Clinical and Technical Aspects of MR-Guided High Intensity Focused Ultrasound for Treatment of Symptomatic Uterine Fibroids

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Abstract

Keywords

- ▶ fibroid
- ▶ MR-guided high intensity focused ultrasound
- ▶ HIFU
- ▶ interventional radiology

Although many women undergo hysterectomy for treatment of uterine fibroids, there are more options than ever before for fibroid treatment. A combination of objective criteria, including clinical parameters, anatomic factors, fibroid characteristics, and patient desires influence the choice of optimal therapeutic modality for a woman with symptomatic uterine fibroids. Magnetic resonance imaging-guided high intensity focused ultrasound (MR-HIFU) is the only noninvasive treatment option for women with symptomatic uterine fibroids unresponsive to medical treatment. The procedure has been shown to be safe and effective. MR-HIFU couples the three-dimensional multiplanar anatomic imaging and thermal monitoring capability of MR imaging with the therapeutic thermal-based coagulative necrosis mechanism of HIFU to safely and effectively ablate limited volume classical fibroids. In the author's experience, a multidisciplinary fibroid clinic facilitates a unified approach between gynecologists, radiologists, and others to individualize the most appropriate fibroid treatment options for each woman. This article describes the MR-HIFU technique and outcomes, as well as patient selection and treatment assessment.

Objectives: Upon completion of this article, the reader will be able to identify the current role of MR-HIFU, and the benefits of a multidisciplinary fibroid clinic for ensuring the most optimal treatment of women with symptomatic fibroids and the indications for the procedure, contraindications, risks, and the technique of performing the procedure.

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Uterine fibroids are a common cause of symptomatic vaginal bleeding and pelvic pain and pressure in women of reproductive and perimenopausal ages. Fibroids are benign tumors that arise from the uterine wall and are subclassified histologically as classical, hypercellular, and degenerated. Fibroid growth is often hormonally sensitive and linked to varying estrogen levels; fibroids tend to grow during high estrogen states, such as pregnancy, and to involute in low estrogen states such as postmenopause. Classical fibroids are composed of uterine smooth muscle cells and fibrous tissue. Hypercellular fibroids contain dense smooth muscle cells

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with a relative paucity of intervening fibrin or collagen. Degeneration can occur as a result of rapid growth during hyperestrogenic states such as pregnancy or as a result of outgrowth of vascular supply.

Clinically, symptoms are related to either bulk effect resulting in pain and compressive symptoms, or endometrial disruption resulting in vaginal bleeding and infertility. Clinical classification is based on anatomic location given the relationship between location and symptoms. Subserosal, large intramural, and pedunculated fibroids are most likely to cause bulk symptoms, including pain and pressure, as they may displace or abut adjacent structures. Submucosal, intracavitary, and larger intramural fibroids are most likely to cause symptoms related to endometrial disruption. If large enough, some fibroids can cause a combination of symptoms.

Ultrasound (US) performed in a gynecologists or family physicians office is the most commonly used diagnostic study for the evaluation of female pelvic pain or bleeding and is thus the primary modality used to detect uterine fibroids. However, US is operator dependent, and excellent sonography requires expertise. Currently approved two-dimensional (2D) and three-dimensional (3D) grayscale and Doppler transabdominal and endovaginal technology is best able to visualize small and intermediate volume fibroids and their relationship to the endometrium. US has limitations in imaging larger fibroids and characterizing fibroid subtypes, and requires operator expertise to reliably distinguish nonfibroid conditions such as adenomyosis, endometrial polyps, or urethral diverticula. Computed tomography has a limited role in assessing fibroids due to poor tissue contrast even after intravenous contrast injection.

Magnetic resonance imaging (MRI), although more expensive and less available than US, is less operator dependent than US, providing the most reliable and comprehensive imaging of uterine fibroids due to its unparalleled soft tissue contrast, spatial resolution, and multiplanar imaging capability. A combination of T1- and T2-weighted and dynamic gadolinium-enhanced T1-weighted MRI sequences allows evaluation of size and number of uterine fibroids, and uniquely allows characterization of classical, hypercellular, and degenerated fibroids, as well as coincidental conditions such as adenomyosis, endometrial polyps, adnexal lesions, and urethral diverticula.

Conservative medical therapy with nonsteroidal anti-inflammatory drugs, contraceptive steroids, and gonadotropin-releasing hormone (GnRH) agonists is the first line of treatment and may be all that is necessary for the majority of women with symptoms. However, for women with continued or worsening symptoms, interventional or surgical therapies are necessary. These have historically included uterine artery embolization (UAE), myomectomy, and hysterectomy. Despite the excellent clinical outcomes of these procedures, their invasive nature and associated risks and complications are undesirable to a significant subset of women. Thus, there remains significant demand for a noninvasive option for treatment of symptomatic uterine fibroids refractory to medical therapy.

