Clinical application of high-intensity focused ultrasound ablation for uterine fibroids

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Abstract HIFU (high-intensity focused ultrasound) ablation is an emerging therapeutic modality that induces thermal coagulative necrosis of biological tissues by focusing high-energy ultrasound waves onto one small spot. This technique is at various stages of clinical applications in several organs. However, it has increasingly been used in the treatment of symptomatic uterine fibroids, a common condition affecting women. Since its first clinical use for symptomatic uterine fibroids, this technique has been recognized for safety, satisfactory therapeutic efficacy in symptom control, uterus-preserving ability, radiation-free nature, and because of the fact that it does not require hospitalization. Owing to its numerous benefits, HIFU ablation is currently one of the major therapeutic options for symptomatic uterine fibroids. In this review, several aspects ranging from the physical principle of HIFU to the long-term outcomes are summarized from the perspective of the clinical application for uterine fibroids.

Keywords High-intensity focused ultrasound · Uterine fibroid · Ablation therapy · Clinical application

1 Introduction

High-intensity focused ultrasound (HIFU) ablation is an emerging therapeutic modality that induces thermal coagulative necrosis of biological tissues by focusing high-energy ultrasound waves onto one small spot. When ultrasound energy is absorbed into the biological tissues, it causes vibration or rotation of the tissue molecules and generates frictional heat. When sufficient ultrasound energy is accumulated, the tissue temperature at the focus is elevated within a few seconds to a degree that threatens tissue viability, which is the mechanism of thermal ablation by HIFU [1]. Ultrasound waves can propagate through the human body as long as it is acoustically transparent; therefore, HIFU therapy has an advantage of being completely non-invasive compared with other therapeutic modalities, which explains its increasing use worldwide.

Since its first clinical use for symptomatic uterine fibroids, HIFU ablation has been recognized for safety, satisfactory therapeutic efficacy in symptom control, uterus-preserving ability, and because of the fact that it is a radiation-free technique and does not require hospitalization [2–5]. Owing to numerous benefits, HIFU ablation is currently one of the treatment modalities of choice for symptomatic uterine fibroids. In this review, a spectrum of relevant knowledge ranging from the physical principle of HIFU to its long-term clinical outcomes is summarized from a perspective of clinical application of this technique for uterine fibroids.

2 Principles of HIFU ablation of uterine fibroids

Benign or malignant tumors including uterine fibroids undergo irreversible coagulative necrosis caused by protein denaturation when the tissues receive a thermal dose

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beyond a certain degree (*i.e.*, a lethal thermal dose). In normal biological tissues, the lethal thermal dose is 240 EM (equivalent minutes at 43°C), which means the equivalent amount of heat when a temperature of 43°C is continued for 240 minutes. The thermal dose of 240 EM is achieved instantaneously (*i.e.*, within 1 to 2 seconds) if a temperature of 65°C is used [6, 7]. In other words, HIFU ablation can kill the tumor immediately at a temperature of 65°C or more.

In HIFU ablation of uterine fibroids, the degree of induced heating is influenced by several internal or external factors. The most important and well-known factor is the relative composition of smooth muscle cells and collagen fibers of the uterine fibroids [8]. Smooth muscle cells are mainly composed of water, which has a relatively higher specific heat capacity, while the specific heat capacity of collagen fibers is much lower ($4.2 \text{ C}_p \text{Jg}^{-1} \text{K}^{-1}$ vs. $1.2\text{--}1.3 \text{ C}_p \text{Jg}^{-1} \text{K}^{-1}$) [9]. Therefore, appropriate heating of cellular uterine fibroids with higher water content by HIFU is difficult. On the contrary, uterine fibroids having abundant collagen fiber content are relatively easily heated, as they use lower acoustic energy [10]. The difference in tissue composition can be easily evaluated on T2-weighted magnetic resonance (MR) imaging [11, 12].

