NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids

Image-guided ultrasound treatment for uterine fibroids

Uterine fibroids are non-cancerous (benign) growths that occur in the womb. They can cause heavy menstruation and reproductive problems. This non-invasive procedure uses magnetic resonance imaging (MRI) to locate the fibroids and direct, high-intensity ultrasound energy to destroy fibroid tissue, with the aim of reducing symptoms.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2011.

Procedure name

- Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids

Specialty societies

- British Society of Interventional Radiology
- Royal College of Obstetricians and Gynaecologists.

Description

Indications and current treatment

Uterine fibroids (also known as uterine leiomyomas or uterine myomas) are benign tumours that develop within the uterine wall. They can be single or multiple.

Uterine fibroids are one of the most common gynaecological problems among women in the UK. They are often asymptomatic but they can cause symptoms such as abnormal uterine bleeding, a feeling of pelvic pressure, pain, and urinary incontinence. They may also be associated with reproductive problems such as infertility and miscarriage.

Treatment depends on whether the fibroids cause symptoms, and on the woman's desire for future childbearing. Asymptomatic fibroids (often discovered incidentally) require no treatment. Depending on their size, number and location, symptomatic fibroids have historically been managed by hysterectomy (surgical removal of the uterus) or myomectomy (surgical removal of the fibroids). Smaller submucous fibroids can be removed by hysteroscopic resection. Uterine artery embolisation may also be used. Other treatments include endometrial ablation, using energy such as microwaves or heat, which may be suitable for some fibroid types.

Hormone-based treatments may be used on a short-term basis to relieve symptoms, or to shrink the fibroids before surgery or other interventional treatment.

What the procedure involves

Magnetic resonance image (MRI)-guided transcutaneous focused ultrasound for uterine fibroids is carried out with the patient lying prone inside an MR scanner, under continuous image guidance and usually under intravenous conscious sedation. A catheter is inserted to drain the urinary bladder and to keep it empty during the procedure. Magnetic resonance imaging is used to identify the fibroid(s), and a low-power sonification (pulse) is delivered, aimed at the centre of the targeted fibroid. Once the targeting of these sonifications is confirmed, higher-power consecutive sonifications are delivered to the target area to ablate the fibroid tissue. MRI has temperature-sensitive parameters, which allow for real-time thermal mapping during the procedure. The head of the sonification device is in contact with the patient's abdominal skin and the patient has the facility to stop the procedure at any time. The patient may have to lie still for up to 3 hours.

After treatment, imaging is used to evaluate the area of the fibroid ablated, as a marker of treatment efficacy. The non-enhanced areas on imaging represent the non-perfused volume (NPV) to which the blood supply has been interrupted by the procedure. This is then compared with the pre-treatment total fibroid volume to give an NPV ratio and assess technical success.

The potential benefit of MRI-guided transcutaneous focused ultrasound is that it is less invasive than hysterectomy and myomectomy, with a faster recovery time.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to MRI-guided transcutaneous focused ultrasound for uterine fibroids. Searches were conducted of the following databases, covering the period from their commencement to 25/10/2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with uterine fibroids.
Intervention/test	MRI-guided transcutaneous focused ultrasound.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 869 patients treated by MRI-guided transcutaneous focused ultrasound from 1 non-randomised comparative study, 6 case series and 2 case reports[1–9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Taran FA (2009)[1]

Non-randomised comparative study

USA, Israel, UK and Germany

Recruitment period: not reported

Study population: premenopausal women with symptomatic uterine fibroids

n = 192 (109 MRgFUS, 83 abdominal hysterectomy)

Mean age (years): 45 (MRgFUS), 44 (hysterectomy)

Patient selection criteria: all the women were at least 18 years old and did not want children in the future. Exclusion criteria included women with a uterus larger than 24 weeks gestational size, haematocrit <25%, a positive pregnancy test, any contraindication to surgery or MRI.

Technique: MRgFUS was performed using the ExAblate 2000 system (Insightec, Israel). Treatment time was limited to 180 minutes. Coagulation volume was limited to 150 ml per treatment. Prophylactic antibiotics were not used before MRgFUS. They were administered preoperatively to all women in the hysterectomy group.

Follow-up: 6 months

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 192 (109 vs 83)

Treatment failures in MRgFUS group = 3.7% (4/109)
4 patients required surgical or interventional treatment (3 hysterectomies and 1 uterine artery embolisation) for continued or recurrent symptoms during the first 6 months of follow-up.

Mean SF-36 health survey questionnaire and disability assessment scores at 1-month follow-up
<table>
<tr><th></th><th>MRgFUS</th><th>Hysterect-omy</th><th>p</th></tr>
<tr><td colspan="4">SF-36 scores</td></tr>
<tr><td>Physical functioning</td><td>80.3</td><td>58.0</td><td><0.0001</td></tr>
<tr><td>Physical role</td><td>55.3</td><td>20.0</td><td><0.0001</td></tr>
<tr><td>Bodily pain</td><td>64.6</td><td>49.3</td><td><0.0001</td></tr>
<tr><td>General health</td><td>68.2</td><td>71.3</td><td>NS</td></tr>
<tr><td>Vitality</td><td>53.9</td><td>44.5</td><td>0.004</td></tr>
<tr><td>Social functioning</td><td>74.9</td><td>56.3</td><td><0.0001</td></tr>
<tr><td>Emotional role</td><td>65.4</td><td>48.7</td><td>0.01</td></tr>
<tr><td>Mental health</td><td>71.8</td><td>74.1</td><td>NS</td></tr>
<tr><td colspan="4">Disability assessment scores</td></tr>
<tr><td>Lost work days</td><td>1.2</td><td>19.2</td><td><0.0001</td></tr>
<tr><td>Days late for work</td><td>0.6</td><td>2.1</td><td>NS</td></tr>
<tr><td>Days spent in bed</td><td>1.3</td><td>9.9</td><td><0.0001</td></tr>
<tr><td>Days kept from usual activities</td><td>2.7</td><td>17.4</td><td><0.0001</td></tr>
</table>
</td>
<td>The most serious complication after MRgFUS was a significant but reversible sciatic nerve palsy in 1 patient.

Total number of significant clinical complication events (defined as fever > 38°C on any 2 post-treatment days, blood transfusion, unintended major surgical procedure, discharge to a rehabilitation facility, discharge with an appliance such as a drain or urinary catheter, outpatient interventional treatment, rehospitalisation, life-threatening event or death within 42 days of treatment):
• MRgFUS = 12.8% (14/109)
• Hysterectomy = 39.8% (33/83), p < 0.0001

Fever >38°C on any 2 post-treatment days:
• MRgFUS = 2.8% (3/109)
• Hysterectomy = 14.5% (12/83), p = 0.005
Transfusion:
• MRgFUS = 2.8% (3/109)
• Hysterectomy = 7.2% (6/83), p = NS
Readmission lasting >24 h:
• MRgFUS = 7.3% (8/109)
• Hysterectomy = 9.6% (8/83), p = NS

Serious adverse events (reported ‘in compliance with the Standard Code of Federal Regulations’ – not defined):
• MRgFUS = 8.3% (9/109)
• Hysterectomy = 9.6% (8/83), p = NS
(Note: these included a pre-existing brain</td>
<td>Patient population overlap with Stewart et al., 2007[2]

Follow-up issues:
• No losses to follow-up were described.

Study design issues:
• 14 centres were involved.
• The two patient groups were recruited from different centres.
• Quality of life was assessed using the SF-36 health survey questionnaire (higher scores indicate better quality of life).

