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REVIEW

MR-guided high-intensity focused ultrasound treatment of uterine fibroids

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Antonia Wiggermann[1]
Michael Beldoch[1]
Friederike Hoellen[2]
Peter Hunold[1]

[1]Clinic for Radiology and Nuclear Medicine, [2]Department of Obstetrics and Gynecology, University Hospital Schleswig-Holstein, Lübeck, Germany

Abstract: Uterine fibroids are benign, encapsulated uterine tumors, representing the most common reason for hysterectomy in premenopausal women. High-intensity focused ultrasound (HIFU; also known as focused ultrasound surgery) is a noninvasive technique leading to tissue heating in a centered focus, inducing a thermal tissue necrosis. Magnetic resonance-guided HIFU (MR-HIFU; also know as MR-guided focused ultrasound surgery) allows to allocate the uterine fibroids as well as to evaluate whether these are accessible for HIFU treatment. Further advantages are MR-based real-time temperature mapping and immediate evaluation of post-procedure therapeutic success by MR imaging. These advantages minimize the patient risk and make the treatment more effective. MR-HIFU is a uterus conserving, low pain-to-painless, and noninvasive treatment option. Here, we review its medical and economic advance to surgical procedures due to the low complication rates combined with proven symptom relief and the enhancement of the quality of life.

Keywords: high-intensity focused ultrasound, focused ultrasound surgery, uterine fibroids, real-time thermometry

Introduction

Uterine fibroids (UFs) are benign, encapsulated uterine tumors, representing the most common reason for hysterectomy in premenopausal women.[1] As there is scarce incidence of UFs under the age of 25 years, there is an age-related cumulation with a prevalence of 20% at the age of 35 years and a growing prevalence up to 80% at the age of 50 years.[2] Fifty-five percent of all UFs are located within the myometrium (intramural) or submucosal, whereas 40% of UFs are directly located below the uterine serosa. Although UFs are not associated with an increased mortality, UFs are frequently leading to a limited quality of life (QoL) by various symptoms, such as dullness and vesicant dysmenorrhea, especially caused by intramural and subserosal UFs. Other symptoms are pollacisuria, constipation, sacral pain, and anemia due to the chronic prolonged blood loss. These symptoms are due to an expulsion phenomenon depending on the UF tumor size and localization. Intramural UFs are enucleated laparoscopically, UFs exceeding the size of 10 cm in diameter might be enucleated by laparotomy. Medical treatment options include progesterone-receptor-modulators which induce amenorrhea and shrinkage of UFs and show less side effects in comparison to GnRH analogues and proved to be more effective in comparison to gestagen-based contraceptives.[3] Another less invasive treatment option is offered by uterine artery embolization (UAE). Here, the application of microspheres via endovascular

Correspondence: Antonia Wiggermann
Clinic for Radiology and Nuclear Medicine, University Hospital Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, Luebeck 23538, Germany
Email Antonia.Wiggermann@uksh.de

catheterization occludes the UF vessel supply.[4–6] Submucosal UFs are preferably treated by hysteroscopic resection. However, in women who have completed family planning, hysterectomy remains the most commonly used treatment of UFs worldwide.[7,8] In women desiring pregnancy, laparoscopic enucleation of UF is the standard treatment. Especially in this case, uterine-conserving ablation technique is warranted. However until today, ablation techniques and embolization is not recommended in guidelines to women who wish to become pregnant, due to the hypothetical risk of myometrial deterioration and consecutive infertility or obstetrical complications. In 2004, the US Food and Drug Administration approved magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU, synonym: MR-guided focused ultrasound surgery) as an entirely noninvasive approach in the treatment of UFs to reduce UF-related symptoms and UF volume by thermal ablation. Due to its noninvasiveness, this technique is becoming more and more clinically relevant.[9,10] It is a very low-pain to painless procedure with excellent therapeutic efficacy that could be consequently performed on an outpatient basis.[11–15] As MR-HIFU is an uterine-conserving treatment technique, it has a high acceptance in the group of women affected by UF. Due to its efficacy, MR-HIFU has emerged also as a treatment modality for prostate cancer and malignant liver tumors.[16,17] For interventional radiologists, MR-HIFU is an attractive therapeutic option for UF and other pathologies.