Another important influencing factor for heating is the degree of vascularity of the uterine fibroids. According to Penne's bio-heat equation [13], the rise in temperature induced by hyperthermic therapy becomes more difficult as the vascularity of the treated tumor increases. This is because of the so-called "heat-sink phenomenon," in which blood flows at body temperature, which deprives the target tumor tissues of heat. Therefore, it is difficult to elevate the temperature of highly vascularized fibroids, as they require higher acoustic energy to induce appropriate heating.

Similar to diagnostic ultrasonography (US), HIFU is also attenuated in the normal body tissue. For instance, if the subcutaneous fat layer of the abdominal wall is too thick or the target fibroid is located too deep beneath the skin, substantial amount of energy is lost before the acoustic wave reaching the focal spot. Therefore, external factors such as the thickness of the fat layer or the location of the target are also important factors that influence heating [14].

3 Imaging guidance and monitoring

In order to precisely locate the HIFU focus at the intended target as well as to assess the therapeutic responses to HIFU, the role of imaging is extremely important. Therefore, clinical HIFU systems use either US or MR imaging. In US-guided HIFU (US-HIFU), echogenic changes at the

focus caused by tissue water boiling or acoustic cavitation are used to identify the target location. US has advantages of real-time capability and motion insensitivity. Besides, US is capable of exactly predicting HIFU propagation in the body owing to the same physical property used between therapy and imaging. However, US is unable to measure the temperature change, and the image quality deteriorates as the treatment progresses [15].

MR imaging has a great advantage over US in term of real-time temperature measurements (*i.e.*, MR thermometry) which uses the proton resonance frequency shift technique [16]. MR thermometric monitoring is applicable not only at the HIFU focus but also in the surrounding structures; thus, the operator is able to recognize whether thermal responses occur at the target as intended, as well as whether undesirable heating takes place in the vicinity of the target. Based on this real-time temperature information, closed-loop feedback control function is available in MR-guided HIFU (MR-HIFU) systems, in which acoustic power and duration of sonication are adjusted on a real-time basis, resulting in a more spatially and temporally stable heating. However, the time resolution of MR imaging is inferior to that of US (*i.e.*, MR imaging refreshes images every 2 to 3 seconds), and, occasionally, it is affected by the motion of the target or the adjacent bowel loops [17] (Table 1).

4 Patient selection

4.1 Indications and contraindications

HIFU ablation is performed in premenopausal women with symptomatic uterine fibroids. Uterine fibroids up to 10~12 cm in diameter can typically be treated in one session of HIFU ablation; however, the results among different centers differ according to the treatment speed of the HIFU devices used [14, 18, 19]. Contraindications for HIFU include pregnant woman, and women with calcified or predominantly degenerated fibroids [14, 20], and those for MR-HIFU include women with cardiac pacemakers.

There are several relative contraindications that should be considered. As previously mentioned, hypercellularity or hypervascularity of uterine fibroids is an important factor to be considered when determining treatment feasibility. An obese patient with a thick subcutaneous fat of the abdominal wall is also predisposed to poor therapeutic responses. In addition, if a scar caused by a previous surgery is present in the sonication path, close attention should be paid because of the possibility of complications such as skin burn or thermal injury of subcutaneous fat. Because all HIFU devices are limited in their penetration depth, it should be checked whether the fibroid is located within the

Table 1 Comparison between US-HIFU and MR-HIFU

	US-HIFU	MR-HIFU
Temperature measurement during treatment	Not feasible	Feasible
Closed-loop feedback control	Not feasible	Feasible
Tissue contrast	Low	High
Field of view	Narrow	Wide
Imaging of organs other than the uterus	Bad	Good
Real-time imaging capability	High	Low
Susceptibility to motion	None	High
Space	Low	High
Cost	Low	High

US-HIFU: Ultrasonography-guided high-intensity focused ultrasound, MR-HIFU: MR-guided high-intensity focused ultrasound

area treatable by the system used. If there is an interposed small or large bowel loop between the abdominal wall and the uterus, it should be evaluated whether the interposed bowel loop can be avoided or displaced out of the sonication path [14, 20].