MRI-guided high intensity focused US (MR-HIFU) is the only noninvasive interventional treatment option for women

with symptomatic uterine fibroids unresponsive to medical treatment. The procedure is an outpatient therapy performed under conscious sedation, which generally allows patients to return to normal activity levels within 24 hours. Reports to date have demonstrated the safety, feasibility, and efficacy of the procedure with sustained fibroid volume reduction and significant subjective symptomatic relief up to 3-year posttreatment.¹⁻¹⁶

Basic Principles of MR-HIFU

MR-HIFU is a thermal ablation treatment modality that uses MRI guidance to precisely deliver high intensity focused US (HIFU) energy to the target fibroid tissue, resulting in tissue heating and cell death. This is achieved by coupling the 2D and 3D anatomic imaging and thermal monitoring capabilities of MRI with the therapeutic capability of a specialized HIFU transducer. Pretreatment multiplanar anatomical MR images are used to visualize the target and adjacent structures so the patient can be appropriately positioned and treatment sonications can be planned. Intraprocedural HIFU beam path visualization and thermal monitoring feedback allow precise control of therapeutic targeting. Immediate posttreatment imaging provides intraprocedural confirmation of the extent of tissue treatment.

The modality has been shown to be effective in the treatment of uterine fibroids. Studies to date have focused on fibroid volume reduction and improvement in subjective symptoms as evaluative outcome parameters. Fibroid volume reduction is based on quantitative analysis of pre- and postprocedure fibroid volume measured on MRI. Patient improvement in subjective symptoms is assessed using a validated symptom questionnaire for patients with uterine fibroids called the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL).¹⁷ The survey is administered before treatment to quantify a baseline symptom score, and then administered at multiple intervals after treatment to evaluate relative changes and quantify symptom relief and other characteristics.

To date, studies assessing the efficacy of MR-HIFU have reported outcomes from 3 months up to 3 years posttreatment.¹⁻¹⁶ These studies have uniformly reported a low complication rate, decrease in fibroid volume, statistically significant improvement in UFS-QOL subjective symptoms, and stability of findings up to 2 to 3 years posttreatment. Data suggest that, with increasing familiarity with the technique and as protocol guidelines become less restrictive, clinical outcomes will continue to improve.^{11,14}

There are three HIFU manufacturers worldwide; one produces an US-guided system (Haifu, Chongching Haifu, Chongching, China), and two produce MRI-guided systems (Sonalleve [Philips Medical Systems, Best, The Netherlands], and ExAblate 2000 and 2100 [Insightec Haifa, Israel]). The ExAblate system is compatible with MRI systems by General Electric Healthcare (Waukesha, WI), and they are the only systems currently approved by the United States Food and Drug Administration (FDA) for the treatment of symptomatic uterine fibroids. In the ExAblate system, the HIFU transducer is embedded within a specially designed table that fits into a

General Electric 1.5 or 3 T gantry and also includes a single channel receiver coil for intraprocedural monitoring. This integrated system, along with system software, enables real-time therapy planning algorithms, thermal dosimetry, and therapy control via the closed loop of MRI.

Patient Selection

Assessment of Patients in a Multidisciplinary Fibroid Clinic

Many factors influence the optimal therapeutic modality for a woman with symptomatic uterine fibroids. Clinical parameters, anatomical details, fibroid character, and patient desires all influence the best treatment option. A multidisciplinary fibroid clinic can optimally unite the gynecologist and interventional radiologist into a single entity for the most efficient and effective treatment of each woman.¹⁸

Any patient presenting with dysfunctional uterine bleeding, pelvic pain, or bulk symptoms should be evaluated with a clinical assessment, physical examination, and imaging. It is beneficial to have each patient fill out an objective symptom questionnaire such as the validated UFS-QOL to quantitatively score bulk and bleeding symptoms. A concurrent US exam demonstrating uterine fibroids prompts pelvic MRI to further delineate the size, location, and character of the fibroid(s). Based on these parameters in conjunction with the clinical assessment, the best alternative amongst the treatment options (alternative therapies, medical, MR-HIFU, UAE, myomectomy, or hysterectomy) may be selected. This decision should incorporate feasibility and prognostic indicators for each therapeutic modality as it pertains to the patient's individual clinical and anatomical details. In consultation with both the gynecologist and interventional radiologist in a unified clinical setting, each woman can be presented with the most appropriate range of options within the same clinical encounter. Appropriate assessment and treatment pathways are more likely to be achieved in this collaborative setting, providing access to all treatment options.