Study population issues:
• Women in the hysterectomy group were less likely to be Caucasian (54 vs 80%, p<0.001) and had higher BMI on average (29.9 vs 25.8, p = 0.001) than women in the MRgFUS group.
• Women in the hysterectomy group had higher levels of symptoms at baseline and significantly worse function on several subsections of the SF-36 questionnaire.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td></td>
<td>
Mean SF-36 health survey questionnaire and disability assessment scores at 6-month follow-up
<table>
<tr><th></th><th>MRgFUS</th><th>Hysterectomy</th><th>p</th></tr>
<tr><td colspan="4">SF-36 scores</td></tr>
<tr><td>Physical functioning</td><td>82.5</td><td>86.9</td><td>NS</td></tr>
<tr><td>Physical role</td><td>68.3</td><td>80.0</td><td>0.05</td></tr>
<tr><td>Bodily pain</td><td>69.1</td><td>79.5</td><td>0.004</td></tr>
<tr><td>General health</td><td>69.3</td><td>75.3</td><td>0.04</td></tr>
<tr><td>Vitality</td><td>59.1</td><td>65.6</td><td>0.04</td></tr>
<tr><td>Social functioning</td><td>79.5</td><td>84.8</td><td>NS</td></tr>
<tr><td>Emotional role</td><td>75.0</td><td>78.1</td><td>NS</td></tr>
<tr><td>Mental health</td><td>73.3</td><td>79.6</td><td>0.008</td></tr>
<tr><td colspan="4">Disability assessment scores</td></tr>
<tr><td>Lost work days</td><td>0.2</td><td>1.7</td><td>NS</td></tr>
<tr><td>Days late for work</td><td>0.1</td><td>0.0</td><td>NS</td></tr>
<tr><td>Days spent in bed</td><td>0.5</td><td>0.5</td><td>NS</td></tr>
<tr><td>Days kept from usual activities</td><td>1.4</td><td>1.7</td><td>NS</td></tr>
</table>
</td>
<td>
tumour and ‘ventricular ectopy’, neither of which were considered to be related to treatment)

At least 1 adverse event:

MRgFUS = 80.7% (88/109)
Hysterectomy = 98.8% (82/83), p < 0.0001

<table>
<tr><th>Adverse event</th><th>MRgFUS (n = 109)</th><th>Hystere-ctomy (n = 83)</th></tr>
<tr><td>Pain</td><td>62.4%</td><td>95.2%*</td></tr>
<tr><td>Gynaecological</td><td>27.5%</td><td>27.7%</td></tr>
<tr><td>Urinary tract</td><td>23.8%</td><td>19.3%</td></tr>
<tr><td>Gastrointestinal tract</td><td>20.2%</td><td>67.5%*</td></tr>
<tr><td>Dermatological system</td><td>15.6%</td><td>34.9%*</td></tr>
<tr><td>Nervous system</td><td>7.3%</td><td>20.5%*</td></tr>
<tr><td>Cardiovascular system</td><td>2.8%</td><td>8.4%</td></tr>
<tr><td>Respiratory tract</td><td>0%</td><td>2.4%</td></tr>
<tr><td>Systemic events</td><td>17.4%</td><td>20.5%</td></tr>
<tr><td>Other</td><td>0%</td><td>7.2%*</td></tr>
</table>
* p < 0.05
</td>
<td></td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Stewart EA (2007)[2]

Case series
USA, Israel, UK

Recruitment period: 2002–6

Study population: premenopausal women with symptomatic uterine fibroids

n = 359

Age (years): 43.9–46.4 (range of means)

Patient selection criteria: all women were at least 18 years old and premenopausal with significant fibroid symptoms, and did not desire future childbearing. Exclusion criteria included a uterus larger than 24 weeks gestation, haematocrit <25%, positive pregnancy test, major medical disease, or contraindication to MRI such as a pacemaker or weight over 250 pounds.

Technique: All procedures were performed with the ExAblate 2000 system (InSightec, Israel). After 2004, treatment protocols were changed – allowed treatment volumes were increased and treatment time was increased from 120 to 180 minutes. Two treatment sessions were allowed if performed within a 14-day period.

Follow-up: 24 months

Conflict of interest/source of funding: all authors have served as clinical trial investigators for Insightec-funded trials. 2 authors have served as consultants to Insightec and 1 has received travel grants from Insightec.</td>
<td>Number of patients analysed: 359

57% of women had a NPV of 20% or less attained during treatment. Fewer than 3% had a NPV ratio of 70% or greater.

Note: The NPV ratio is calculated as the ratio of the sum of the NPV of all treated fibroids divided by the volume of all uterine fibroids (treated and untreated).

Mean symptoms severity score (assessed using the Uterine Fibroid Symptoms Quality of Life scale, 100 indicates maximum symptoms)
<table>
<tr><th>Follow-up</th><th>Post-treatment NPV ratio 20% or less</th><th>Post-treatment NPV ratio >20%</th></tr>
<tr><td>Baseline</td><td>62</td><td>63</td></tr>
<tr><td>3 months</td><td>38</td><td>32*</td></tr>
<tr><td>6 months</td><td>38</td><td>32*</td></tr>
<tr><td>12 months</td><td>39</td><td>33*</td></tr>
<tr><td>24 months</td><td>40</td><td>34*</td></tr>
</table>
(all results have been estimated from graphical presentation)
*p < 0.001 (high NPV ratio vs low NPV ratio)

For both groups, the symptom severity score 3 months after treatment was significantly reduced from baseline.

At 12 and 24 months, there was a significant effect of NPV ratio attained during treatment on the number of women undergoing additional fibroid treatment (p = 0.012 and p < 0.001, respectively).

With a NPV ratio of 20% attained during treatment, the probability of additional treatment at 24 months was approximately 40%.</td>
<td>‘No new serious adverse events were observed’.</td>
<td>Includes studies by Taran et al, 2009 and Fennessy et al, 2007.

Study design issues:
• Patients were included from 4 different trials.

Follow-up issues:
• All patients had scheduled follow-up at 3,6,12 and 24 months. Clinical information was collected at each visit and MRI performed.
• The proportion of patients lost to follow-up is not stated.
• There was no difference between the group of patients lost to follow-up and the rest of the patients with regard to age, body mass index, total leiomyoma load, mean baseline symptom severity score and mean treated leiomyoma volume.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Okada A (2009)[3]

Case series

Japan

Recruitment period: 2003–6

Study population: patients with symptomatic uterine fibroids

n = 287

Mean age: 42.5 years (range 24–60)

Patient selection criteria: exclusion criteria were pregnant women, women wishing for future pregnancy, contraindication to MRI, patients with abdominal scars, bowel in the path of the ultrasound beam or fibroids located close to the sacral surface.

Technique: The ExAblate 2000 (InSightec, Israel) system was used.

Follow-up: 12 months

Conflict of interest/source of funding: several authors have received travel grants from Insightec.</td>
<td>Number of patients analysed: 287

8.3% (19/228) patients underwent additional treatments for fibroids during the 12-month follow-up.

Mean NPV ratio attained during treatment = 46.6% (n = 279, 8 patients were not included because of an allergy to the contrast agent).

Mean NPV ratio
• Group I (2003–5) = 39.3% (range 0–91.3)
• Group II (2005–6) = 54% (range 0–00)
p < 0.001

Alternative treatments by 6-month follow-up (n = 228):
• Group I (2003–5) = 5% (5/105)
• Group II (2005–6) = 2% (3/123)
p = 0.34

Alternative treatments by 12-month follow-up (n = 228):
• Group I (2003–5) = 12% (13/105)
• Group II (2005–6) = 5% (6/123)
p = 0.04</td>
<td>Postprocedure adverse events

<table>
<tr><th></th><th>Group I (2003-5) n = 144</th><th>Group II (2005-6) n = 143</th></tr>
<tr><td>Abdominal pain</td><td>17 (12%)</td><td>16 (11%)</td></tr>
<tr><td>Lower back or leg pain</td><td>9 (6%)</td><td>11 (8%)</td></tr>
<tr><td>Vaginal discharge or bleeding</td><td>12 (8%)</td><td>11 (8%)</td></tr>
<tr><td>Fever</td><td>7 (5%)</td><td>9 (6%)</td></tr>
<tr><td>Skin burns</td><td>10 (7%)</td><td>2 (1%)*</td></tr>
</table>
*p = 0.04

All skin burns resolved within 2 weeks without surgical intervention.

