdominal/open myomectomies each year [3]. As with all surgical procedures, hysterectomy and myomectomy are associated with complications. The incidence of major complications for hysterectomy is approximately 3% [4]. Although the incidence of major complications for myomectomy is less well defined, the procedure is associated with long-term problems such as fibroid recurrence, adhesion formation and the increased possibility of uterine rupture during pregnancy and vaginal delivery [5]. Clearly, effective non-surgical therapies are needed to provide patients with less-invasive options for treating uterine fibroids.

The past few years have seen the emergence of minimally invasive treatments, namely uterine artery embolization (UAE) and, more recently, MR guided thermal-ablative techniques such as MR guided focused ultrasound surgery (MRgFUS). While the ability of high intensity focused ultrasound to cause coagulative necrosis within areas of tissue has been known for a long time, the feasibility of an MR guided system was only first described in 1995 [6]. Studies using this technique have been carried out in many different areas including tumors of the breast, brain, and liver. However, the largest body of work has been generated in women with uterine fibroids. MRgFUS was developed as a non-invasive alternative to conventional surgical techniques, and the U.S. Food and Drug Administration approved the technology for use in this indication in 2004. Data supporting the safety and efficacy of MRgFUS as an alternative treatment option for symptomatic uterine fibroids have been published previously [7,8].

MRgFUS offers several advantages for treating uterine fibroids, in that it is a completely non-invasive, out-patient procedure that requires minimal sedation and allows a speedy recovery time. Patients undergoing MRgFUS typically return to work within 24 h, compared with 10 days after UAE and six weeks after myomectomy or hysterectomy. Additionally, patient's desire for future fertility is not currently a contra-indication for MRgFUS treatment in Europe. Fertility data available to date are promising [9–12], with no evidence that MRgFUS is detrimental to a patient's pre-treatment fertility status or the labor process. At this time, there

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are insufficient data to determine if MRgFUS may actually improve fertility in women who have diminished reproductive capacity as a result of uterine fibroids.

Previous experience with UAE has shown that a key factor in the acceptance of novel treatment options for uterine fibroids is the development and dissemination of consistent and informative patient selection criteria. The patient selection criteria for UAE are now well known and include both relative and absolute contra-indications. Absolute contra-indications for UAE include: a viable pregnancy, pedunculated fibroids, active infection and a suspicion of malignancy. Relative contra-indications include: coagulopathy, renal impairment, the desire to maintain childbearing potential, and the concurrent use of a GnRH analogue.

St. Mary's Hospital in Paddington, London, currently is the only center in the U.K and was one of the first worldwide to utilize MRgFUS, performing the procedure in more than 350 women with symptomatic uterine fibroids. Based on our institution's extensive experience using MRgFUS in the treatment of symptomatic uterine fibroids, we have developed selection criteria that are designed to maintain the safety and efficacy of the technique, while also making it available to as many patients as possible. The aim of the current report was to assess the selection criteria used to determine eligibility for MRgFUS and to assess the percentage of patients who are suitable for MRgFUS.

Table 1
Patient exclusion criteria.

1.	Hemoglobin <10
2.	Patient has hemolytic anemia
3.	Patient has unstable cardiac status including: • Unstable angina pectoris on medication • Documented myocardial infarction within six months of protocol entry • Congestive heart failure requiring medication (other than diuretic) • Currently taking anti-arrhythmic drugs • Severe hypertension (diastolic BP > 100 on medication) • Presence of cardiac pacemaker
4.	Patient has severe cerebrovascular disease (multiple CVA or CVA within six months)
5.	Patient is on anti-coagulation therapy or has an underlying bleeding disorder
6.	Evidence of uterine pathology other than leiomyoma
7.	Patient has an active pelvic infection
8.	Patient has an undiagnosed pelvic mass outside the uterus.
9.	Patient weight >110 kg
10.	Patient with extensive longitudinal abdominal scarring in an area of the abdomen directly anterior to the treatment area.
11.	Patient with standard contra-indications for MR imaging such as non-MRI compatible implanted metallic devices.
12.	Individuals who are not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 h.)

2. Materials and methods

All MRgFUS procedures were performed using the ExAblate 2000 (InSightec, Haifa, Israel), which is fully integrated with a 1.5 Tesla MR scanner (GE Medical Systems, Milwaukee, WI).

