Sonalleve MR-HIFU

Frequently Asked Questions

1	What are the **clinical indications** for Philips Sonalleve MR-HIFU system?	2
2	**How does** the Sonalleve **MR-HIFU** therapy for uterine fibroid **work**?	2
3	**Which fibroids** can be treated, which ones not?	2
4	What **percentage of a fibroid** should be treated, how close to the border should it be treated?	3
5	How is **patient preparation** done, what is the required care after the procedure, and how is the follow-up done?	3
6	Do patients feel **pain** during the procedure?	4
7	How does **necrosis** develop within the fibroid during treatment? How does necrosis develop after treatment? Is it reabsorbed, how, and over what period of time?	4
8	How to **manage the risk** that the targeted fibroid is in fact a **uterine sarcoma**?	4
9	To what extent do patient **symptoms improve** after treatment, especially bleeding?	5
10	What are the known (most common) **complications** of the procedure?	6
11	Does the HIFU procedure **preserve fertility**?	6
12	Is MR-HIFU **cost-effective** relative to hysterectomy?	7
13	What is the rate of **recurrence** in fibroids treated with MRI guided HIFU?	7
14	After this technique will the efficiency of **ovarian hormones** decrease?	7
15	What is **fibroid shrinkage pattern** after treatment with MRI guided HIFU?	7
16	Will there be **infection** caused as a result of HIFU as the dead tissue is left within the body.	8
17	What is **volumetric ablation** and what are its advantages?	8
18	How MRI guided HIFU does in **comparison** with other fibroid **treatment methods**?	9

PHILIPS

sense and simplicity

1 What are the clinical indications for Philips Sonalleve MR-HIFU system?

Sonalleve is indicated for ablation of uterine tissue as a treatment for symptomatic uterine leiomyomas in pre- or peri-menopausal women who desire a uterine sparing treatment. It is also indicated for ablation of adenomyosis tissue and pain palliation for bone metastases.

2 How does the Sonalleve MR-HIFU therapy for uterine fibroid work?

Magnetic Resonance Imaging guided High Intensity Focused Ultrasound (MR-HIFU) is a non-invasive therapy technique. Focused ultrasound waves are used to heat and coagulate tissue deep inside the body without damaging surrounding tissue. During HIFU treatment, the ultrasound energy beam penetrates through the skin and soft tissue, causing localized high temperatures in the focus area, leaving the skin and intermediate tissue unharmed. The targeted area for ablation is referred to as a treatment cell. Large fibroid volumes are ablated by placing multiple treatment cells in the desired target area, and targeting them one by one.

MR-HIFU combines HIFU therapy with magnetic resonance (MR) guidance, enabling accurate treatment targeting and simultaneous temperature monitoring. With MR guidance, 3D anatomical images provide the reference data for treatment planning, while real-time temperature monitoring images are used to follow the ablation process.

Through real-time feedback from the temperature monitoring images, it is possible to apply a controlled thermal dose to each targeted treatment cell. A typical targeted ablation volume or treatment cell is heated uniformly to 60 - 65 degrees C to insure tissue necrosis. With the application of temperature monitoring and real-time feedback algorithms, the system will adjust the duration of heating to assure that areas with slower heating rates (due to perfusion or tissue heterogeneity in the beam path) receive a longer duration, whereas tissues that heats more rapidly will receive less.

3 Which fibroids can be treated, which ones not?

Nearly all types of fibroids can be treated provided they are accessible to the HIFU beam without intervening bowel. Subserosal, intramural, and submucosal fibroids can be treated routinely. Subserosal fibroids can be treated up to a margin of 1.5 cm from serosal surface. If the patient does not desire for future pregnancies, submucosal fibroids can be treated up to the endometrial surface. Pedunculated fibroids with thin stalk sizes should be avoided.

As MR is used to plan the treatments, MR characteristics have been examined to determine which fibroids respond better to HIFU treatment. Lénárd et. al. showed that fibroids with low signal intensity on pre-treatment T2-weighted images (dark fibroids) were more likely to shrink than ones with high signal intensity (bright fibroids).

In 2007, Funaki and colleagues coined a typing system whereby the signal intensity of the fibroid on T2-weighted imaging was roughly correlated to the responsiveness of fibroids to MR-HIFU therapy. Funaki typing of fibroids is based on the average intensity measured over the fibroid as compared to the average intensity of the skeletal tissue and the myometrium (Funaki 2007).

Following their initial report, Funaki et al showed a correlation between the reintervention rate and the fibroid type. Fibroids that appear to be hyperintense on T2-weighted imaging (Type 3) tend to be highly perfused fibroids, which can be difficult to ablate due to the rapid cooling of the more perfused tissues (Funaki 2009). Unfortunately, the typing system is not full-proof in that fibroids are heterogeneous and cannot be categorized exclusively by the average signal intensity described in Funaki's classification system.

Recently, Kim and colleagues applied dynamic contrast material-enhanced (DCE) MR imaging to refine their understanding of the relationship between perfusion of the fibroid and treatment outcomes. Their results showed a significant negative correlation between the K^{trans} value taken at baseline and the resulting non-perfused volume achieved post-treatment (Kim 2012).

Due to fibroid tissue heterogeneity and patient-specific physiological differences in the near field, it is expected that methods for determining fibroid type prior to MR-HIFU therapy will require consideration of additional factors like DCE-MR. Thus, a combination of anatomical findings and MR image characteristics should be used to determine whether MR-HIFU is the best treatment option for given patient.