4.2 Prediction of therapeutic response (treatment planning)

MR imaging is essential before treatment to assess most of the aforementioned conditions. Previous studies have reported a screening pass rate of only 16–25% in women with symptomatic uterine fibroids who required therapy. Although the rate substantially improved with experience [21], it is still lower than that of other therapeutic modalities for detecting uterine fibroids. Appropriate patient selection based on clinical information and MR imaging findings cannot be overemphasized because it prevents unnecessary treatment, ultimately contributing to improved clinical outcomes. If the therapeutic response is expected to be suboptimal, other therapeutic modalities such as uterine artery embolization are suggested.

The most important as well as best-known MR imaging finding for the prediction of therapeutic responses is signal intensity of uterine fibroids in a T2-weighted image. Funaki et al. [22] classified uterine fibroids into three types, based on their T2 signal intensity. Type I implied fibroids with a signal intensity comparable to or lower than that of skeletal muscle. Type II indicated fibroids with a signal intensity higher than that of skeletal muscle but lower than that of normal myometrium. Type III fibroids were those with signal intensity comparable to or higher than that of normal myometrium. In the study by Funaki et al., type I fibroids showed the best outcomes after HIFU ablation, and type III fibroids demonstrated the worst results. This classification is easy to perform, and is therefore widely adopted. However, the assessment is subjective, and the results are susceptible to changes, because the myometrial signal

intensity is often inconsistent. In order to overcome this drawback, some researchers have adopted a new methodology using a signal intensity ratio of uterine fibroids relative to the skeletal muscle [23, 24]. Regardless of the methods, uterine fibroids with very high signal intensity in T2-weighted MR images should be excluded from treatment because of the expected poor therapeutic responses. Based on a recent study on T2 signal intensity of fibroids in correlation with the histopathology findings, it was demonstrated that T2 signal intensity of the fibroids reflected their relative composition of smooth muscle cells and collagen fibers [2, 10].

Perfusion MR imaging enables evaluation of vascularity of the fibroid, which is another important influencing factor. Volume transfer constant (K^{trans}) in dynamic contrast-enhanced MR imaging and relative peak enhancement (RPE) in semiquantitative perfusion MR imaging of uterine fibroids were found to be negatively correlated with immediate therapeutic responses after MR-HIFU ablation [25, 26]. RPE in semiquantitative perfusion MR imaging is known to be inversely correlated with T2 signal intensity of fibroids, except in endometrially protruding fibroids. Therefore, in a substantial number of cases, the degree of perfusion can be estimated just by visualization of T2-weighted images [27]. Kim et al. [24] suggested prediction models for immediate therapeutic responses after MR-HIFU ablation of uterine fibroids by integrating the T2 signal intensity, degree of perfusion, and subcutaneous fat thickness, which seemed to be useful for patient selection in clinical practice.

5 HIFU therapy and post-therapeutic assessment

5.1 Preparation

Overnight fasting before treatment is recommended because of the possibility of nausea/vomiting related to a

sensation of pain or long-lasting immobility. Shaving and depilation of the lower abdominal and pubic areas are essential in order to prevent skin burn. Intravenous catheterization is necessary to administer medications during the treatment. Foley catheterization is also important to prevent the uterus from moving due to filling of the urinary bladder as well as to perform a bowel manipulation maneuver. Bowel preparation using a suppository-based laxative is helpful in cases where injection of a rectal gel is required.

5.2 HIFU therapy

The patient is placed in either a prone or supine position, according to the design of the HIFU system used. Acoustic coupling should be achieved using degassed water or ultrasound gel. Care should be taken to remove any foreign body or air bubble at the skin–HIFU window interface, to prevent skin burn. In MR-HIFU, a so called “bubble scan” is available, which can detect an interposed foreign body or air bubble.

