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

Antonia Wiggermann¹  
Michael Beldoch¹  
Friederike Hoellen²  
Peter Hunold¹  
¹Clinic for Radiology and Nuclear Medicine, ²Department 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 known 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...
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 as well as by magnetic resonance imaging (MRI) guidance. For interventional radiologists, MR-HIFU is an attractive therapeutic option for UF and other pathologies.

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...
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%.\textsuperscript{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 UF.\textsuperscript{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.\textsuperscript{4} As surgical approaches are often accompanied...
by complications, such as intraoperative hemorrhage, injury of the uterus, and risk of emergency hysterectomy, MR-HIFU is an alternative low-risk treatment.\textsuperscript{44} MR-HIFU as well as UAE have lower complication rates and similar therapeutic success in terms of symptom and QoL improvement.\textsuperscript{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.\textsuperscript{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).\textsuperscript{48} The complication rate of MR-HIFU therapy for UFs has been reported to be significantly lower than after surgical procedures.\textsuperscript{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).\textsuperscript{10,48} 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.\textsuperscript{31,48,50-54}

Table 1 Indications for MR-HIFU therapy of UFs

<table>
<thead>
<tr>
<th>UF-associated symptoms</th>
<th>Safe access window or the ultrasound beam to the UF</th>
<th>UF size 3–10 cm</th>
<th>Number of UFs $&lt;5$</th>
</tr>
</thead>
</table>

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

Table 2 Contraindications for MR-HIFU treatment of UFs

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

Note: Data from Beck et al.\textsuperscript{48}  
Abbreviations: HIFU, high-intensity focused ultrasound; MR, magnetic resonance imaging; UF, uterine fibroid.

Outlook

As new technical approaches offer new therapeutic 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.\textsuperscript{16,55-57} Especially, targeted vessel ablation by MR-HIFU could mean an interesting approach in curative as well as palliative oncologic treatments.\textsuperscript{38} MR-HIFU treatment of breast cancer is now in development as tumor necrosis of up to 100% has been reported.\textsuperscript{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

<table>
<thead>
<tr>
<th>Adverse effects and complications after MR-HIFU therapy of UFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during the MR-HIFU treatment procedure (slight and only short-termed in most cases)</td>
</tr>
<tr>
<td>(Slight) skin burns (Slight) inflammation of the abdominal subependymal fat and muscle tissue</td>
</tr>
<tr>
<td>Leg paresthesia due to nerve irritation or damage</td>
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<tr>
<td>Deep leg or pelvic vein thrombosis (very rare)</td>
</tr>
<tr>
<td>Intestinal perforation (extremely rare)</td>
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</tbody>
</table>

Note: Data from Beck et al.\textsuperscript{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.

References