HIFU – application methods and physical mechanisms of tissue damage

The main principle of HIFU is to deliver mechanical energy to the tissue by propagating through a solid or liquid medium. Contrary to diagnostic ultrasound probes that diverge ultrasound waves, HIFU probes are spherically curved to focus the ultrasound waves in a center. This means a 100-fold increase in mechanical (ultrasound) energy. The fundamental physical mechanism of HIFU is ultrasound absorption by tissues and its conversion into heat, leading to necrotic foci. These necrotic areas are defined as the so-called nonperfused volume (NPV). HIFU could be applied by sonographic guidance, as well as by magnetic resonance imaging (MRI) guidance. For sonographic-guided HIFU, penetration depth >14 cm and NPV >80% have been reported.[18–20] The NPV as well as the tissue temperature distribution can be detected and quantified by contrast-enhanced MRI. Although the mechanisms are not yet totally understood, necrotic tissue destruction of UFs leads to volume shrinkage and a relief of various clinical symptoms. Reaching high NPVs is the mainstay predictor of therapeutical success in the MR-HIFU treatment of UFs.[21–24] Another nonthermal tissue damaging effect of HIFU is caused by acoustic cavitation. This mechanical process occurs at high acoustic intensities and leads to the vaporization of tissue water and the formation of rapidly expanding microbubbles, which subsequently collapse with the release of shock waves and high-speed liquid jets, leading to tearing forces, which are followed by direct tissue damage.[25–28] Thus, according to the recent US Food and Drug Administration safety criteria, safety margins of 1.5 cm between the treated UF volume and the adjacent peritoneal serosa have to be considered.[24]

Inclusion criteria and limitations for MR-HIFU of UF

UFs ranging from 2 cm to >10 cm in size are basically suitable for MR-HIFU treatment.[29] Scarring of the abdominal wall, eg, after cesarean section or laparatomy, might be the relative contraindications of MR-HIFU as far as it could not be bypassed by the ultrasound beam through dynamic focusing or movement of the HIFU probe.[30] As there is the possibility of nerve damage, close allocation of the treated uterine fibroid next to the lumbar plexus should raise an enhanced level of attention. As the MR-HIFU beam is capable to propagate through tissues to a maximum depth of 14 cm, UFs allocated deeper than 14 cm from the abdominal surface could not be reached. Thus, UFs of a retroflected uterus or in an adipose patient may not be accessible by MR-HIFU. In UFs allocated deeper than the maximum depth, filling the rectum with ultrasound gel might be an appropriate measure to reposition the uterus ventrally and mobilize the UF into the focus of the HIFU beam. As UFs can be relatively large tumors, intermittent cooling of the tissue could be necessary to prevent further damage. The relatively long treatment times of MR-HIFU could here mean a limitation in clinical practice.[31]

HIFU therapy: treatment cells and temperature mapping

Before executing HIFU treatment, a preparatory T2-weighted planning MRI in prone patient position is necessary to allocate the exact anatomical position and the tissue composition of the UF. Here, evaluation of the UF and target volume as well as of the accessibility for the HIFU beam is made. As the target volume is defined, it is then sonicated step by step as a cluster of so-called treatment cells of 4–16 mm in diameter (Figure 1). Due to the oscillatory movements of the ultrasound probe as well as using dynamic focusing of the HIFU beam in outwardly moving, concentric circles make volumetric sonication of