All adverse events were managed conservatively, did not require surgical intervention and resolved at follow-up.</td>
<td>Follow-up issues:
• 21% (59/287) of patients were lost to follow-up.
• There were no differences in the patients lost to follow-up with regard to age, total fibroid load and nonperfused volume ratio.

Study design issues:
• Patients were treated at 4 different centres.
• The patient population was divided into 2 equal groups according to the treatment period.

Study population issues:
• A statistically significantly higher proportion of patients in Group II reached the 6 and 12-month follow-up compared with patients in Group I.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Fennessy FM (2007)[4]

Case series

USA

Recruitment period: 2003–4

n = 160

Population: premenopausal women with symptomatic fibroids

Mean age: 46 years

Patient selection: premenopausal women with symptomatic uterine leiomyomas who were not planning future childbearing. Pregnant women, postmenopausal women and those with MRI contraindications were excluded. Patients with extensive scars on the anterior abdominal wall were also excluded.

Technique: MRI-guided focused ultrasound. First 96 patients treated with original protocol, 64 patients treated with less restrictive, modified protocol. (Key differences: greater fibroid treatment volume, greater treatment time, and second treatments were permitted).

Follow-up: n = 144 at 6 months, 76 at 12 months (mean and range not stated)

Conflict of interest: Study was supported and funded by Insightec Ltd (manufacturer)</td>
<td>Number of patients analysed: 149 at 3 months
Symptom severity (assessed using the UFSQoL self-assessment questionnaire 100-point scale, measuring effect of treatment on leiomyoma-related symptoms)
<table>
<tr><th>10-point improvement in baseline SSS score</th><th>All patients</th><th>Original treatment (more restrictive protocol)</th><th>Modified treatment (less restrictive, including greater NPV)</th></tr>
<tr><td>3 months</td><td>79% (118/149)</td><td>76% (69/91)</td><td>85% (49/58)</td></tr>
<tr><td>6 months</td><td>79% (114/114)</td><td>74% (65/88)</td><td>88% (49/56)</td></tr>
<tr><td>12 months</td><td>78% (59/76)</td><td>72% (40/55)</td><td>91% (19/21)</td></tr>
</table>
The odds of a 10-point improvement at 12 months after treatment was 2.8 in those with an NPV of 30% or greater compared with those with an NPV < 30% (p < 0.038)

Non-perfused volume (assessed by MR imaging immediately post-operatively)
<table>
<tr><th></th><th>Original treatment</th><th>Modified treatment</th></tr>
<tr><td>NPV</td><td>59.4 ml (range 0 – 349.3)</td><td>131.6 ml (range 0 – 352.1)</td></tr>
<tr><td>NPV ratio*</td><td>16.6% (n = 88)</td><td>25.8% (n = 44)</td></tr>
</table>
* p < 0.001

Additional treatments

Within 12 months, 37% (32/87) of the original protocol group had sought alternative treatment.

Within 12 months, 28% (8/29) of the modified protocol group had sought alternative treatment.

(assuming treatment failure in those lost to follow-up)</td>
<td>Adverse events

No serious adverse events were reported.

290 adverse events were reported in total (mean 1.8 per patient):

– 13% of original treatment group reported no adverse events

– 25% of modified treatment group reported no adverse events (p = 0.06)

Pain or discomfort was the most common adverse event, reported in 54% of original treatment group and 47% of modified treatment group.

2 important adverse events reported in original treatment group:

– parasthesia at cannulation site which resolved within 6 weeks

– mild sonification-related leg pain which resolved within 2 days</td>
<td>Included in table 2 of original overview.

Patient overlap with Stewart et al, 2007.

Follow-up issues:
• At 6 and 12 months after the procedure, patients returned for clinical evaluation and MRI.
• 6% (10/160) of patients were lost to follow-up at 12 months.

Study design issues:
• Symptom severity was assessed using an eight-item section of a uterine fibroid symptom and quality of life (UFSQOL) questionnaire.

Study population issues:
• A modified treatment protocol was used for the last 64 patients treated. This was less restrictive and permitted a greater fibroid treatment volume, longer treatment time, and second treatments were permitted within a 14-day period).</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Gorny KR (2011)[5]

Case series

Canada

Recruitment period: 2005 – 9

Study population: women with symptomatic uterine leiomyomas

n = 130

Mean age = 46 years (range 32 – 59)

Patient selection criteria: not reported

Technique: ExAblate 2000 device (InSightec) was used. A typical 3-hour treatment session consisted of 60–100 sonifications. Sonification energies were continually adjusted to achieve treatment temperatures sufficient for tissue ablations. 59 patients had 2 sessions performed on 2 consecutive days.

Follow-up: 12 months

Conflict of interest/source of funding: one of the authors was a clinical trial investigator for Insightec Ltd (manufacturer).</td>
<td>Number of patients analysed: 130
The prescribed treatment was modified in 3 patients: 1 treatment was interrupted because of equipment problems and in 2 patients, subcutaneous oedema was observed after the first treatment session but had resolved by the time of the second treatment session, at 8 and 12 months, respectively.

Mean NPV ratio immediately after treatment = 45.4% (median 42.7%, range 0.2– 100%)

Additional procedures for continued fibroid-related symptoms within 1 year = 6.2% (7 hysterectomies, 1 endometrial ablation)

Symptom relief
Symptom improvement at 3 months = 85.7% (90/105)
No symptom relief at 3 months = 13.3% (14/105)
Worsening of symptoms at 3 months = 1% (1/105)

Symptom improvement at 6 months = 92.9% (92/99)
No symptom relief at 6 months = 7.1% (7/99)

Symptom improvement at 12 months = 87.6% (78/89)
No symptom relief at 6 months =12.4% (11/89)

<table>
<tr><th></th><th colspan="3">Follow-up</th></tr>
<tr><td>Degree of symptom relief</td><td>3 months n = 63</td><td>6 months n = 74</td><td>12 months n = 70</td></tr>
<tr><td>Insignificant</td><td>1 (1.6%)</td><td>2 (2.7%)</td><td>1 (1.4%)</td></tr>
<tr><td>Moderate</td><td>8 (12.7%)</td><td>11 (14.9%)</td><td>6 (8.6%)</td></tr>
<tr><td>Considerable</td><td>18 (28.6%)</td><td>14 (18.9%)</td><td>12 (17.1%)</td></tr>
<tr><td>Excellent</td><td>36 (57.1%)</td><td>47 (63.5%)</td><td>51 (72.9%)</td></tr>
</table>
There was no statistically significant correlation between tumour appearance on T2-weighted imaging and 12-month outcomes.</td>
<td>Complications

• Mild abdominal oedema = 8.5% (11/130)
• Subcutaneous fat oedema = 6.2% (8/130)
• Subcutaneous fat and abdominal muscle oedema = 1.5% (2/130)
• Subcutaneous fat oedema and skin erythema = 0.8% (1/130)
• Lower back discomfort = 3.8% (5/130) (resolved at 12 months)
• Deep vein thrombosis = 0.8% (1/130) (treated with anticoagulation therapy)</td>
<td>Follow-up issues:
• An additional 14 patients completed treatment but denied use of their data for research purposes. Six patients were excluded because the prescribed treatment was not completed (3 patients could not tolerate the prone position and 1 could not tolerate the pain).
• Patients were interviewed by phone at 3-, 6- and 12 month intervals after treatment.