Patients attending the tertiary Fibroid Clinic at St. Mary's Hospital between September 2005 and December 2006, and who specifically expressed interest in minimally invasive treatments for their fibroids, were included in this retrospective analysis. The patients were referred by their general practitioner or by a local gynecologist. Each patient was seen by a clinical research fellow (SZ) who obtained the patient's medical history, performed a clinical examination, and assessed uterine fibroid symptoms according to the SSS-QOL questionnaire [13]. A full blood count was done to measure hemoglobin levels. Patients were then informed about their options for managing their fibroid symptoms by a consultant gynecologist specializing in uterine fibroids. Patients' eligibility for MRgFUS was assessed according to the inclusion–exclusion criteria derived from the ExAblate commercial treatment guidelines (Table 1). In general, patients were excluded if they had contra-indications for MR imaging such as non-MRI compatible implanted metallic devices, obesity, or inability to tolerate prolonged stationary position inside the MRI scanner. Patients deemed unable to comprehend instructions or communicate sensations during treatment were also excluded, as safe treatment relies on the ability of the patient to communicate sensations such as leg, buttock, skin or back pain to the operator. Other factors for exclusion were severe medical conditions such as unstable cardiac status or cerebrovascular disease, hemolytic anemia, anti-coagulation therapy or underlying bleeding disorder. Patients with uterine pathology other than leiomyoma, active pelvic infection or pelvic mass outside the uterus were also excluded.

If the patient was clinically eligible and interested in MRgFUS, she was then referred for a screening MRI scans. Screening was performed in prone position, and consisted of three orientations including both T2 weighted images and T1 weighted images before and after gadolinium injection. A radiologist experienced in MRgFUS (WG) analyzed the screening MR images to determine patient suitability for the procedure.

Patients were deemed technically suitable for MRgFUS if their fibroids mass seemed accessible by the system and treatable in a reasonable time. The majority of the fibroids mass should be no more than 12 cm depth away from the skin line, as this is the upper limit of the system. Patients with bowel that could not be shifted from the potential beam path were also excluded from consideration, as air bubbles or hard particles present in the bowel may reflect or absorb the ultrasonic energy. Patients with more than six uterine fibroids of more than 4 cm size each were excluded, as usually in these cases some of the fibroids will be close to the sacrum or hidden behind bowel and thus will be inaccessible. Patients with longitudinal scars in the beam path, including those that could not be seen on the MR images, also were excluded, as scar tissue may absorb the ultrasound energy and cause pain or even a skin burn. Other factors for exclusion are calcified fibroids, which ultrasound energy cannot penetrate into; patients with non-enhancing fibroids that are already dead; pedunculated fibroids, that might disconnect after the treatment into the abdominal cavity; and patients with pathologies other than uterine fibroids, such as adenomyosis.

Patients who had total fibroids volume of more than 500 cubic centimeter, or a hyper-intense fibroid on T2 weighted imaging were pre-treated with a GnRH analogue for three months in an effort to reduce the size and vascularity of the fibroid [14].

3. Results

Between September 2005 and December 2006, 144 patients attended the Fibroid Clinic at St. Mary's Hospital, in search of minimally invasive treatment for their fibroids. 100 patients requested to have the non-invasive MRgFUS treatment, and 44 patients opted for surgical management, UAE or no treatment. The 100 patients requesting MRgFUS form the initial patient group. Demographics and patient characteristics of this group are described in Table 2.

All 100 patients requesting MRgFUS were found to be clinically eligible and were sent for screening MRI scans. Of them, 74 patients were assessed as being technically suitable for MRgFUS and 26 patients were deemed not suitable. Of the 26 patients not suitable for MRgFUS, seven had bowel completely occluding the acoustic window, with no potential for mitigation, four had a mixed picture of adenomyosis and fibroids, three had 20 or more fibroids of

Table 2
ExAblate potential patient demographics $N = 100$.