During sonication, the patient usually complains of various degrees of pelvic pain that is similar to menstrual cramps in terms of the pattern and degree. Heating sensation of the skin is also a common symptom. Some HIFU systems adopt an active cooling technique not only to decrease the heating sensation but also to prevent complications. When HIFU sonications stimulate sacro-coccygeal bones, the patient usually feels a sensation of tightening or even pain in the lower back or coccygeal area. If HIFU sonication stimulates a sciatic nerve, various symptoms such as heating or tingling sensation, pain, and tightening are felt. Such stimulating symptoms on a bone or a nerve usually disappear spontaneously, as soon as HIFU sonication is discontinued. If the symptoms persist even after HIFU sonication is stopped, occurrence of a complication such as nerve injury could be considered. Therefore, obtaining symptom feedback from patients undergoing HIFU therapy is very important, and deep sedation or general anesthesia is not desirable during this treatment. To control pain, an opioid analgesic is used in many centers.

HIFU therapy is performed by repeating sonications to stack up the thermal lesions, because the HIFU thermal lesion is very small, usually measuring a few millimeters in axial diameter. Certain HIFU systems adopted a volumetric ablation technique, in which the HIFU focus is electronically steered along a circular or other trajectory to form a larger thermal lesion by one sonication [6]. Between sonications, cooling intervals are necessary to prevent complications arising out of near-field heat accumulation, such as skin burn or fat injury. Volumetric ablation system requires longer cooling intervals. Treatment speed among different systems varies, and volumetric ablation technique

is known to accelerate the treatment speed [19]. In general, however, the treatment requires longer time, as the size of the uterine fibroids increases. Therefore, the operator should be aware of the maximum size of uterine fibroid ablated by one session of treatment.

After 1 to 2 hours of observation following HIFU therapy, the patient is discharged and usually resumes normal activity on the next day.

5.3 Post-therapeutic assessment

Immediately after HIFU ablation, gadolinium-based contrast-enhanced MR imaging or microbubble-based contrast-enhanced US is performed to evaluate the treatment results. The unenhanced portion of the treated uterine fibroid on imaging represents the non-perfused volume (NPV) and is known to best reflect coagulation necrosis. NPV ratio (*i.e.*, ratio of NPV to fibroid volume) is the most important parameter in post-therapeutic assessment, because the ratio at immediate follow-up is correlated with the decrease in the volume of the fibroid as well as with symptom improvement in mid- to long-term follow-ups [4, 28, 29].

Although microbubble contrast enhancement is used to visualize treatment results after US-HIFU on the spot, quantitative analysis is difficult. Quantification of NPV or NPV ratio and evaluation of the occurrence of procedure-related complications are feasible only through contrast-enhanced MR imaging [30].

6 Complications

6.1 Symptoms after therapy

Pelvic discomfort or mild pain is common after treatment. General symptoms include malaise and/or a mild febrile sensation for varying durations (*i.e.*, days to weeks), as a post-ablation syndrome. These symptoms can be managed symptomatically, for instance, by using oral analgesics.

6.2 Skin burn, thermal injury of subcutaneous fat

Repeated high-powered HIFU sonications without sufficient cooling intervals may cause skin burn or subcutaneous fat injury owing to near-field heat accumulation, which is the most common complication of HIFU ablation for uterine fibroids [31–33]. The majority of skin burns are of first or second degree. A scar of skin or fat tissue is more susceptible to this complication because of its higher US absorption rate and decreased blood flow, although passage of a small number of HIFU sonications through the scar is not a matter of concern. To prevent skin burn or

subcutaneous fat injury, ensuring a sufficient cooling interval is important. If available, a scar patch [34] that reflects 100% of US or the beam shaping function of MR-HIFU system should be used. Active cooling technique adopted by some recent HIFU systems is also beneficial [21].