Study design issues:
• Retrospective study.
• Data on symptom relief were self-reported.
• There was no validated symptom questionnaire.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kim HS (2011)[6]

Case series

USA

Recruitment period: not reported

Study population: pre- or perimenopausal women with symptomatic uterine fibroids

n = 40 (51 fibroids)

Mean age: 46 years

Patient selection criteria: age at least 18 years. Exclusion criteria included positive pregnancy test result and the desire to become pregnant after treatment, uterine size larger than 24 weeks' gestation, or with skin scar in the area of the expected ultrasound beam path.

Technique: ExAblate 2000 (InSightec, Israel) system used.

Follow-up: 3 years

Conflict of interest/source of funding: supported in part by InSightec grant.</td>
<td>Number of patients analysed: 40

Symptoms (transformed symptom severity scale [0–100] with lower scores indicating better relief of symptoms)
<table>
<tr><th>Time</th><th>Mean score (95% CI)</th><th>Mean change (95% CI)</th></tr>
<tr><td>baseline</td><td>64.8 (59.1 to 70.6)</td><td></td></tr>
<tr><td>3 months</td><td>35.3 (29.3 to 41.3)</td><td>-29.5 (-37.8 to -21.3)</td></tr>
<tr><td>6 months</td><td>32.2 (26.3 to 38.2)</td><td>-32.6 (-40.9 to -24.3)</td></tr>
<tr><td>1 year</td><td>40.5 (32.5 to 48.7)</td><td>-24.3 (-34.2 to -14.3)</td></tr>
<tr><td>2 years</td><td>18.0 (8.0 to 28.1)</td><td>-46.8 (-58.4 to -35.2)</td></tr>
<tr><td>3 years</td><td>17.0 (8.9 to 25.1)</td><td>-47.8 (-57.7 to -37.9, p < 0.001)</td></tr>
</table>
Health-related quality of life (transformed scores [0–100] with higher scores indicating better quality of life)
<table>
<tr><th>Time</th><th>Mean score (95% CI)</th><th>Mean change (95% CI)</th></tr>
<tr><td>baseline</td><td>44.1 (37.7 to 50.6)</td><td></td></tr>
<tr><td>3 months</td><td>68.8 (62.1 to 75.6)</td><td>24.6 (15.4 to 34.1)</td></tr>
<tr><td>6 months</td><td>68.6 (61.9 to 75.4)</td><td>24.5 (15.2 to 33.9)</td></tr>
<tr><td>1 year</td><td>68.7 (59.6 to 77.9)</td><td>24.6 (13.4 to 35.8)</td></tr>
<tr><td>2 years</td><td>86.1 (74.8 to 97.5)</td><td>42.0 (28.9 to 51.2)</td></tr>
<tr><td>3 years</td><td>83.9 (74.5 to 93.3)</td><td>39.8 (28.3 to 51.2, p < 0.001)</td></tr>
</table>
</td>
<td>Complications:

There were no long-term minor or major complications related to MRgFUS. Specifically, no chronic skin burns or tissue changes along the path of the ultrasound treatment, or chronic back or leg pain.</td>
<td>Follow-up issues:
• 72.5% (29/40) of patients had completed the follow-up at 3 years. 11 patients were lost to follow-up.

Study design issues:
• Prospective study with consecutive patients.
• The primary endpoint was the assessment of long-term clinical effectiveness, defined by the changes in patient symptoms.
• The Uterine Fibroid Symptom and Quality of Life questionnaires were used, which have been validated.
• Raw scores were converted to a transformed score (range 0–100) for comparison.</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
	Mean reduction in treated fibroid volume at 3 years = 32% (p < 0.001) **Mean reduction in uterus volume at 3 years = 27.7% (p < 0.001)** Within 3 years of MRgFUS, 9 patients received alternative treatments for failed symptom control or recurred symptoms: 2 patients had hysterectomies, 2 patients had myomectomies and 5 patients had uterine artery embolisation. No patient attempted pregnancy.		

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

Study details	Key efficacy findings	Key safety findings	Comments
Rabinovici J (2010)[7] **Case series** USA, Israel, UK, Germany, Japan, Russia and South Korea Recruitment period: not reported Study population: women who conceived after MRgFUS for symptomatic uterine fibroids **n = 51 (54 pregnancies)** Mean age: 37 years (range 28–49) Patient selection criteria: all women who conceived after MRgFUS. Women presented with a variety of initial symptoms for treatment by MRgFUS: 50% had menorrhagia, 38% had abdominal pressure and 38% had infertility (defined as inability to get pregnant for more than 12 months as reported by the patient). 38% of the patients had never been pregnant and 58% had never had a delivery. Technique: ExAblate 2000 (InSightec, Israel) system used. Conflict of interest/source of funding: not reported.	Number of patients analysed: **51 (54 pregnancies)** Mean time to pregnancy = 8 ± 7 months after MRgFUS treatment. **Post-treatment by MRgFUS** 41% (22/54) of pregnancies resulted in deliveries and 20% (11/54) were ongoing at the time of reporting beyond 20 weeks. Elective pregnancy termination = 13% (7/54) Miscarriage = 26% (14/54) Of the miscarriages, 79% occurred by the 10th week of pregnancy, 14% (2/14) occurred at 12–13 weeks and 1 woman had a 2nd trimester loss. Term delivery rate = 93% (14/15) (1 preterm birth occurred at 36 weeks) 64% of women had a vaginal delivery and 36% a Caesarean delivery. No infant met the criteria for low birth weight (< 2.5 kg). Mean NPV after MRgFUS treatment = 117 ml Mean NPV ratio > 40% (range 5.5–100)	**Pregnancy complications:** • Abnormal bleeding = 27% (6/22) • Gestational diabetes = 14% (3/22) • Myoma growth = 9% (2/22) • Placenta praevia = 9% (2/22) 36% (8/22) of women had no antepartum complications. One patient had a breech presentation and an intramural fibroid that obstructed the pelvic outlet. After an elective Caesarean section with myomectomy, the patient bled vaginally and developed hypotension and disseminated intravascular coagulation. She underwent repeat laparotomy without any abnormal surgical findings. The patient then developed adult respiratory distress syndrome and spent 3 days in intensive care. Her second pregnancy was complicated by a placenta praevia.	**Study design issues**: • All sites were required to report pregnancies to the manufacturer of the device as a part of post-approval monitoring by the FDA. • Prospective data from 13 sites in 7 countries. **Study population issues**: • 8 of these pregnancies occurred as part of clinical trials designed for women who had completed their families. • One group of pregnancies (n = 20) were reported from an ongoing study specifically for women trying to conceive.

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

Study details	Key efficacy findings	Key safety findings	Comments
Kim KA (2011)[9] **Case report** Korea Study period: not stated **n = 1** Population: 38 year old woman Indications: Had undergone focused ultrasound therapy for uterine fibroids Technique: MRI-guided focused ultrasound therapy. Follow-up: not reported Conflict of interest: not reported	A NPV ratio of 80% was obtained. 3-month follow-up MRI showed a volume reduction of 36% in the treated myomas (total myoma volume of 80 ml).	**Complication** Two weeks after treatment the woman presented with a palpable vaginal mass. The treated myomas were found to be situated in the vagina with a narrow stalk extending from the uterus. Two weeks after the initial detection of vaginal myoma expulsion, there was no change in the status of the expelled myomas within the vagina. They were therefore removed by hysteroscopic resection without any adverse events. Follow-up MRI at 3 months showed no residual myoma tissue or abnormality in the endometrial lining.	

Abbreviations used: CI, confidence interval; MRgFUS, MRI-guided transcutaneous focused ultrasound; MRI, magnetic resonance imaging; NPV, non-perfused volume; NS, not significant

Study details	Key efficacy findings	Key safety findings	Comments
Leon-Villapalos J (2005)[8] **Case report** UK Study period: not stated **n = 1** Population: 39 year old woman Indications: Had undergone focused ultrasound therapy for uterine fibroids Technique: MRI-guided focused ultrasound therapy. Follow-up: not reported Conflict of interest: not reported	Outcomes measured: no efficacy measures reported (not the aim of the paper).	**Complication** Two weeks after treatment the woman presented with a full thickness burn in the lower abdomen and other areas of partial thickness surrounding the area. The authors noted that the burns were non-sensate, leathery white in appearance, and overlying palpable uterine fibroids. Injuries were treated by elliptical excision of the burned area and direct closure. The burn had extended to the abdominal fascia where the effects of the injury were clearly visible. The woman was discharged 1 day after surgery.	Included in table 2 of original overview. Woman was referred 2 weeks after treatment.