Clinical Contraindications

Clinical contraindications to MR-HIFU include non-MRI compatible implanted metallic devices, the inability to tolerate prolonged prone position for up to 3 hours, unstable medical conditions, coagulopathy or current anticoagulation therapy, pelvic infection, or current pregnancy.

Future Pregnancy

MR-HIFU for uterine fibroids was originally FDA approved only for women who did not desire future pregnancy. However, data demonstrating successful pregnancies and deliveries posttreatment have accumulated,^{19–26} suggesting the relative safety of MR-HIFU in women who desire future pregnancy.

Imaging

Along with patient clinical factors and goals of care, several factors must be considered in determining amenability of

fibroids to treatment with HIFU. Contrast-enhanced MRI of the pelvis is necessary to determine accessibility, time required to treat, and presence of threats to safety before selecting patients for MR-HIFU.

Nonfibroid Uterine Pathology

The identification of unexpected uterine pathology during screening MRI, such as a lesion suspicious for malignancy, is a contraindication to MR-HIFU. Uterine malignancy should be suspected in peri- or postmenopausal women with MRI features uncharacteristic of a fibroid, such as irregular margins or variable signal intensity on all image phases including T1-weighted, T2-weighted, and postcontrast T1-weighted images. These patients should be excluded from MR-HIFU and redirected for biopsy and surgical removal.²⁷

Adenomyosis may often be found at screening MRI in symptomatic women. The use of MR-HIFU is not currently FDA approved for the treatment of adenomyosis. However, it is used for this application outside the United States, and several reports suggest it has the potential to effectively treat adenomyosis.^{9,19,28,29}

Fibroid Location

The anatomic location of the fibroid(s) within the uterus has implications for safe treatment. Intramural, sessile submucosal, and sessile subserosal fibroids are considered safe targets for MR-HIFU. Pedunculated subserosal fibroids have generally been considered contraindicated due to the theoretical risks of subsequent torsion or separation of the treated fibroid from its uterine stalk with shedding into the peritoneal cavity. However, early experience in using a stalk-preserving treatment approach has shown that MR-HIFU has the potential to treat pedunculated fibroids without adverse effect.³⁰

Safe treatment of submucosal pedunculated or intracavitary fibroids has not been definitively demonstrated. It has been suggested that MR-HIFU treatment of an intracavitary fibroid > 3 cm could result in shedding of the treated fibroid into the endometrial cavity where it may be difficult to retrieve via hysteroscopy due to size limitations.³¹ Jung et al have reported HIFU treatment of a 2.5-cm intracavitary fibroid with subsequent spontaneous vaginal expulsion without adverse effect and with good clinical outcome.³²

Fibroid Size and Number

The target fibroid volume must be amenable to treatment within the maximum treatment time of 180 minutes allowed by the FDA. Thus, target fibroid size and number may be a limiting factor to successful treatment. Postmarketing studies to date generally report favorable outcomes treating single fibroids less than 10 cm in size or multiple smaller fibroids.³ However, larger fibroids can potentially be treated during sequential, temporally spaced 3-hour treatment sessions. In addition, pre-MR-HIFU treatment with GnRH agonists has been shown to result in decreased fibroid volume and possible increased ablation efficacy,^{33,34} increasing the potential for successful treatment of fibroids larger than 10 cm with MR-HIFU.

There is no theoretical limit to the number of fibroids treatable by MR-HIFU; the approved procedure time is the limiting factor. The size of each individual fibroid ultimately determines how many fibroids can be treated within the treatment time such that a larger number of smaller fibroids or a smaller number of larger fibroids can be treated in one setting.

Development of newer techniques such as volumetric MR-HIFU may enable treatment of increased size and number of fibroids. A volumetric MR-guided HIFU modality (Sonalleve) has been evaluated for safety, technical feasibility, and histologic and imaging outcomes, but lacks significant efficacy data and is not yet approved by the FDA for noninvestigational use.^{35–38}

Fibroid Composition

The amenability of fibroids to treatment is also dependent on histologic composition, which correlates with appearance on MRI. Classical fibroids are isointense to myometrium on T1-weighted images, hypointense to myometrium on T2-weighted images, and avidly enhance after administration of gadolinium. Hypercellular fibroids are hyperintense to myometrium on T2-weighted images, with a variable avid enhancement pattern after intravenous gadolinium. T2 hyperintense fibroids have been shown to have less effective volume reduction, less subjective symptom improvement, and higher reintervention rates post-MR-HIFU compared with T2 hypointense fibroids.^{8,10,39}

Degenerated fibroids have a wide variety of appearances on MRI with the primary features being increased heterogeneity on all phases and lack of enhancement after gadolinium administration. Degenerated fibroids already contain areas of necrosis and thus have a low chance of further improvement in symptoms after MR-HIFU.⁴⁰ Notably, calcified fibroids cannot be penetrated by the US beam and thus are not amenable to treatment.