There are sometimes practical aspects that could limit an MR-HIFU therapy. Depending on the patient characteristics, deeper fibroids may be difficult to treat with MR-HIFU. The geometrical focus of the transducer is 12 cm and 14 cm from the transducer surface in the earlier hardware release and V2 systems, respectively. For the two systems, the distance from the skin to the center of the fibroid should be approximately 8 cm (earlier hardware release) and 10 cm (V2) to facilitate the treatment. If a patient has a very thick subcutaneous fat layer or a very posterior fibroid, reaching the full fibroid volume for treatment could require advanced patient positioning techniques (Zaher 2009).
Also, large scars from former pelvic operations should be handled with care if they are in the ultrasound beam path. Ultrasound energy should not be passed through fresh and/or extensive scars, as it could lead to local tissue heating. These structures may be avoided through patient positioning to alter the beam path, using the beam shaping feature in the MR-HIFU software, or placing a protective covering over the scar tissue (Yoon 2011). Finally, all contraindications (e.g. pacemakers) for an MRI examination also apply in MR-HIFU therapy.

4 What percentage of a fibroid should be treated, how close to the border should it be treated?

Numerous MR-HIFU studies have investigated the correlation between the percentage of treated fibroid volume and outcomes. The percentage of treated fibroid volume is measured using contrast-enhanced imaging immediately post-treatment and defined as the non-perfused volume (NPV) as a percentage of the total fibroid volume (%NPV, or simply "NPV"). For the best outcomes, as much of the fibroid as possible should be ablated (LeBlang 2010, Fennessy 2007). A minimum NPV of 60% produced significantly more sustained symptom relief over 24 month study length (Stewart 2007, Fennessy 2007).

Initial MR-HIFU studies limited the allowed fibroid treatment volume to 33%, as regulatory bodies had concerns for patient safety with a new technology (Hindley 2004). Since those early studies, the US FDA raised the limit in 2007 to 50% (Stewart 2007, Fenessey 2007) and in 2009, they removed the limit all together (LeBlang 2010). Currently, there is no limit on the percentage of the fibroid that can be treated with MR-HIFU.

Studies are underway to evaluate the potential for additional improvements in symptom relief and durability in lieu of the expanded treatment guidelines. Physicians currently aim to relieve the patient's most acute symptoms, which may mean targeting a single fibroid over others and/or compromising the total treatment volume. Since the outcomes data from Gorny et al. showed the correlation of treatment volume to symptom relief at 12-months follow-up, the current recommendation is to plan a treatment volume of at least 50-60% of the total fibroid volume.

5 How is patient preparation done, what is the required care after the procedure, and how is the follow-up done?

Prior to treatment day, the patient is asked to depilate/shave the pelvic skin area. This should be done one to three days prior to treatment. No creams are allowed on the patient skin after depilation/shaving. In addition, patients are requested to fast for 12 hours prior to treatment.

On treatment day, an intravenous catheter is inserted to deliver medication such as mild sedation and MR contrast media (post treatment). In addition, a Foley catheter is introduced to control the bladder volume. Patient body temperature is measured. In the MR suite, the patient is asked to lie face down on the HIFU patient table. A semi-flexible RF coil is positioned around the patient's body. The patient is given a stop button and instructed on its usage. In some cases, filling the bladder and/or rectum is needed in order to manipulate the anatomical location of the uterus.

After treatment, the patient is moved to a recovery area and vital signs are monitored for few hours to assess the effects of treatment and sedation. If no adverse side-effects are noted, the patient is typically sent home the same day with pain medication prescription and instructions to use as needed. The patient is monitored via follow-up calls or visits at 6, and 12 months either by the gynecologist, nurse or the treating radiologist. At 6 and 12 months the patient should be followed up by the interventional radiologist who performed the procedure. These patient procedures are well-documented in numerous studies (Hindley 2004, Stewart 2007, Taran 2009).

6 Do patients feel pain during the procedure?

Although mostly mild, discomfort and some pain are the most common side effects of the MR-HIFU procedure. Positional pain arising from sustained prone positioning on the MR table during therapy is the most commonly reported discomfort. Pain may also arise from the HIFU beam during treatment, especially when targeting cells near the capsule of the fibroid. Fibroid tissue itself is not innervated. Some patients report stimulation of sciatic and other nerves due to interaction of the ultrasound energy and nerve tissue. Monitoring during the therapy and consistent communication with the patient are critical to assure that no permanent damage is incurred.

The coagulation of myoma tissue with MR-HIFU-controlled heating is immediate. Initially, there was some concern that in the week(s) following MR-HIFU treatment patients may experience pain comparable to the pains associated with Uterine Artery Embolization syndrome. Fortunately, this is not the case for MR-HIFU and has only been reported in a very limited number of cases where feeding vessels of the fibroid have been targeted.

7 How does necrosis develop within the fibroid during treatment? How does necrosis develop after treatment? Is it reabsorbed, how, and over what period of time?

As with most thermal ablation techniques, HIFU ablation is a coagulative necrosis process. The coagulation process has been confirmed with histology studies in treat-and-resect patients after hysterectomy (Tempany 2003, Venkatesan 2012). Coagulation occurs within the timeframe of the HIFU treatment and can be clearly observed immediately post-treatment on MR imaging (Hindley 2004, McDonnald 2006). In addition, local edema around the ablation zones can be observed. The edema can cause pressure rises within the fibroid thereby increasing the eventual necrosis volume of fibroid (Hindley 2004, McDonnald 2006). In addition, if larger feeder vessels are ablated, the eventual necrosis zone may be extended to those infracted areas feed by the vessel (de Melo 2009). The edema subsides over days to weeks, leaving a non-vascular necrosed zone, followed by overall shrinkage of the fibroid and symptom relief (Stewart 2007, Fenessey 2007, Rabinovici 2007, Lénárd 2008). Typical of tissue injury response, the necrotic zone passes through an inflammation response in the short term, then a phase when cellular debris is re-absorbed, and finally a fibrosis phase.