Efficacy

Symptom relief/quality of life

A non-randomised comparative study of 192 patients treated by MRgFUS or abdominal hysterectomy reported improvements in all 8 SF-36 domain scores for both treatment groups, although at 6 months scores were better for patients in the hysterectomy group than the MRgFUS group (significant for 5 of the 8 domains with p values from 0.004 to 0.05)[1].

A case series of 359 patients reported that the symptom severity score at 3 months after MRgFUS was significantly lower from baseline (38 for patients with a non-perfused volume ratio of 20% or less and 32 for patients with a non-perfused volume ratio greater than 20% compared with 62 and 63, respectively)[2].

A case series of 160 patients reported a 10-point improvement in baseline symptom severity score in 76% (69/91) and 72% (40/55) of patients treated by MRgFUS using the original protocol, and in 85% (49/58) and 91% (19/21) of patients treated by a modified protocol at 3- and 12-month follow-up, respectively[4].

A case series of 130 patients reported that 88% (78/89) of patients had symptom relief at 12-month follow-up[5].

A case series of 40 patients reported a mean improvement in symptom severity score of 48 (scale 0–100, $p < 0.001$) and a mean improvement in quality of life score of 40 (scale 0 –100, $p < 0.001$) at 3-year follow-up[6].

Fibroid volume/non-perfused volume ratio

A case series of 287 patients reported a mean non-perfused volume ratio (the sum of the non-perfused volume of all treated fibroids divided by the volume of all uterine fibroids, treated and untreated) of 39% for patients treated between 2003–5 and 54% for patients treated between 2005–6 ($p < 0.001$)[3].

A case series of 80 patients with 147 fibroids treated by MRgFUS reported a mean fibroid shrinkage of 31% at 6 months ($n = 81$, $p < 0.0001$)[6].

A case series of 40 patients reported a mean volume decrease in treated fibroid of 32% at 3-year follow-up ($p < 0.001$)[6].

Re-interventions

A non-randomised comparative study of 192 patients treated by MRgFUS or abdominal hysterectomy reported re-interventions in 4% (4/109) of patients treated by MRgFUS (3 hysterectomies, 1 UAE) at 6-month follow-up[1].

Two case series reported additional treatments in 8% (19/228) and 34% (40/116, assuming treatment failure in those lost to follow-up) of patients, respectively, at 12-months follow-up[3,4]. A case series of 80 patients reported a re-intervention rate of 15% with a median follow-up of 34 months[5]. Two case series of 130 and 80 patients reported that 5% (7/130) and 10% (8/80), respectively, of patients had hysterectomies within 12 months after MRgFUS[5,6].

A case series of 359 patients reported that the probability of undergoing additional fibroid treatment significantly reduced with increasing ablation as indicated by an increased non-perfused volume ratio ($p = 0.012$ at 12 months)[2].

A case series of 40 patients reported that 23% (9/40) received alternative treatments for failed symptom control or symptom recurrence (2 hysterectomies, 2 myomectomies and 5 uterine artery ablations)[6].

Pregnancy outcomes

A case series of 51 women who conceived after MRgFUS reported that 41% (22/54) of pregnancies resulted in deliveries and 20% (11/54) were currently ongoing beyond 20 weeks[7]. 13% (7/54) of pregnancies were electively terminated and miscarriage occurred in 26% (14/54). The mean time to pregnancy was 8 months after MRgFUS treatment.

The term delivery rate was 93% (14/15); 64% of women had a vaginal delivery and 36% a Caesarean delivery. No infant met the criteria for low birth weight.

Safety

Bowel perforation

Bowel perforation following treatment by the procedure was reported in a patient (report submitted to the Food and Drug Administration [FDA] Manufacturer and User Facility Device Experience [MAUDE] database). Surgical management was required, confirming perforations in 3 bowel sites (denominator not reported)[10].

Nerve damage

A non-randomised comparative study including 109 patients treated by MRgFUS reported sciatic nerve palsy in 1 patient after MRgFUS.[1]

Skin burns

There was 1 case report of a full-thickness burn in the lower abdomen and other areas of partial thickness surrounding the area. The injuries were treated by elliptical excision of the burned area and direct closure[8].

A case series of 287 patients reported skin burns in 7% (10/144) of patients treated between 2003–5 compared with 1% (2/143) of patients treated between

2005–6 (p = 0.04). All skin burns resolved within 2 weeks without surgical intervention[3]. A case series of 80 patients reported minor skin burns in 2.5% (2/80) (resolved with topical cream)[6].

Deep vein thrombosis

A case series of 130 patients reported that 1 patient developed deep vein thrombosis, which was treated with anticoagulation therapy[5].

Pain

The non-randomised comparative study of 192 patients treated by MRgFUS or abdominal hysterectomy reported pain in 62% and 95% of patients, respectively after the procedure[1]. A case series of 287 patients reported abdominal pain in 11% (33/287) of patients and lower back or leg pain in 7% (20/287) of patients[3]. A case series of 160 patients reported mild sonification-related leg pain in 1 patient, which resolved within 2 days[4]. A case series of 130 patients reported lower back discomfort in 4% (5/140) of patients[5.] A case series of 80 patients reported mild temporary sciatica in 1 patient (1%)[6].

Other

The case series of 160 patients reported 1 case of paraesthesia at the cannulation site, which resolved within 6 weeks[4].

The case series of 80 patients reported 1 case of endometritis. The authors noted that it was unclear whether incomplete management of a yeast infection immediately before the onset of endometritis led to the endometritis or if it was a procedure-related complication[6].

Spontaneous vaginal expulsion of treated fibroid tissue was reported in a patient in a case report; it required hysteroscopic removal[9].

Validity and generalisability of the studies

- There were no randomised controlled trials.
- In the non-randomised comparative study, women treated by MRgFUS had less severe symptoms than those treated by hysterectomy. They were also more likely to be Caucasian and had a lower mean body mass index[1].
- The natural history of fibroid symptoms without treatment is difficult to predict and some of the symptom improvement reported in studies may not be attributable to the MRgFUS treatment.
- Four studies only included women who did not desire to become pregnant in the future[1,2,3,4].
- After 2004, treatment protocols were modified and fewer restrictions were placed on the use of MRgFUS. This included an increase in the permitted

treatment volume. Some of the studies report on patients treated before and after the change in protocol.

Existing assessments of this procedure

The Australia and New Zealand Horizon Scanning Network (ANZHSN) published a Prioritising Summary Update of MRI-guided high-intensity ultrasound for the non-invasive treatment of uterine fibroids in August 2008[11]. The report concluded that 'The studies included for assessment in this Prioritising Summary update support the effectiveness of MRgFUS in the treatment of uterine fibroids, in terms of fibroid-related symptom improvement after treatment. The incidence of serious adverse events after MRgFUS is low and appears to decrease with increasing physician experience. In addition, MRgFUS is likely to be cost-effective among various treatment options. However, the fact that from 10–37 per cent of patients seek treatment alternatives after MRgFUS indicates the need for further research on this technology.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Magnetic resonance image-guided focused ultrasound for uterine fibroids. NICE interventional procedures guidance 231 (2007). Available from www.nice.org.uk/guidance/IPG231 [current guidance]
- Uterine artery embolisation for fibroids. NICE interventional procedures guidance 367 (2010). Available from www.nice.org.uk/guidance/IPG367
- Laparoscopic techniques for hysterectomy. NICE interventional procedures guidance 239 (2007). Available from www.nice.org.uk/guidance/IPG239
- Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids. NICE interventional procedures guidance 30 (2003). Available from www.nice.org.uk/guidance/IPG30
- Laparoscopic laser myomectomy. NICE interventional procedures guidance 23 (2003). Available from www.nice.org.uk/guidance/IPG23

Clinical guidelines

- Heavy menstrual bleeding. NICE clinical guideline 44 (2007). Available from www.nice.org.uk/guidance/CG44

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr N Hacking, Professor J Moss, Ms E O'Grady, Dr A Pankhania, Dr A Sebastian (British Society of Interventional Radiology), Professor MA Lumsden (Royal College of Obstetricians and Gynaecologists).