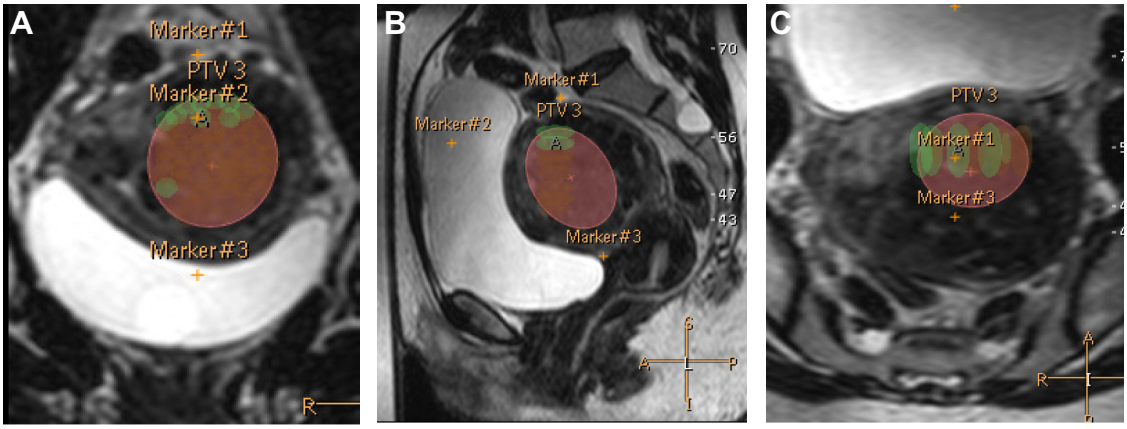

Figure 1 MR-HIFU treatment planning with superimposed MRI in three planes, such as coronal (**A**), sagittal (**B**), and transversal (**C**); pretreatment T2-weighted planning MR images show a uterine fibroid with low signal intensity. Red circles indicate the target volume for HIFU treatment as defined by the borders of the UF with a safety margin; green ellipsoids indicate the anticipated volumes of sonication.
Abbreviations: HIFU, high-intensity focused ultrasound; MR, magnetic resonance; MRI, magnetic resonance imaging; PTV, planned treatment volume.

these predetermined treatment cells feasible. Multiplanar real-time MR thermometry allows efficient monitoring of the ablation temperatures as well as structures at increased risk, especially in large volume UF ablations.[32,33] Thus, energy of the HIFU beam can be adapted at any time during the ablation procedure ensuring an optimal tissue heating while minimizing the patient risk. This makes the treatment more effective and less time consuming.[34,35]

Therapeutic outcome

The most used parameter to evaluate the early therapeutic success is MRI evaluation of the UF necrosis immediately after the MR-HIFU procedure (Figure 2). Here, nonenhancing areas within the UF in contrast-enhanced T1-weighted images correspond with the NPV, which is the fundamental underlying correlation of midterm UF shrinkage. The so-called NPV ratio, determined as the NPV/UF volume, is the most reliable predicting factor for UF volume shrinkage.[11,15,21–24] Using conventional MR-HIFU ablation technique without temperature mapping, very high NPV ratios up to 50% and in some cases >90% are reported.[22,37–39] Here, it has to be critically mentioned that those very high NPV ratios might be due to the lower safety criteria leaving the patients at an increased risk of post-MR-HIFU complications.[21,40] For clinical follow-up and assessment after MR-HIFU, UF symptom severity and health-related QoL questionnaires have been developed. Here, a significant increase in QoL 1 year after MR-HIFU is reported, even if the reduction of UF volume was only 25%.[37,38,40,41]

Advantages for MR-HIFU treatment of UF

As MR-HIFU is a noninvasive, uterus-conserving treatment method, it means an interesting treatment option especially for younger women still desiring pregnancy, pregnancy and healthy deliveries are possible after MR-HIFU treatment of UFs.[42,43] Due to its noninvasiveness, MR-HIFU is significantly more cost effective, and thus, in economic advance compared to more invasive methods, such as UAE and hysterectomy.[4] As surgical approaches are often accompanied

Figure 2 Sagittal T2-weighted MRI for planning purposes (**A**) shows a homogeneously hypointense UF in the anterior wall. Sagittal T1-weighted, fat-saturated and contrast-enhanced MRI immediately (**B**) as well as 1 month (**C**) after the MR-HIFU procedure with a satisfying NPV.
Abbreviations: HIFU, high-intensity focused ultrasound; MR, magnetic resonance; MRI, magnetic resonance imaging; NPV, nonperfused volume; UF, uterine fibroid.

by complications, such as intraoperative hemorrhage, injury of the uterus, and risk of emergency hysterectomy, MR-HIFU is an alternative low-risk treatment.[44] MR-HIFU as well as UAE have lower complication rates and similar therapeutic success in terms of symptom and QoL improvement.[45,46] Thus, MR-HIFU might mean a more complementary therapeutic approach in UF treatment in future. As targeted vessel ablation is feasible with MR-HIFU, this could be an interesting advancement of UF therapy combining the advantages of UAE and MR-HIFU: on demand, three-dimensional real-time reconstruction of the vessel supply on MRI followed by targeted MR-HIFU means a seminal approach in the therapy of UF and other pathologies.[31,32,47]