8 How to manage the risk that the targeted fibroid is in fact a uterine sarcoma?

The prevalence of malignant transformation of a leomyoma is very rare at less than 0.5% (Baggish 1974, Seki 1992). In postmenopausal women, the increase in size of the fibroid is a reliable sign of malignant transformation, whereas in pre- or peri-menopausal women rapid growth is not directly correlated to an increased risk of malignancy (Parker 1994). Abnormal leiomyoma identified on MRI findings should be further analyzed and as with myomectomy and UAE, the presence of malignancies should be excluded before MR-HIFU treatment. Since MRI is required as a part of patient screening for MR-HIFU, sarcoma prior to uterine fibroid treatment is more likely to be found than in the cases of myomectomy as these patients are often treated based solely on ultrasound findings. In the extremely rare case that the diagnosis of sarcoma is missed, the subsequent risks are thought to be similar to risks in myomectomy or UAE treated patients.

9 To what extent do patient symptoms improve after treatment, especially bleeding?

Below is a summary of the larger MR-HIFU studies. In the majority of these studies, the Uterine Fibroids Symptoms – Quality of Life (UFS-QOL) questionnaire was used as the outcome measure. This validated questionnaire was also used extensively in UAE studies and provides a measure to quantify all fibroid symptoms including bleeding, bulk effects, and urinary symptoms. The measure for symptom qualification is known as the Symptom Severity Score (SSS). In addition to the SSS, the UFS-QOL provides scores in 6 other areas including Concern, Activities, Energy/mood, Control, Self-consciousness, and Sexual Function. When larger treatment volumes were allowed by regulatory bodies, outcomes as measured by symptom severity scores improved. The table below shows the progressive improvement in outcomes following the expanded treatment guidelines.

Author	Year	Study Size	Results
Hindley et. al.	2004	n = 109 MR-HIFU n = 83 hysterectomy	• Achieved a 10-point or greater reduction in SSS at 6 month / 12 month follow-up: - HIFU: 70.6% / 38.5% - Hysterectomy: Not reported / Not reported • 21% of those treated by HIFU needed additional surgical treatment, and 4% underwent a repeat HIFU by 12 months • Serious adverse events - HIFU: 9 patients (8%), total of 10 SAEs - Hysterectomy: 22%: 8 patients (10%), total of 10 SAEs
Stewart et. al.	2007	n = 359	• Symptom improvement was significantly better when a higher volume percentage of the uterine fibroids were treated with HIFU • Sustained symptom relief was shown throughout the study period of 24 months
Fennessy et. al.	2007	n = 96 standard protocol n = 64 modified protocol	• Significant decrease in SSS (>10 points) at 12 months: - Standard protocol: 73% - Modified protocol: 91% • Adverse effects were less common for patients undergoing the modified protocol, although the difference was not statistically significant (P=0.06) • Chose alternative treatment: - Standard protocol: 37% - Modified protocol: 28%
Taran et al.	2009	n = 109 MR-HIFU n = 83 hysterectomy	• Number of adverse events was lower in the MR-HIFU group • Recovery was faster in the MR-HIFU group • Patients in the MR-HIFU group had steady improvement in all parameters throughout the 6-month follow-up period

10 What are the known (most common) complications of the procedure?

In general, MR-HIFU is regarded to be a safe method for the treatment of uterine fibroids. Discomfort and pain are the most common side effects of MR-HIFU treatment of uterine fibroids and are considered minor. The number of serious adverse effects (SAEs) is low and has been shown to decrease with the experience of the operator (Stewart 2007, Okada 2009, Fennessy 2007). As more and more studies have been performed with MR-HIFU, mitigations have been implemented to reduce side effects and avoid SAEs overall.

Side-effects of uterine therapy include not only the possible effects during therapy, but also the recovery time from the intervention. MR-HIFU recovery time is short in comparison to other uterine fibroid therapies. In contrast to hysterectomy where a typical full recovery time is 6-8 weeks, the majority of patients treated with MR-HIFU return to normal activity and/or work in 1-2 days post-treatment. Treatment-related fatigue and backache are possible, yet they typically require only over-the-counter pain medication (Hesley 2006). Procedures can routinely take up to 3 hours, and in some cases the entire procedure has been reported to last up to about 5 hours (Tempany 2003). Long treatment times increase the likelihood of discomfort and subsequent pain. Less common minor complications include diarrhea in three of the 42 patients in Hesley and colleagues 2006 study and nausea, both presumed to be related to post-treatment opioids (Hesley 2006).

The most serious, but uncommon complications include sustained leg and buttock pain and skin burns. Hindley et al. (2004) reported the first sustained leg and buttock pain were this event was linked to the heating of the sciatic nerve. Despite initial concern and patient discomfort, according to MR neurography and electromyography there was no intrinsic nerve damage caused. This case lead to a change in operator practices. In all reported cases, these symptoms have resolved.

Although infrequent, skin burns have occurred through the course of the use of MR-HIFU. Mild skin burns have been report by several groups (Stewart 2003, Stewart 2006, Rabinovici 2007, Mikami 2008, Morita 2008, Zhang 2008, Okada 2009, Taran 2009). Most of the cases were mild first degree burns that were often caused by imperfect hair removal or air bubbles trapped between the gel pad and skin of the patient.