- None of the Specialist Advisers have ever performed the procedure.
- Two Specialist Advisers have taken part in patient selection or referred a patient at least once.
- Four Advisers described the procedure as definitely novel and of uncertain safety and efficacy; two considered it to be established practice and no longer new.
- The technology is still evolving.
- Theoretical adverse events include damage to the bladder or bowel.
- Adverse events reported in the literature include skin burns, reversible nerve injury, fibroid migration into the uterine cavity and expulsion or obstruction requiring hospitalisation.
- Theoretical adverse events or safety concerns include bowel and bladder injury, and fertility and pregnancy problems.
- There is uncertainty about subsequent fertility.
- Key efficacy outcomes include quality of life, symptom improvement, freedom from further surgery or treatment, subsequent fertility.
- The benefits of the procedure appear very limited and short lived.
- There is a lack of long-term data.
- There are only 1 or 2 centres in the UK with the equipment to perform this procedure.
- The procedure requires long MRI time (average 2–3 hours).
- Patient selection is important.
- One Adviser thought that the procedure is likely to have a major impact on the NHS, in terms of use of resources and numbers of patients eligible for treatment; three thought it would have a moderate impact and two thought the impact would be minor.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 20 questionnaires to trusts for distribution to patients who had the procedure (or their carers). NICE received 4 completed questionnaires.

The Patient Commentators' views on the procedure were consistent with the published evidence and the opinions of the Specialist Advisers.

Issues for consideration by IPAC

None other than those discussed above.

References

1. Taran FA, Tempany CMC, Regan L et al. (2009) Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas. Ultrasound in Obstetrics and Gynecology 34: 572–8.

2. Stewart EA, Gostout B, Rabinovici J et al. (2007) Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. Obstetrics and Gynecology 110: 279–87.

3. Okada A, Morita Y, Fukunishi H et al. (2009) Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population: impact of the learning curve on patient outcome. Ultrasound in Obstetrics and Gynecology 34: 579–83.

4. Fennessy FM, Tempany CM, McDannold NJ et al. (2007) Uterine leiomyomas: MR Imaging-guided focused ultrasound surgery – results of different treatment protocols. Radiology 243: 885–93.

5. Gorny KR, Woodrum DA, Brown DL et al. (2011) Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. Journal of Vascular and Interventional Radiology 22: 857–64.

6. Kim HS, Baik J-H, Pham LD et al. (2011) MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata: long-term outcomes. Academic Radiology 18: 970–6.

7. Rabinovici J, David M, Fukunishi H et al. (2010) Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertility and Sterility 93: 199–209.

8. Leon-Villapalos J, Kaniorou-Larai M, Dziewulski P. (2005) Full thickness abdominal burn following magnetic resonance guided focused ultrasound therapy. Burns 31: 1054–5.

9. Kim KA, Yoon SW, Yoon BS et al. (2011) Spontaneous vaginal expulsion of uterine myoma after magnetic resonance-guided focused ultrasound surgery. Journal of Minimally Invasive Gynecology 18: 131–4.

10. Food and Drug Administration (FDA). Manufacturer and User Facility Device Experience (MAUDE) database. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=1001500

11. Australia and New Zealand Horizon Scanning Network. MRI-guided high intensity ultrasound for the non-invasive treatment of uterine fibroids. Horizon Scanning Technology Prioritising Summary Update. Adelaide, South Australia, August 2008.

Appendix A: Additional papers on magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Arleo EK, Khilnani NM, Ng A et al. (2007) Features influencing patient selection for fibroid treatment with magnetic resonance-guided focused ultrasound. Journal of Vascular & Interventional Radiology 18: 681–5.	Case series n = 26	A substantial proportion of women were anatomically ineligible, including too much fibroid volume (19%), presence of bowel in the ultrasound beam path (13%), and significant adenomyosis (12%). Overall, 14% of women inquiring about MRgFUS were eligible for it, a percentage that increased when additional institutional review board restrictions were lifted.	Focuses on factors influencing patient selection.
Behera MA, Leong M, Johnson L et al. (2010) Eligibility and accessibility of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of uterine leiomyomas. Fertility and Sterility 94: 1864–8.	Case series n = 27	47% (80/169) of patients were determined clinically eligible for the procedure. Of these, 16% (27/169) were found to be eligible for MRgFUS based on imaging results.	Focuses on eligibility and accessibility of MRgFUS.
Bouwsma EVA, Gorny KR, Hesley GK et al. (2011) Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. Fertility and Sterility 96: e9-e12.	Case report n = 1	Successful pregnancy with full-term vaginal delivery.	Case report.
de Melo FC, Diacoyannis L, Moll A et al. (2009) Reduction by 98% in uterine myoma volume associated with significant symptom relief after peripheral treatment with magnetic resonance imaging-guided focused ultrasound surgery. Journal of Minimally Invasive Gynecology 16: 501–3.	Case report n = 1	MRgFUS treatment only at the periphery of the myoma resulted in a 98% reduction in tumour volume at 8 months posttreatment The patient's symptoms, as assessed using the Uterine Fibroids Symptom and Quality of life (UFS-QOL) questionnaire, were substantially improved at both 6 and 12 months posttreatment	Case report.
Fennessy FM, Kong CY, Tempany CM et al. (2011) Quality-of-life assessment of fibroid treatment options and outcomes. Radiology 259: 785-792.	Non-randomised comparative study n = 197	Quality of life increased after all fibroid treatments. The waiting trade-off method is feasible for assessing the quality-adjusted morbidity of treatment procedures.	The main focus was to obtain ‘utilities’ for uterine fibroids and to measure short-term utilities.
Fukunishi H, Funaki K, Ikuma K et al. (2007) Unsuspected uterine leiomyosarcoma: magnetic resonance imaging findings before and after focused ultrasound surgery. International Journal of Gynecological Cancer 17: 724–8.	Case report n = 1	Uterine leiomyosarcoma, initially diagnosed as leiomyoma on MRI, was disclosed after focused ultrasound surgery. The early stages of uterine leiomyosarcoma are clinically difficult to diagnose; therefore, both careful monitoring during FUS and close follow-up after the procedure are vital.	Case report.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Funaki K, Fukunishi H, Sawada K. (2009) Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. Ultrasound in Obstetrics and Gynecology 34: 584–9.	Case series n = 91 Follow-up = 24 months	Reintervention rate = 15% (12/80)	Larger studies are included.
Funaki K, Sawada K, Maeda F et al. (2007) Subjective effect of magnetic resonance-guided focused ultrasound surgery for uterine fibroids. Journal of Obstetrics & Gynaecology Research 33: 834–9.	Case series n = 69 Follow-up = 6 months	No severe adverse events. 7 patients required alternative treatment after MRgFUS. Mean symptom scores were all reduced after MRgFUS.	A larger, more recent study from the same centre is included.
Funaki K, Fukunishi H, Funaki T et al. (2007) Mid-term outcome of magnetic resonance-guided focused ultrasound surgery for uterine myomas: from six to twelve months after volume reduction. Journal of Minimally Invasive Gynecology 14: 616–21.	Case series n = 35 Follow-up = 12 months	At present, type 3 myomas should be exempted from the application of MRgFUS, because the nonperfused ratio immediately after the procedure was small compared with that in type 1 and type 2 myomas, and the subsequent volume change was unfavourable	A larger, more recent study from the same centre is included.
Funaki K, Fukunishi H, Funaki T et al. (2007) Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. American Journal of Obstetrics & Gynecology 196: 184–6.	Case series n = 63 Follow-up = 6 months	The efficacy of MRgFUS correlates with the signal intensity of T2-weighted magnetic resonance images. Type 1 and type 2 fibroids are suitable candidates for MRgFUS, whereas type 3 fibroids are not	A larger, more recent study from the same centre is included.
Gavrilova-Jordan LP, Rose CH, Traynor KD et al. (2007) Successful term pregnancy following MR-guided focused ultrasound treatment of uterine leiomyoma. Journal of Perinatology 27: 59–61.	Case report n = 1	Successful term pregnancy after MRgFUS, with no complications.	Case report.
Hanstede MM, Tempany CM, Stewart EA. (2007) Focused ultrasound surgery of intramural leiomyomas may facilitate fertility: a case report. Fertility & Sterility 88: 497.	Case report n = 1	MRgFUS changed the configuration of the endometrial cavity, and a subsequent pregnancy resulted in a term delivery.	Case report.
Harding G, Coyne KS, Thompson CL et al. (2008) The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health & Quality of Life Outcomes 6: 99.	Case series n = 102 Follow-up = 6 months	Significant improvements were observed in UFS-QOL Symptom Severity and all Health-Related Quality of Life (HRQL) subscale scores at 6 months ($p < 0.0001$). Significant improvements were noted in all 8 SF-36 subscales.	The study focuses on the responsiveness of UFS-QOL questionnaire.
Hesley GK, Felmlee JP, Gebhart JB et al. (2006) Noninvasive treatment of uterine fibroids: early Mayo Clinic experience with magnetic resonance imaging-guided focused ultrasound. Mayo Clinic Proceedings 81: 936–42.	Case series n = 42 Follow-up = 6 months	40% (17/42) women underwent additional treatments after MRgFUS.	Larger studies are included. *Included in table 2 of original overview.*