Highly vascular fibroids are less amenable to treatment with MR-HIFU due to the “heat sink” phenomenon. Increased blood flow allows faster dissipation of thermal energy away from the target area, resulting in subtherapeutic temperature at the target site.^{8,40} It has been suggested that patients with hypervascular fibroids can be pretreated with a GnRH agonist to reduce vascularity before treatment.^{33,34} However, it may be difficult to determine the extent of fibroid vascularity by MRI; in patients refractory to thermal ablation, hypervascularity should be considered.

Adjacent Structures

Procedural safety is largely dependent on excluding adjacent anatomic structures from the beam pathway. The target fibroid must be a safe distance from the sacral bone surface and the adjacent lumbosacral nerves to prevent nerve damage. To prevent visceral tissue damage, including bowel perforation, the target fibroid must not have intervening bowel loops or ovaries in the sonication path. Patients identified on screening MRI with bowel interpositioned between the target fibroid and the expected path of the ultrasonic beam can undergo maneuvers to shift the structures. During the procedure, the patients' urinary bladder may be empty or filled and may safely be used as sonication window. The

uterus may be optimally positioned by using a variety of maneuvers, including emptying or filling the urinary bladder with saline, or using US gel to distend the rectosigmoid colon. If a clear and safe beam path to the target fibroid cannot be created after repositioning, the procedure cannot be safely performed.

Abdominal cutaneous scars, such as from prior laparotomy or cesarean section, in the pathway of the beam may absorb energy at a higher rate, resulting in skin burns. Abdominal scars can also be manipulated with patient repositioning.

Performing MR-HIFU

Planning and Mapping Phase

Before the procedure, the patient is instructed to shave from the umbilicus to the symphysis pubis to minimize air bubbles entrapped in body or pubic hair. The patient lies prone on the modified MR table over the embedded phased-array HIFU transducer. A gel pad bathed in degassed water and US gel is placed between the patient and the table to achieve acoustic coupling.

Pretreatment T2-weighted MRI of the pelvis is performed to produce an anatomic template for therapeutic planning. At the authors' institution, multiplanar T2-weighted fast recovery fast spin-echo images are obtained. The interventionalist evaluates the images at an operator workstation in the MRI control room. Anatomy of the uterus, fibroids, and adjacent structures such as bowel, ovaries, urinary bladder, and sacrum is delineated. Using system software at the workstation, the radiologist contours the bowel, lumbosacral neural plexus, and symphysis pubis to ensure exclusion of these structures from planned sonications to avoid nontarget thermal injury.

If bowel or bladder is interpositioned between the target fibroid and the expected path of the HIFU beam, maneuvers can be performed to manipulate these structures out of the beam pathway. Manual bowel massage, saline instillation into the urinary bladder, or filling of the vagina or rectum with saline or gel can be performed to achieve ideal anatomic positioning of target structures and avoid adjacent nontarget structures. HIFU can be safely performed through a distended urinary bladder.

The boundaries of the target fibroid(s) are then contoured by the operator on multiplanar MR images. Using this template, the planning software calculates the treatment volume, treatment dose, and number of required HIFU sonications required to completely treat the defined region while minimizing total treatment time.

Therapeutic Phase

After planning a target volume, the therapeutic portion of the procedure begins with delivery of low power test sonications to the target tissue to align the US beam with MRI. Sequential delivery of multiple, user defined, high-energy treatment sonications follows to ablate the entire target volume. The parameters of the HIFU beam can be adjusted to produce a variably ellipsoidal focal point with dimensions of approximately 8 mm in the direction of the beam and 3 mm perpendicular to the beam at a distance of 12 to 17 cm distance from

Figure 1 Intraprocedural MR thermal map (A) gives feedback as to the orientation of the beam (light blue) with its focal point (blue rectangle) and the temperature of the tissue at the focal point represented by green and red color overlays, which correspond to the temperature graph created and (B) for that specific focal point over a given time period. This allows real-time feedback such that sonication parameters can be adjusted accordingly. The darker blue color overlay in (A) represents the tissue already treated by sonications earlier in the procedure. MR, magnetic resonance.