The majority of the reported burns occurred in the early phases of the technology. Globally, over 9000 women have now been treated using MRI-guided HIFU. In addition, with the application of Philips Sonalleve multi-plane MR temperature monitoring and careful monitoring of the near-field temperature images during therapy, these types of burns can be avoided.

11 Does the HIFU procedure preserve fertility?

To understand the relationship between HIFU and fertility, it is first important to look at the literature on the effect of uterine fibroids and fertility. In some cases, fibroids are known to negatively impact a patient's ability to conceive (Stovall 1998), as well as increase her chances of obstetric complications if she is able to conceive (Klatsky 2008). Fibroids may be the cause of infertility and it is thought that the location of the fibroid within the uterus is the most important factor in terms of the effect on fertility (Casini 2006).

A systematic review of fibroids in infertility was performed in 2001 and again in 2009. In these studies the authors looked at fertility outcomes of patients with fibroids in various locations as compared to patients without fibroids. The authors found that subserosal fibroids had no effect on fertility outcomes, while intramural fibroids appear to negatively impact fertility and lead to increased pregnancy loss and submucosal fibroids impact both implantation and pregnancy rates. Despite these associations, only in the case of submucosal fibroids is there statistically significant evidence for improved pregnancy outcomes with myomectomy. Conclusive data for all types of fibroids on the impact of myomectomy, considered the standard of care for this patient population, is not yet available (Pritts 2009). As myomectomy aims to treat the fibroid impacting fertility, there have been correlations made to a similar approach with MR-HIFU, yet this requires further study.

Currently there is insufficient evidence to make formal recommendations on fertility and MR-HIFU. There have been eight case reports published on pregnancy following MR-HIFU (Hanstede 2007, Gavrilova-Jordan 2007, Morita 2007, Zaher 2010, Yoon 2010, Zaher 2011, Bouwsma 2011, Kim 2011). As these are single cases and while the results are promising, they cannot be translated to proven evidence.

A larger retrospective study was published by Rabinovici et al., who reported data on 54 pregnancies in 51 women after MR-HIFU treatment of uterine leiomyomas. Live births occurred in 41% of pregnancies, with a 28% spontaneous abortion rate, an 11% rate of elective pregnancy termination, and 11 (20%) ongoing pregnancies beyond 20 gestational weeks. The mean birth weight was 3.3 kg, and the vaginal delivery rate was 64%. The authors of this study conclude that preliminary pregnancy experience after MR-HIFU is encouraging, with a high rate of delivered and ongoing pregnancies.

12 Is MR-HIFU cost-effective relative to hysterectomy?

Two studies have examined the cost-benefit of MR-HIFU relative to the other uterine fibroids therapies: hysterectomy, UAE, myomectomy, and medication. O'Sullivan et. al. reported that MR-HIFU is in the range of currently accepted criteria for cost-effectiveness based on QALYs (Quality Adjusted Life Year) and cost per QALYs, along with hysterectomy and UAE (2009). The QALY is measure of disease burden and factors in both the quality and length of life. Based in the United Kingdom, Zowall et. al., in their analysis, also concluded that a treatment strategy for symptomatic uterine fibroids starting with MR-HIFU is likely to be cost-effective. This analysis was performed in comparison to the other treatment options, including hysterectomy. While direct costs may be a key concern, the overall burden of a recurrent and chronic disease like uterine fibroids must be considered. This is a particular concern where hysterectomy is not considered a suitable treatment option for the patient. In a 2011 study, the authors analyzed the overall societal burden of uterine fibroids in the United States market, taking into account all of the treatment options as well as the number of patients who are unlikely to seek treatment due to its side effects(Cardozo 2011). The study showed that obstetrics' complications where a significant contributor to the cost burden of the disease. The authors also concluded that costs associated with lost-work hours may account for the largest portion of the societal burden of uterine fibroids.

13 What is the rate of recurrence in fibroids treated with MRI guided HIFU?

The rate of recurrence in fibroids treated with MRI guided HIFU has been assessed up to 24-months post-therapy and is less than or comparable to other uterus preserving fibroid treatment procedures for results observed in up to 24 months. The recurrence rate has been reported to be 7.4% at 12 months (Gorny 2011) and at 14% for type I/2 fibroids at 24 months, while 21.7% for type 3 fibroids (Funaki 2009). 5-year follow-up data is still being captured. 5-year cumulative recurrence rate has been reported to be 32% for uterine artery embolization and 5.7-33% with myomectomy.

14 After this technique will the efficiency of ovarian hormones decrease?

When performing HIFU, ovaries should be avoided in the ultrasound beam path to safeguard the ovaries. In addition, any temperature change is also monitored in real time during the procedure.

15 What is fibroid shrinkage pattern after treatment with MRI guided HIFU?

Fibroid continues to shrink for one year after ablation. However, most of the shrinkage happens within first six months. The percentage of fibroid shrinkage from baseline is highly dependent on the level of ablation achieved during the treatment, as shown in the below figure from LeBlang and colleagues (LeBlang 2010).