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Lanard ZM, McDannold NJ, Fennessy FM et al. (2008) Uterine leiomyomas: MR imaging-guided focused ultrasound surgery-imaging predictors of success. Radiology 249: 187–94.	Case series n = 66 Follow-up = 12 months	Fibroids with low signal intensity (SI) on pretreatment T2-weighted MR images were more likely to shrink than were ones with high SI. The larger the NPV immediately after treatment, the greater the volume reduction and symptom relief were.	Larger studies are included.
LeBlang SD, Hoctor K, Steinberg FL. (2010) Leiomyoma shrinkage after MRI-guided focused ultrasound treatment: report of 80 patients. American Journal of Roentgenology 194: 274–80.	Case series n = 80 Follow-up = 6 months	The average nonperfused volume ratio was 55%+/-25% immediately after treatment. Six months after treatment, the average volume of treated fibroids had decreased to 112+/-141 cm3 (n = 81) ($p < 0.0001$) with an average volume reduction of 31%+/-28%.	Studies with longer follow-up are included.
Lin Y-H, Leung T-K, Wang H-J et al. (2009) Treatment of uterine fibroids by using magnetic resonance-guided focused ultrasound ablation: The initial experience in Taiwan. Chinese Journal of Radiology 34: 263–71.	Case series n = 3 Follow-up = 3 months	The fibroid volume reduction after 3 months was 30.8% in average, and SSS reduction after 3 months was 30.6%.	Larger studies are included.
Machtinger R, Tempany CM, Kanan Roddy A et al. (2011) Successful MRI-Guided Focused Ultrasound Uterine Fibroid Treatment Despite an Ostomy and Significant Abdominal Wall Scarring. ISRN Obstetrics & Gynecology 962621.	Case report n = 1	Successful MRgFUS in a patient with extensive anterior abdominal wall scars from 2 longitudinal laparotomies, a total colectomy and ileostomy.	Case report.
Mikami K, Murakami T, Okada A et al. (2008) Magnetic resonance imaging-guided focused ultrasound ablation of uterine fibroids: early clinical experience. Radiation Medicine 26: 198–205.	Case series n = 48 Follow-up = 12 months	Treatment was unsuccessful in 33% (16/48) of patients, due to obesity or high signal intensity of the fibroid.	Larger studies are included.
Morita Y, Ito N, Hikida H et al. (2008) Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids - early experience. European Journal of Obstetrics, Gynecology, & Reproductive Biology 139: 199–203.	Case series n = 48 Follow-up = 12 months	4% (2/28) of patients required surgical interventions after MRgFUS. Mean reduction in fibroid volume at 6 months = 33%.	Larger studies are included.
Morita Y, Takeuchi S, Hikida H et al. (2009) Decreasing margins to the uterine serosa as a method for increasing the volume of fibroids ablated with magnetic resonance-guided focused ultrasound surgery. European Journal of Obstetrics, Gynecology, & Reproductive Biology 146: 92–5.	Case series n = 83 Follow-up = 12 months	Reducing the margin between the fibroid treatment area and the uterine serosa, when possible, enables MRgFUS treatment of greater fibroid volume, while maintaining a high safety profile	Studies focuses on the effect of reducing the margin between the fibroid and uterine serosa.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Rabinovici J, Inbar Y, Revel A et al. (2007) Clinical improvement and shrinkage of uterine fibroids after thermal ablation by magnetic resonance-guided focused ultrasound surgery. Ultrasound in Obstetrics & Gynecology 30: 771–7.	Case series n = 35 Follow-up = 6 months	69% (24/35) of 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. 17% (6/35) women underwent hysterectomy during the follow-up period.	Larger studies are included.
Ren XL, Zhou XD, Zhang J et al. (2007) Extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound: imaging and histopathologic evaluation. Journal of Ultrasound in Medicine 26: 201–12.	Case series n = 119 Follow-up = 12 months	82% (51/62) biopsy specimens revealed obvious signs of necrosis under light microscopy. Follow-up images showed absence or reduction of blood supply in the lesions after HIFU ablation. Median reductions in tumor size 12 months = 49%.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Smart OC, Hindley JT, Regan L et al. (2006) Gonadotrophin-releasing hormone and magnetic-resonance-guided ultrasound surgery for uterine leiomyomata. Obstetrics and Gynecology 108: 49–54	Case series n = 49 Follow-up = 12 months	Symptom severity score at 6 months was reduced by 45% compared with that at enrolment and was 48% lower at 12 months compared with enrolment (no absolute numbers given).	Larger studies are included. *Included in table 2 of original overview.*
Smart OC, Hindley JT, Regan L et al. (2006) Magnetic resonance guided focused ultrasound surgery of uterine fibroids. The tissue effects of GnRH agonist pre-treatment. European Journal of Radiology 59: 163–7	Case series n = 50	The use of hormone increased the potential of the procedure	Larger studies are included.
So MJ, Fennessy FM, Zou KH et al. (2006) Does the phase of menstrual cycle affect MR-guided focused ultrasound surgery of uterine leiomyomas? European Journal of Radiology 59: 203–7	Case series n = 58	Menstrual cycle phase does not influence treatment outcomes	Study evaluated phase of menstrual cycle to treatment
Stewart EA, Gedroyc WM, Tempany CM et al. (2003) Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. American Journal of Obstetrics and Gynecology 189: 48–54	Case series n = 55	No major complications Few clinical outcomes were reported	Larger and more recent study included.
Tempany CM, Stewart EA, McDannold N et al. (2003) MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. Radiology 226: 897–905	Case series n = 9	No major complications Few clinical outcomes were reported	Larger and more recent study included.
Yoon SW, Kim KA, Kim SH et al. (2010) Pregnancy and natural delivery following magnetic resonance imaging-guided focused ultrasound surgery of uterine myomas. Yonsei Medical Journal 51: 451–3.	Case report n = 1	Patient conceived naturally 4 months after MRgFUS. At 39 weeks, she gave birth to a healthy baby girl, via a vaginal delivery. There were no complications.	Case report.
Zaher S, Gedroyc WM, Regan L. (2009) Patient suitability for magnetic resonance guided focused ultrasound surgery of uterine fibroids. European Journal of Obstetrics, Gynecology, & Reproductive Biology 143: 98–102.	Case series n = 144	100% of patients interested in MRgFUS were deemed clinically eligible for the procedure and 74% were deemed technically suitable to proceed with treatment.	Focuses on patient suitability.
Zaher S, Lyons D, Regan L. (2010) Uncomplicated term vaginal delivery following magnetic resonance-guided focused ultrasound surgery for uterine fibroids. Biomedical Imaging and Intervention Journal 6: e28.	Case report n = 1	Uncomplicated term vaginal delivery after MRgFUS.	Case report.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Zaher S, Lyons D, Regan L (2011) Successful in vitro fertilization pregnancy following magnetic resonance-guided focused ultrasound surgery for uterine fibroids. Journal of Obstetrics and Gynaecology Research 37: 370-373.	Case report n = 1	IVF pregnancy and delivery after MRgFUS for a symptomatic fibroid.	Case report.
Zhang L, Chen WZ, Liu YJ et al. (2010) Feasibility of magnetic resonance imaging-guided high intensity focused ultrasound therapy for ablating uterine fibroids in patients with bowel lies anterior to uterus. European Journal of Radiology 73: 396–403.	Case series n = 21 Follow-up = 3 months	After the bowel was compressed with a degassed water balloon, MRgFUS treatment is safe and feasible in ablating uterine fibroids in patients with bowel lies anterior to uterus	Larger studies are included.