Age (years)	
Mean (Years)	42.8
Range (Years)	22–57
BMI (kg/m^2)	
Mean	24.9
Range	19–38
Hormonal status	
Pre-menopausal	89%
Post-menopausal	11%
Race	
White	48%
Asian	12%
African	40%
Number of fibroids	
Patients with a single fibroid	61%
Patients with multiple fibroid	39%
Fibroids intensity on T2w images (relative to myometrium)	
Patients with hyper-intense fibroids	12%

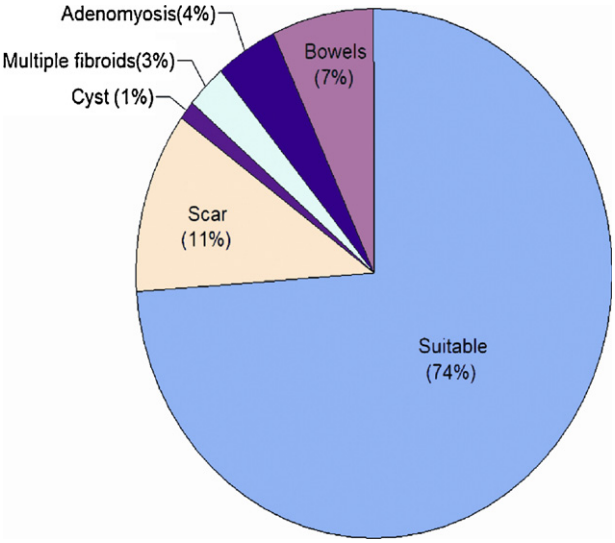

Fig. 1. Breakdown of patients eligible for MRgFUS following MRI screening ($N = 100$).

approximately 1 cm diameter, 11 had scars occluding the treatment window, seven had transverse scars located anterior to the fibroid and four had longitudinal scars, all could not be potentially avoided by re-positioning or angling of the beam path. One patient had a dermoid cyst for which surgical removal was planned and therefore this patient opted for surgical removal of the fibroid as well. Suitability results are summarized in Fig. 1.

Of the suitable patients, one patient had bowel across the acoustic window, covering the front of the fibroid. This patient was re-assessed following bladder filling and deemed technically suitable for MRgFUS. The filled bladder had elevated the whole uterus, thereby pushing the bowel clear from the acoustic window (Fig. 2).

All 74 suitable patients underwent the MRgFUS procedure with no complications. All patients were discharged on the same day of the procedure, with no in-patient stay required. Twenty-eight (38%) patients required two sessions of MRgFUS treatment due to the presence of large or multiple fibroids.

Sixty-five (88%) of the treated patients were given three injections of a GnRH analog prior to the treatment, in order to shrink the fibroid (see Fig. 3) and to improve the response to MRgFUS for fibroids that were hyper-intense on T2 weighted imaging. In our experience at St. Mary's, we have found that pre-treatment with GnRH greatly potentiates the thermal effects and as such we have a low threshold for pre-treatment.

All patients were followed up at six months in the out-patient clinic and during this period, no patients reported adverse events resulting from the treatment and none required alternative treatments for their fibroids.

4. Comment

St. Mary's Hospital in Paddington, London, currently is the only center in the U.K and was one of the first worldwide to install the ExAblate 2000 system. Over the past five years, the MR therapy unit in this institution has developed substantial expertise in performing the MRgFUS procedure using the ExAblate 2000 system including participation in initial clinical studies and routine treatment of eligible patients. The Fibroid Clinic currently is a tertiary referral center offering complete treatment services for women with fibroids, including hysterectomy, myomectomy (laparoscopic and abdominal), UAE and MRgFUS.

With an increasing numbers of patients looking for treatment options that afford them the least amount of disruption to their

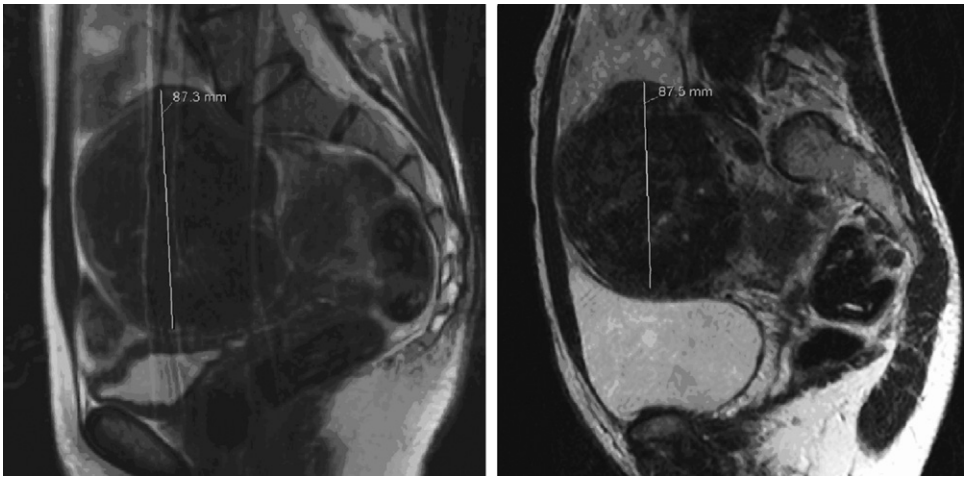

Fig. 2. Left image is pre-bladder filling. Bowel can be seen right across the acoustic window, covering the front of the fibroid. Right image is post-bladder filling. The filled bladder has elevated the whole uterus, thereby pushing the bowel clear of the treatment window.