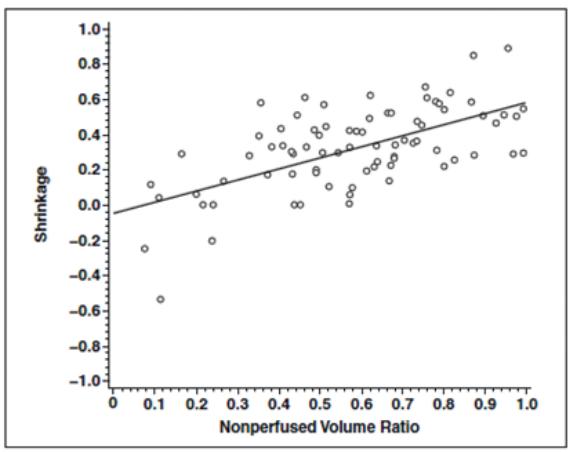

Figure 1: Graph shows relation between non-perfused volume ratio immediately after MRI-guided focused ultrasound treatment and leiomyoma shrinkage 6 months after treatment. Shrinkage is calculated as percentage change in volume of treated leiomyomas from treatment. Line represents results of regression analysis ($p<0.0001$) (LeBlang 2010)

16 Will there be infection caused as a result of HIFU as the dead tissue is left within the body.

Endometrium is not breached during the treatment and the necrosed area remains in the intact fibroid sac and thus separate from the external environment. Although fever has been reported in 5-6% of cases, infection has not been reported in the necrosed areas.

17 What is volumetric ablation and what are its advantages?

At the outset of the technology's introduction in 2004, MRI-guided HIFU systems used point by point ablation method which allowed ultrasound to be focused on a small area where the heated volume was equivalent to the size of a grain of rice. Large volume heating and ablation was done in series and required longer time.

Introduced in 2009, the volumetric ablation technique of Philips Sonalleve allows larger volume heating by moving the point of the ultrasound beam focus in concentric circles that range from 4-16 mm in diameter (Kohler 2009). In 2011 Kim and colleagues were able to correlate increased efficiency of the treatment with increased treatment cell size (Kim 2011). As an extension of this approach, the authors have explored techniques for treatment cell placement to allow for effective MR-HIFU therapy of large volumes which has led to a further enhancement of treatment speed and efficiency. In a recent report, the group from Samsung Medical Center reported treatment speed of 110.6 ml/h ± 36.1 with Sonalleve and the application of a one-layer treatment strategy, as compared to previous reported average treatment speed range of 19.8-42.4 ml/h with point by point ablation (Kim 2012).

18 How MRI guided HIFU does in comparison with other fibroid treatment methods?

Different fibroid treatment methodologies have been compared in the following table.

Treatment Factors	MR-HIFU	Uterine Artery Embolization	Myomectomy (abdominal & laparoscopic)	Hysterectomy (abdominal & laparoscopic)
Prospective Patient Population	• Suitable for most patients with symptomatic (including multiple and medium to large fibroids) • Women wishing to preserve their uterus and may/may not be family complete	• Women with fibroids that are not subserous, submucosal or pedunculated • Minimally invasive, more rapid recovery than surgery • Women who wish to preserve their uterus but are not interested in future fertility	• Symptomatic intramural and subserosal uterine fibroids • Patients who want to become pregnant and who do not have contraindications for surgery	• Patient has failed prior minimally invasive therapy • Patient has completed childbearing and has significant symptoms, multiple tumors, and desires definitive symptom relief • Acute hemorrhage (intraoperative conversion during myomectomy)
Hospital Stay	• Outpatient procedure, no hospital stay	• 1 day	• 2-5 days (laparoscopic) (Palomba 2007) • 3-5 days (abdominal)	• 0-2 days for laparoscopic, 1-5 days for full abdominal hysterectomy (Hehenkamp 2005, Mara 2008)
Disadvantages or Risks	• Limits on types and location of fibroids that can be accessed. • Minor risks of abdominal pain (11-12%), transient lower leg or back pain (6-8%), vaginal discharge or bleeding (8%), fever (5-6%) or skin burns (1-7%) (Okada 2009)	• Possible surgical risks of infection and bleeding.	• Surgical risks and perioperative morbidity. Laparoscopic myomectomy complication rates of 9% minor and 2% major complications (Burke 2011). Post-operative adhesion rate of 35.6% (Dubuisson 1998).	• Surgical risks and perioperative morbidity. Major, permanent operation with possible adverse events including hot flashes, weight gain, depression, diminished sexual interest and anxiety • (Farquhar 2006, Carlson 1994)
Return to Normal Activity	• 1-3 days (Taran 2009)	• 10-14 days (Pinto 2003; FIBROID Registry, 2005)	• 2.9 ± 1.8 weeks (laparoscopic) • 3.7 ± 2.9 weeks (abdominal) (Holzer 2006)	• 2-5 weeks (Taran 2009; Pinto, 2003)
Future Fertility	• Insufficient data to date, Multiple reported cases in addition to 54 pregnancies in 51 women. 64% vaginal delivery, 36% cesarean delivery (Rabinovici 2010)	• Not recommended. 12% risk of placental abnormalities (Laughlin 2011). Risk of ovarian failure, amenorrhea reported in <15% (Parker 2007)	• Yes, although risks shown in pregnancy post-procedure (Dubuisson 1998)	• No
Recurrence Rate*	• 7.4% at 12 months (Gorny 2011). 14% at 24 months for type 1 or 2 fibroids, 21.7% at 24 months for type 3 fibroids (Funaki 2009)	• 2-year recurrence rate of 10% (Marret 2003) • 5-year cumulative recurrence rate 32% (Moss 2011)	• 3-year recurrence rate of 21.79% (Rossetti 2001) • 5-year cumulative recurrence rate 5.7-33% (Fauconnier 2000; Burke 2011)	• Definitive treatment

* Reported studies on UAE and myomectomy provide only 2, 3 or 5-year data, whereas only 12 and 24 month data exists for MR-HIFU at this time.