Complications and contraindications of MR-HIFU

According to the German radiological-gynecological consensus meeting, MR-HIFU treatment of UFs is indicated in patients with UF-associated symptoms. Safe access for the HIFU beam is a prerequisite. In patients with an UF size varying between 3 and 10 cm and an UF number <5, MR-HIFU treatment might be indicated (Table 1).[48] The complication rate of MR-HIFU therapy for UFs has been reported to be significantly lower than after surgical procedures.[49] Pregnancy, suspicion of a uterine malignancy, and acute lower pelvic inflammations do mean an absolute contraindication for MR-HIFU therapy. Relative contraindications are UFs that might not be safely accessible by the ultrasound beam (due to huge abdominal wall scarring or interposed intestine), eg, patients with >5 UFs and UF size >10 cm or <3 cm. Here, decision for HIFU therapy has to be made on a case-by-case basis (Table 2).[30,48] Postinterventional abdominal discomfort, sciatic nerve paresthesia or simply leg pain, and slight skin burns of the abdominal wall are the commonly reported side effects of MR-HIFU treatment (Table 3). Only one case of severe skin burns that needed surgical intervention after MR-HIFU treatment is reported, further underlining the noninvasiveness of this method.[31,48,50–54]

Table 1 Indications for MR-HIFU therapy of UFs

UF-associated symptoms
Safe access window or the ultrasound beam to the UF
UF size 3–10 cm
Number of UFs <5

Note: Data from Beck et al.[48]
Abbreviations: HIFU, high-intensity focused ultrasound; MR, magnetic resonance; UF, uterine fibroid.

Table 2 Contraindications for MR-HIFU treatment of UFs

Suspicion of an uterine malignancy (absolute)
Pregnancy (absolute)
Acute lower pelvic inflammation (absolute)
UF size >10 cm (relative)
UF size <3 cm (relative)
Number of UFs >5 (relative, decision on a case-by-case basis)
UFs not safely accessible by the ultrasound beam (eg, interposed intestine, huge abdominal wall scarring, and dorsal allocation of the UF) (relative)
Pedunculated subserosal UF (relative)
Close allocation of the UF to the os sacrum or UF allocated to the posterior uterine wall (relative)
Contraindications for MRI contrast agents (relative)
General MRI contraindications

Note: Data from Beck et al.[48]
Abbreviations: HIFU, high-intensity focused ultrasound; MR, magnetic resonance; MRI, magnetic resonance imaging; UF, uterine fibroid.

Outlook

As new technical approaches offer new therapeutical perspectives, the application of HIFU is not limited to UF. MR-HIFU technique is an emerging treatment option in prostate and pancreatic cancers as well. Here, especially sonographic-guided HIFU applications have already been well established, whereas MR-HIFU approaches are now upcoming therapeutic advancements.[16,55–57] Especially, targeted vessel ablation by MR-HIFU could mean an interesting approach in curative as well as palliative oncologic treatments.[58] MR-HIFU treatment of breast cancer is now in development as tumor necrosis of up to 100% has been reported.[59,60] Here, thermal-induced changes of vascular permeability for targeted drug delivery by HIFU might offer further interesting therapeutic opportunities.

Conclusion

MR-HIFU means a noninvasive, low pain-to-painless treatment option for UF, which has shown a significant improvement in QoL due to the reduction in UF symptoms.

Table 3 Adverse effects and complications after MR-HIFU therapy of UFs

Pain during the MR-HIFU treatment procedure (slight and only short-termed in most cases)
(Slight) skin burns
(Slight) inflammation of the abdominal subepidermal fat and muscle tissue
Leg paresthesia due to nerve irritation or damage
Deep leg or pelvic vein thrombosis (very rare)
Intestinal perforation (extremely rare)

Note: Data from Beck et al.[48]
Abbreviations: HIFU, high-intensity focused ultrasound; MR, magnetic resonance; UF, uterine fibroid.

As it is an uterus-conserving therapeutic approach, which further is in economic advance of surgical treatment procedures of UF, it should be offered especially to younger women. Relative contraindications for MR-HIFU of UF might be scarring of the abdominal wall, which could not be bypassed by the HIFU beam, as well as an extraordinary high body mass index.

Disclosure

Peter Hunold has received lecture fees from Philips Healthcare. The other authors report no conflicts of interest in this work.

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