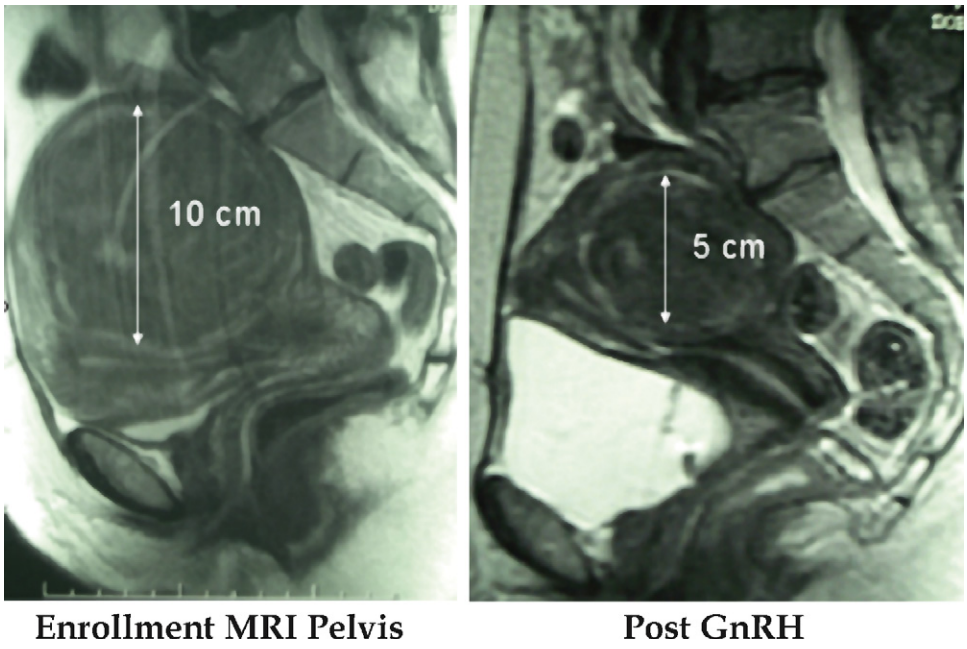

Fig. 3. A sagittal T2w image of a patient with 10 cm fibroid (left image). Patient was treated with three months of GnRH analog to shrink the fibroid prior to the treatment (right image).

daily routine, the appeal of MRgFUS is clear and growing. While MRgFUS provides an effective non-invasive treatment option [8] for uterine fibroids, the ability to make the procedure broadly available to women who may benefit from it requires the establishment of patient selection and suitability criteria that are less restrictive than the company guidelines previously developed, when the MRgFUS technology was initially implemented. For clinical eligibility in our hospital, minimal age, menstrual status and minimal symptoms severity score were not factors for exclusion. In addition, patients who desire future pregnancy also are approved for treatment, as there are case reports showing successful live birth after treatment [9–12]. Additionally, several mitigation techniques are used to increase the technical eligibility and allow the treatment of some patients who according to the original company guidelines should have been excluded, due to bowel obstructing the beam path, too large fibroid volumes, scars, or desire to preserve fertility.

For patients with obstructing bowel, simple measures such as rectal and bladder filling effectively clear bowel away from the acoustic window, allowing for increased treatment capacity. 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. We previously have reported results of a study in which 50 women with fibroids greater than 10 cm in diameter were treated with a three-month course of a GnRH analog prior to MRgFUS [15]. Results show that 83% of patients treated with this regimen described significant improvement in their uterine fibroid symptoms at 24 months post-MRgFUS.

We also have identified an original method of highlighting transverse scars, which has improved our visualization of scar tissue and enabled us to treat patients who were previously excluded. With this method, scars are painted with a solution of nail varnish and paramagnetic iron oxide particles, providing an obvious artifact along the line of the scar, which can easily be avoided by appropriate positioning and angling of the ultrasound beam (Fig. 4).