References

- Baggish MS. Mesenchymal tumors of the uterus. Clin Obstet Gynecol. 1974;17:51Y88.
- Behera MA, Leong M, Johnson L, Brown H. 2009. Eligibility and accessibility of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of uterine leiomyomas. Fertil Steril. 2009 Nov 18.
- Bouwsma EV, Gorny KR, Hesley GK, Jensen JR, Peterson LG, Stewart EA. Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. Fertil Steril. 2011 Jul;96(1):e9-e12.
- Burke, Charles, et. al., "ACR Appropriateness Criteria on Treatment of Uterine Leiomyomas," J Am Coll Radiol, 8 (2011): 228-334.
- Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. American Journal of Obstetrics & Gynecology. 206(3): 211.
- Carlson, Karen, et al., "The Maine Women's Health Study: Outcomes of Hysterectomy," Obstet Gynecol, 83 (1994):556-565.
- Casini ML, Rossi, F, Agostini, R, Unfer, V. Effects of the position of fibroids on fertility. Gynecological Endocrinology 2006;22(2):106-09.
- De Melo FC, Diacoyannis L, Moll A, Tovar-Moll F. 2009. Reduction by 98% in uterine myoma volume associated with significant symptom relief after peripheral treatment with magnetic resonance imaging-guided focused ultrasound surgery . J Minim Invasive Gynecol. Jul-Aug;16(4):501-3.
- Dubuisson, Jean-Bernard, et al., "Second Look After Laparoscopic Myomectomy," Human Reprod 1998;13(8):2102-2106.
- Elizabeth A. Pritts, William H. Parker, David L. Olive. Fibroids and infertility: an updated systematic review of the evidence. Fertility and Sterility. 2009; 91:4;1215-1223
- Enholm JK, Kohler MO, Quesson B, Mougenot C, Moonen CTW, Sokka SD. Improved Volumetric MR-HIFU Ablation by Robust Binary Feedback Control. IEEE Transactions on Biomedical Engineering. 57(1): 103-113.
- Fauconnier, Arnaud, et al. "Recurrence of Leiomyomata after Myomectomy," Human Reprod Update, 6.6 (2000):595-602.
- Farquhar, CM, "A prospective study of 3 Years of Outcomes After Hysterectomy with and without oophorectomy," Am J Obstet Gynecol, 194 (2006):711-717.
- Fennessy FM, Tempany CM, McDannold NJ, So MJ, Hesley G, Gostout B, Kim HS, Holland GA, Sarti DA, Hynynen K, Jolesz FA, and Stewart EA. 2007. Uterine leiomyomas: MR imaging guided focused ultrasound surgery--results of different treatment protocols. Radiology. 243(3): 885-893.
- Funaki, K, et. al., "Clinical outcomes of magnetic resonance-guided focused Ultrasound surgery for uterine myomas: 24-month follow-up," Ultrasound Obstet Gynecology,34 (2009): 584–589.
- Funaki K, Fukunushi H, Funaki T, and Kawakami C. 2007. Mid-term outcome of magnetic resonance guided focused ultrasound surgery for uterine myomas: From six to twelve months after volume reduction. J Minim Invasive Gynecol. 14(5):616-621.
- Funaki K, Fukunushi H, Funaki T, Sawada K, Kaji Y, and Maruo T. 2007. Magnetic resonance guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted MR images. Am J Obstet Gynecol. 196(2):184.e1-6.
- Funaki K, Fukunushi H, Sawada K. 2009. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. Ultrasound Obstet Gynecol. 34(5):584-589.
- Gavrilova-Jordan LP, Rose CH, Traynor KD, Brost BC, Gostout BS. Successful term pregnancy following MR-guided focused ultrasound treatment of uterine leiomyoma. J Perinatol 2007;27:59–61.
- Gorny, Krzysztof, et. al., "Magnetic Resonance–guided Focused Ultrasound of Uterine Leiomyomas: Review of a 12-month Outcome of 130 Clinical Patients," J Vasc Interv Radiol 2011
- Gorny, Krzysztof, et. al., Magnetic Resonance–guided Focused Ultrasound of Uterine Leiomyomas: Review of a 12-month Outcome of 130 Clinical Patients. J Vasc Interv Radiol 2011.
- Hanstede MM, Tempany CM, and Stewart EA. 2007. Focused ultrasound surgery of intramural leiomyomas may facilitate fertility: a case report. Fertil. Steril. 88(2): 497.
- Hehenkamp, Wouter, et al. "Uterine Artery Embolization versus Hysterectomy in the Treatment of Symptomatic Uterine Fibroids (EMMY trial): Peri-and postprocedural Results from a Randomized Controlled Trial," Am J Obstet Gynecol, 193 (2005):1618-1629.
- Hesley GK, Felmlee JP, Gebhart JB, Dunagan KT, Gorny KR, Kesler JB, Brandt KR, Glantz JN, and Gostout, B.S. 2006. Noninvasive treatment of uterine fibroids: early Mayo Clinic experience with magnetic resonance imaging-guided focused ultrasound. Mayo Clin. Proc. 81(7): 936-942.
- Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynynen K, et al. 2004. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. AJR Am J Roentgenol. 183(6): 1713-9.
- Holzer A. et. al., "Laparoscopic versus open myomectomy: A Double-Blind Study to Evaluate Postoperative Pain," Anesth Analg, 2006;102:1408-4.
- Kim YS, Keserci B, Partanen A, Rhim H, Lim HK, Park MJ, Kohler MO. 2011. Volumetric MR-HIFU ablation of uterine fibroids: Role of treatment cell size in the improvement of energy efficiency. Eur Journal of Radiology. 2011 Sept 27 [Epub ahead of print].
- Kim YS, Kim JH, Rhim H, Lim HK, Keserci B, Bae DS, Kim BG, Lee JW, Kim TJ, Choi CH. 2012. Volumetric MR-guided high-intensity focused ultrasound ablation with a one-layer strategy to treat large uterine fibroids: initial clinical outcomes. Radiology. 2012 May;263(2):600-9. Epub 2012 Mar 8.

- Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. AJOG 2008;198(4);357-66.
- Kohler MO, Mougenot C, Quesson B, Enholm J, Le Bail B, Laurent C, Moonen CTW, Ehnholm GJ. 2009. Volumetric HIFU ablation under 3D guidance of rapid MRI thermometry. Med Phys.36(8): 3521-3535.
- Laughlin, Shanon, et al., "Uterine Leiomyomas: Individualizing the Approach to a Heterogenous Condition," Obstet Gynecol, 117.2 (2011): 396-403.
- LeBlang SD, Hoctor KM and Steinberg FL. 2010. Leiomyoma Shrinkage After MRI-Guided Focused Ultrasound Treatment: Report of 80 Patients. AJR 2010; 194:274-280.
- Lénárd ZM, McDanold NJ, Fennessy FM, Stewart EA, Jolesz FA, Hynynen K, and Tempany CM 2008.Uterine leiomyomas: MR imaging-guided focused ultrasound surgery – imaging predictors of success. Radiology. 249(1):187-194.
- Leon-Villapalos J, Kaniorou-Larai M, and Dziewulski P. 2005. Full thickness abdominal burn following magnetic resonance guided focused ultrasound therapy. Burns. 31(8):1054-1055.
- Mara, Michal, et al. "Midterm Clinical and First Reproductive Results of a Randomized Controlled Trial Comparing Uterine Fibroid Embolization and Myomectomy," Cardiovasc Intervent Radiol 2008;31:73-85.
- MAUDE Adverse event report, available online: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=780599.
- McDannold N., Tempany C.M., Fennessy F.M., So M.J., Rybicki FJ, Stewart EA, Jolesz FA, Hynynen K. Uterine leiomyomas: MR imaging-based thermometry and thermal dosimetry during focused ultrasound thermal ablation. 2006. Radiology. 240(1):263-72.
- Morita Y, Takeuchi S, Hikida H, Ohashi H, and Ito N. 2009. Decreasing margins to the uterine serosa as a method for increasing the volume of fibroids ablated with magnetic resonance-guided focused ultrasound surgery. Eur J Obstet Gynecol Reprod Biol. 146:92-95.
- Morita Y, Ito N, Ohashi H. Pregnancy following MR-guided focused ultrasound surgery for a uterine fibroid. Int J Gynaecol Obstet 2007;99: 56–7.
- Moss et al. "Randomised Comparison of Uterine Artery Embolisation (UAE) with Surgical Treatment in Patients with Symptomatic Uterine Fibroids (REST trial): 5-year Results," BJOG (2011), E-pub ahead of print.
- Okada A, et. al., "Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population," Obstetrics and Gynecology 34 (2009): 579–83.
- Okada A, Morita Y, Fukunishi H, Takeichi K, Murakami T. 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 Obstet Gynecol. 34(5):579-83.
- O'Sullivan AK, Thompson D, Chu P, Lee DW, Stewart EA, and Weinstein MC. 2009. Cost effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids. Int J Technol Assess Health Care. 25(1):14-25.
- Palomba, S. et. al., "A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: short-term outcomes," Fertility and Sterility, 88, 4 (October 2007): 942-951.
- Parker, WH, "Uterine myomas: management," Fertility Sterility, 88.2 (2007): 255-271.
- Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83:414Y418.
- Pilatou MC, Stewart EA, Maier SE, Fennessy FM, Hynynen K, Tempany CMC., and McDannold N. 2009. MRI-based thermal dosimetry and diffusion-weighted imaging of MRI-guided focused ultrasound thermal ablation of uterine fibroids. J Magn Reson Imag. 29:404-411.
- Pinto et al. "Uterine Artery Embolization versus Abdominal Hysterectomy for Treatment – A Prospective, Randomized, and Controlled Clinical Trial," Radiology, 226 (2003):425-431.
- Rabinovici, Jaron, et. al., "Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids," Fertility and Sterility, 93.1 (January 2010): 199-209.
- Rabinovici J, Inbar Y, Revel A, Zalel Y, Gomori JM, Itzchak Y, Schiff E, and Yagel S. 2007. Clinical improvement and shrinkage of uterine fibroids after thermal ablation by magnetic resonance guided focused ultrasound surgery. Ultrasound Obstet Gynecol. 30(5):771-777.
- Rabinovici J, David M, Fukunushi H, Morita Y, Gostout BS, Stewart EA, MRgFUS Study Group. 2010. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids Fertil Steril. Jan;93(1):199-209. Epub 2008 Nov 14.
- Salman T, and Davis C, "Uterine Fibroids, Management and Effect on Fertility," Curr Opinion Obstetrics and Gynecology, 22 (2010): 295-303.
- Sang-Wook Yoon, Seok Ju Seong, Sang-Geun Jung, Sun Young Lee, Hye Sun Jun, and Jong Tae Lee. Mitigation of Abdominal Scars during MR-guided Focused Ultrasound Treatment of Uterine Leiomyomas with the Use of an Energy-blocking Scar Patch. J Vasc Interv Radiol 2011.
- Seki K, Hoshihara T, Nagata I. Leiomyoscarcoma of the uterus: ultrasonography and serum lactate dehydronase level. Gynecol Obstet Invest 1992; 33: 114-8.
- Spies JB, Coyne K, Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. 2002. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet. Gynecol. 99(2):290-300.