the therapeutic transducer. The tissue at the focal point receives the therapeutic energy of the HIFU beam while the tissue proximal and distal to the focal point within the beam path is spared of the therapeutic-level energy. The targeted tissue is heated to a temperature of 65 to 85°C, irreversibly ablating the tissue via thermal coagulative necrosis. The amount of thermal tissue damage can be modulated by changing US intensity, US frequency, or duration of exposure.⁴¹

Over the course of the procedure, the focal point of the HIFU beam is repositioned many times with a series of point-by-point sonications performed to cover the volume of the target fibroid tissue. Each sonication lasts approximately 10 to 30 seconds followed by a cooling duration of 45 to 120 seconds between sonications to minimize transfer of heat to adjacent nontarget uterine tissue and to prevent skin burns. The planning software calculates the order of successive sonications to maximize therapeutic efficacy and minimize cooling duration such that sonications are not necessarily performed in a contiguous fashion. There is a maximum 3-hour treatment time per session mandated by the FDA due in part to concerns for deep venous thrombosis with longer procedures.

During the procedure, MR thermometry is used to noninvasively measure tissue temperature within and surrounding the target to ensure both adequate dose delivery to the target tissue for complete ablation and preservation of nontarget tissue.^{42–46} This technique uses phase map imaging to detect molecular level changes in vibration due to tissue heating. These changes are translated into a thermal map display and temperature graph of the target and surrounding tissues at specified time intervals as imaging is performed^{47,48} (►Fig. 1). The delivered thermal dose can be measured and the effectiveness of each sonication can be judged in real time, allowing intraprocedural operator adjustment of therapeutic energy and sonication time based on feedback. An MR thermal dosimetry map is produced for correlation of delivered energy dose with desired anatomic target tissue and for correlation with posttreatment contrast-enhanced MRI evaluation (►Fig. 2).

Treatment Evaluation

Once the total sonication dose is delivered to the entire fibroid in the above manner, dynamic T1-weighted spoiled gradient

Figure 2 Coronal T2 MR image (A) immediately after treatment, with blue overlay produced by the system software demonstrating the anatomical region of accumulated thermal dose within the target fibroid after multiple sonications. Coronal T1 postgadolinium MR image 1 month after treatment (B) shows hypoenhancement in the treated fibroid tissue corresponds to the region of accumulated thermal dose in (A), accounting for slight angulation of coronal acquisition in (A). MR, magnetic resonance.

Figure 3 Pretreatment sagittal T1 postgadolinium MR image (A) demonstrated multiple, large, homogeneously enhancing fibroids. The most inferior fibroid and a portion of the superior fibroid were treated with MR-HIFU. Immediate posttreatment sagittal T1 postgadolinium MR image (B) demonstrated a large NPV (> 80% of the original fibroid tissue). Interval, repeat MR-HIFU of the superior fibroid was performed (not shown). One month posttreatment sagittal T1 postgadolinium MR image (C) demonstrated a significant volume reduction in both fibroids. The nonenhancing necrotic tissue within the treated inferior fibroid corresponds to the NPV seen in (B). The nonenhancing necrotic tissue within the more superior fibroid is greater than the NPV in (B) because repeat interval MR-HIFU was performed to treat a larger volume of tissue. MR-HIFU, magnetic resonance imaging-guided high intensity focused ultrasound; NPV, nonperfused volume.

echo images are obtained after intravenous power injection of gadolinium to assess the efficacy of the procedure by determining the extent of lesion ablation. The unenhanced portion of the fibroid represents the nonperfused volume (NPV) and is an important surrogate marker of efficacy. Posttreatment NPV correlates with necrotic tissue and predicts fibroid volume reduction and subjective symptom improvement in addition to correlating with a decreased rate of subsequent intervention requirement.^{5,49} MR-based software calculates the NPV as the ratio of the volume of nonperfused tissue divided by the volume of total pretreatment fibroid tissue based on pretreatment and immediate posttreatment gadolinium-enhanced MRI. Larger NPVs predict larger volume reduction and greater improvement in symptoms compared with smaller NPVs^{39,50} (–Fig. 3).

Conclusion

Uterine fibroids are a common pathologic entity causing many women to seek treatment. MR-HIFU has emerged as the only noninvasive treatment option in patients who have failed conservative and medical therapy. This modality has been shown to be safe, feasible, and effective in reducing symptoms in women with symptomatic fibroids amenable to treatment. This is achieved by coupling the anatomic imaging and thermal monitoring capabilities of MRI with the therapeutic capability of HIFU. The therapy is ideal for a subset of women; however, careful clinical selection is important for safety and good outcomes. A multidisciplinary fibroid clinic can optimally unite the gynecologist and interventional radiologist to provide the most efficient and effective treatment of each woman.

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