In a previous study [16] 63% of patients inquiring about MRgFUS treatment for symptomatic uterine fibroids were clinically eligible, per study exclusion criteria. Of these patients, 25% were found anatomically eligible following MRI screening. In the retrospective analysis reported here, patients participating in the study had 100% clinical eligibility and 74% anatomical suitability for MRgFUS. The increase in clinical eligibility and technical suitability likely results from differences in inclusion-exclusion criteria (see Table 3).

The strength of this report lies in the number of uterine fibroid patients that have been treated with MRgFUS at this institution

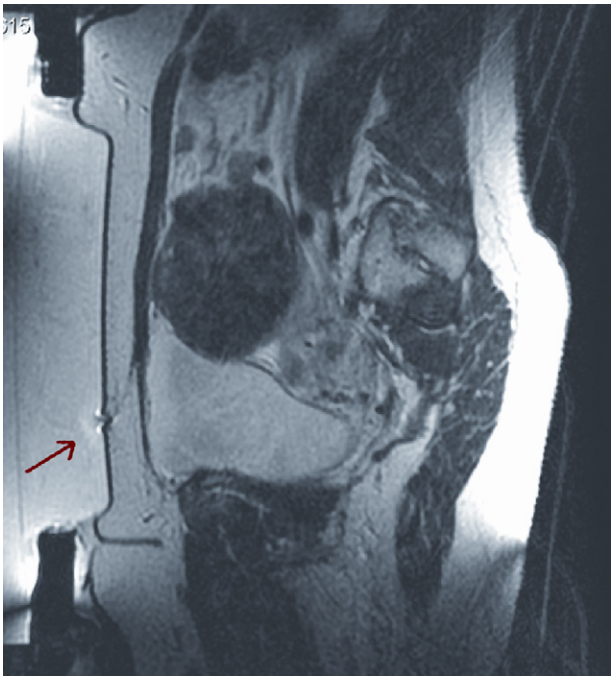

Fig. 4. A sagittal T2w image of a patient with a scar. The solution of nail varnish and paramagnetic iron oxide particles painted on the patient scar highlights the scar in the image (marked with arrow). Bladder fill was performed in order to enable a beam path that would avoid passing through the scar.

Table 3
Comparison of assessment criteria used in earlier studies and the St. Mary's centre.

Clinical factor	Prior study	St. Mary's
Insufficient symptoms of fibroids	SSS <21 excluded	Not relevant
Age < 40 or >60 years	Excluded	Not relevant
Desires pregnancy	Excluded	Not relevant
Menopausal	Excluded	Not relevant
Obesity	>250lbs excluded	>250lbs excluded
Prior UFE	Excluded	Not relevant
IUD, MR imaging incompatibility	Excluded	Excluded
Technical factor	**Prior study**	**St. Mary's**
Too much fibroid volume	>900 cc excluded	Not relevant
Bowel obstructing beam path	Excluded	Partly mitigated
Significant adenomyosis	Excluded	Excluded
Pedunculated fibroids	Excluded	Excluded
Fibroids too small or no fibroids	Excluded	Excluded
Bright T2 fibroid	Excluded	Partly mitigated
Degenerating, necrotic, or infarcted fibroids	Excluded	Excluded
Arterial–venous malformation, calcified fibroids, or conglomerate of fibroids or septated fibroids hard to transmit heat across	Excluded	Excluded

and long-term experience of the staff in selecting patients for the procedure. This experience has enabled the identification of a variety of techniques that may be used to expand the pool of patients for which MRgFUS may provide a safe and effective treatment for uterine fibroids. Consequently, guidelines developed from this experience base are expected to provide a greater number of women with a non-invasive approach to managing symptomatic uterine fibroids. The main weakness of the report is that the statistics do not show the suitability of MRgFUS for the general population of women suffering from uterine fibroids symptoms. We have no information regarding the selection process by which referring gynecologists referred patients to us and on which basis these patients were referred.

In conclusion, we have found that MRgFUS can be offered to a majority of patients suffering from symptomatic uterine fibroids. Furthermore the use of broader inclusion criteria as well as the mitigation techniques described above makes it possible to offer MRgFUS to a much larger subset of patients than previously believed. Further studies to evaluate these techniques may help to refine further the selection and suitability criteria for MRgFUS as a treatment for symptomatic uterine fibroids.

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