- Spies JB, Myers ER, Worthington-Kirsch R, Mulgund J, Goodwin S, Mauro M, FIBROID Registry investigators. 2005. The fibroid registry: symptom and quality-of-life status 1 year after therapy. Obstet. Gynecol. 106(6):1309-1318.
- Stewart EA, Gedroyc WM, Tempany CM, Quade BJ, Inbar Y, Ehrenstein T, Shushan A, Hindley JT, Goldin RD, David M, Sklair M, and Rabinovici J. 2003. Focused ultrasound treatment of uterine fibroid tumors: Safety and feasibility of a non-invasive thermoablative technique. Am J Obstet Gynecol. 189(1): 48-54.
- Stewart EA, Rabinovici J, Tempany CMC, Inbar Y, Regan L, Gastout B, Hesley G, Kim HS, Hengst S, and Gedroye WM 2006. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 85:22-29.
- Stewart EA, Gostout B, Rabinovici J, Kim HS, Regan L, and Tempany C.M. 2007. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. Obstet Gynecol. 110(2 Pt 1): 279-287.
- Stovall DW, Parrish SB, Van Voorhis BJ, Hahn SJ, Sparks AE, Syrop CH. Uterine leiomyomas reduce the efficacy of assisted reproduction cycles: results of a matched follow-up study. Hum Reprod 1998;13:192-7.
- Suzanne D. LeBlang, Katherine Hoctor, Fred L. Steinberg. Leiomyoma Shrinkage After MRI-Guided Focused Ultrasound Treatment: Report of 80 Patients AJR:194, January 2010.
- Taran FA, et. al., "Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas," Ultrasound Obstet Gynecol, 34 (2009): 572–578.
- Taran FA, Tempany CM, Regan L, Inbar Y, Revel A, Stewart EA, and MRgFUS group. 2009. Magnetic resonance-guided focused ultrasound (MRgFUS) compared with abdominal hysterectomy for treatment of uterine leiomyomas. Ultrasound Obstet Gynecol. 34(5):572-578.
- Tempany CM, Stewart EA, McDannold NJ, Quade BJ, Jolesz FA and Hynynen KH. 2003. MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. Radiology, 226(3):897-905.
- "The FIBROID Registry: Report of Structure, Methods and Initial Results," AHRQ Publication No. 05(06)-RG008, www.ahrq.gov/research/fibroid/.
- Venkatesan AM, Partanen A, Pulanic TK, Dreher MR, Fischer J, Zurawin RK, Muthupillai R, Sokka S, Nieminen HJ, Sinaii N, Merino M, Wood BJ, Stratton P. 2012. Magnetic Resonance Imaging–guided Volumetric Ablation of Symptomatic Leiomyomata: Correlation of Imaging with Histology. Journal of Vascular and Interventional Radiology, 23(6):786-794.
- Viswanathan M, Hartmann K, McKoy N, Stuart G, Rankins N, Thieda P, Lux LJ. and Lohr KN. 2007. Management of uterine fibroids: an update of the evidence. Evid Rep Technol Assess (Full Rep). 154:1-122.
- Yoon SW, Kim KA, , Hwang YY, Lee C, Cha SH, Lee SY . 2008. Magnetic Resonance Imaging-guided Focused Ultrasound Surgery for Uterine Fibroids: Initial Experience in Korea. Korean J of Obstetrics & Gynecology, 2008, 51(9):1-5.
- Yoon SW, Kim KA, Kim SH, Ha DH, Lee C, Lee SY, Jung SG, Kim SJ. 2010. Pregnancy and Natural Delivery Following Magnetic Resonance Imaging-Guided Focused Ultrasound Surgery of Uterine Myomas. Yonsei Medical Journal 51(3):451-453.
- Zaher S, Regan L. Uncomplicated term vaginal delivery following magnetic resonance-guided focused ultrasound surgery for uterine fibroids. Biomed Imaging Interv J 2010; 6(2):e28.
- Zaher S, Gedroyc WM, Regan L. Patient suitability for magnetic resonance guided focused ultrasound surgery of uterine fibroids. European Journal of Obstetrics & Gynecology and Reproductive Biology 143 (2009) 98–102.
- Zhang L, Chen WZ, Liu YJ, Hu X, Zhou K, Chen L- Peng S, Zhu H, Zou HL, Bai J, and Wang ZB. 2008. Feasibility of magnetic resonance imaging-guided high intensity focused ultrasound therapy for ablating uterine fibroids in patients with bowel lies anterior to uterus. Eur J Radiol. In press.
- Zowall H, Cairns JA, Brewer C, Lamping DL, Gedroyc WM, Regan L. 2008. Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids. BJOG. 115(5):653-62.

HIFU is not approved for use in Canada and the USA for bone or adenomyosis.

Please visit www.philips.com/sonalleve

PHILIPS

Philips Healthcare is part of Royal Philips Electronics

www.philips.com/healthcare
healthcare@philips.com

Printed in The Netherlands
4522 962 89571 * OCT 2012