Appendix B: Related NICE guidance for magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids

Guidance	Recommendations
Interventional procedures	**Uterine artery embolisation for fibroids. NICE interventional procedures guidance 367 (2010)** 1.1 Current evidence on uterine artery embolisation (UAE) for fibroids shows that the procedure is efficacious for symptom relief in the short and medium term for a substantial proportion of patients. There are no major safety concerns. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance and audit. 1.2 During the consent process patients should be informed, in particular, that symptom relief may not be achieved in some women, that symptoms may return and that further procedures may therefore be required. Patients contemplating pregnancy should be informed that the effects of the procedure on fertility and on pregnancy are uncertain. 1.3 Patient selection should be carried out by a multidisciplinary team, including a gynaecologist and an interventional radiologist. 1.4 NICE encourages further research into the effects of UAE compared with other procedures to treat fibroids, particularly for women wishing to maintain or improve their fertility. **Laparoscopic techniques for hysterectomy. NICE interventional procedures guidance 239 (2007)** 1.1 Current evidence on the safety and efficacy of laparoscopic techniques for hysterectomy (including laparoscopically-assisted vaginal hysterectomy [LAVH], laparoscopic hysterectomy [LH], laparoscopic supracervical hysterectomy [LSH] and total laparoscopic hysterectomy [TLH]) appears adequate to support their use, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians should advise women that there is a higher risk of urinary tract injury and of severe bleeding associated with these procedures, in comparison with open surgery.

	1.3 Advanced laparoscopic skills are required for these procedures, and clinicians should undergo special training and mentorship. The Royal College of Obstetricians and Gynaecologists has developed an Advanced Training Skills Module, 'Benign Gynaecological Surgery: Laparoscopy' (www.rcog.org.uk/index.asp?PageID=1951). This would need to be supplemented by further training in order to achieve the skills required for total laparoscopic hysterectomy. **Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids. NICE interventional procedures guidance 30 (2003)** 1.1 Evidence on safety and efficacy outcomes of MR image-guided percutaneous laser ablation of uterine fibroids is insufficient to support its use without special arrangements for consent and for audit or research. Clinicians wishing to undertake MR image-guided percutaneous laser ablation should inform the clinical governance leads in their Trusts. They should ensure that women offered the procedure understand the uncertainty about its safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present. **Laparoscopic laser myomectomy. NICE interventional procedures guidance 23 (2003)** 1.1 Current evidence on the safety and efficacy of laparoscopic laser myomectomy does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake laparoscopic laser myomectomy should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present. 1.2 Clinicians undertaking this procedure should undergo

	training as recommended by the Royal College of Obstetricians and Gynaecologists Working Party on Training in Endoscopic Surgery (www.rcog.org.uk).
Clinical guidelines	**Heavy menstrual bleeding. NICE clinical guideline 44 (2007).** • For women with large fibroids and HMB, and other significant symptoms such as dysmenorrhoea or pressure symptoms, referral for consideration of surgery or uterine artery embolisation (UAE) as first-line treatment can be recommended. • UAE, myomectomy or hysterectomy should be considered in cases of HMB where large fibroids (greater than 3 cm in diameter) are present and bleeding is having a severe impact on a woman's quality of life. • When surgery for fibroid-related HMB is felt necessary then UAE, myomectomy and hysterectomy must all be considered, discussed and documented. • Women should be informed that UAE or myomectomy will potentially allow them to retain their fertility. • UAE is recommended for women with HMB associated with uterine fibroids and who want to retain their uterus and/or avoid surgery. • Prior to scheduling of UAE or myomectomy, the uterus and fibroid(s) should be assessed by ultrasound. If further information about fibroid position, size, number and vascularity is required, MRI should be considered. • If a woman is being treated with gonadotrophin-releasing hormone analogue and UAE is then planned, the gonadotrophin-releasing hormone analogue should be stopped as soon as UAE has been scheduled. *Note: The guideline does not mention MR-image guided transcutaneous focused ultrasound for the treatment of uterine fibroids*

Appendix C: Literature search for magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/10/2010	October, 2010	6
Database of Abstracts of Reviews of Effects – DARE (CRD website)	25/10/2010	NA	6
HTA database (CRD website)	25/10/2010	NA	3
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/10/2010	October, 2010	11
MEDLINE (Ovid)	25/10/2010	1950 to October Week 2 2010	284
MEDLINE In-Process (Ovid)	25/10/2010	October 22, 2010	6
EMBASE (Ovid)	25/10/2010	1980 to 2010 Week 42	522
CINAHL (NLH Search 2.0 or EBSCOhost)	25/10/2010	NA	65
BLIC (Dialog DataStar)	25/10/2010	NA	0

Trial sources searched on 25/10/2010

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched on 25/10/2010

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp Magnetic Resonance Imaging/
2	mri.tw.
3	(therm* adj3 map*).tw.
4	(magnet* adj3 resonanc*).tw.
5	(MR adj3 (guid* or imag*)).tw.
6	or/1-5
7	Ultrasonics/
8	Ultrasonic Therapy/
9	High-Intensity Focused Ultrasound Ablation/
10	sonicat*.tw.
11	(ultras* adj3 (therap* or surger*)).tw.
12	Ultrasonography/
13	ultrasonograph*.tw.
14	soundwave*.tw.
15	(sound adj3 wave*).tw.
16	sound-wave*.tw.
17	(focus* adj3 ultraso*).tw.
18	exablat*.tw.
19	(hifu* or fus*).tw.
20	((ultraso* or tissue* or non?invasiv*) adj3 ablat*).tw.
21	or/7-20
22	leiomyoma/ or leiomyomatosis/
23	Myoma/
24	(leiomyoma* or leiomyomat* or leiomyomatosis* or myoma* or fibromyoma*).tw.
25	((uter* or subseros* or intramural* or submucosal*) adj3 fibroid*).tw.
26	Uterine Neoplasms/us [Ultrasonography]
27	(uter* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*)).tw.
28	or/22-27
29	6 and 21 and 28
30	animals/ not humans/
31	29 not 30