6.3 Sciatic nerve injury

When the HIFU focus is shifted to the posterior pelvic cavity and the high-powered HIFU sonication is repeated, HIFU may directly injure the sciatic nerve or may indirectly induce a nerve injury via the heated bony structure. Sciatic nerve stimulation by HIFU can be recognized based on the symptoms of the patient, which is very important to prevent this complication. The possible symptoms caused by thermal injury of the sciatic nerve include a tingling sensation, numbness, pain, and even motor weakness such as foot drop of the ipsilateral leg following the treatment [31].

If the patient complains of nerve stimulating symptoms during sonication, careful attention should be paid. Sufficient cooling intervals and/or the use of lower acoustic power are important to prevent this complication. In most cases, the symptoms spontaneously resolve after a few weeks to a few months.

6.4 Genitourinary complications

Vaginal discharge or bleeding may occur. This might be related to endometrial injury; therefore, it is more common after treating submucosal fibroids. The symptoms usually resolve spontaneously. Occasionally, fragments or lumps of the necrotized fibroid are excreted or expelled through the vagina.

The wall of the urinary bladder may be thermally injured if the sonication site is close to the bladder. The risk increases especially when the tip of Foley catheter in contact with the bladder wall is included in the sonication path. Transient gross hematuria is the most common symptom, and perforation of the urinary bladder has not been reported. A urinary tract infection such as urethritis or cystitis may be complicated via Foley catheterization.

6.5 Thermal injury of small/large intestines

Interposed small or large intestines could be injured because of the accumulated near-field heat if the bowel loops are included in the sonication path. The risk increases especially when the bowel loop contains air, because the air–mucosa interfaces are more susceptible to heating. During the procedure, it is very important to verify the location of the bowel loops by imaging, because peristaltic movement of the intestine is unpredictable.

If the bowel loops are included in the sonication path with the patient in a prone position, the use of a balloon filled with degassed water or a convex gel pad interposed between the abdominal wall and the HIFU window helps to displace the bowel loops peripherally [35]. In cases where the patient is in the supine position, compression of the abdominal wall by the HIFU transducer plays a similar role. In addition, the so called BRB maneuver, which involves steps such as filling of the urinary bladder with saline, rectal filling with ultrasound gel, and emptying of the urinary bladder, is reported to be very useful to displace the interposed bowel loops out of the sonication path [36].

Bowel perforation due to thermal injury, although very rare, is manifested as peritonitis symptoms and signs, usually several days after the treatment.

7 Clinical outcomes

Gizzo et al. [37] performed a meta-analysis of the relevant studies published till 2014. The reported immediate NPV ratios ranged from 16.3% to 98.0% and the volume reduction ratios of the fibroids ranged from 19.9% to 80.0%. The mean symptom severity score in the Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire decreased from 56.3 to 31.0 at the 6-month follow-up. The poor NPV ratio in some studies might be attributed to the strict restriction in treatment volume (*i.e.*, 33% of the fibroid volume) in early FDA (Food and Drug Administration of the United States) studies, owing to safety concerns, which is now released to allow complete ablation (*i.e.*, 100% of the fibroid volume).

Funaki et al. [38] reported 2-year re-intervention rates of 14.0% in type I and type II fibroids, and 21.6% in type III fibroids. Gorny et al. [39] reported 3-year and 4-year re-intervention rates of 19% and 23%, respectively, which are comparable to those observed after other uterus-preserving therapeutic modalities. In this study, younger age and high and/or heterogeneous T2 signal intensity of the fibroids were poor prognostic factors.

Several studies have shown that a higher NPV ratio at immediate follow-up is associated with a greater volume reduction ratio as well as greater symptom improvement. Therefore, achievement of complete or near-complete ablation is important as long as the safety is ensured, in order to improve clinical outcomes. Mindjuk et al. [40] reported that patients with NPV ratios greater than 80% showed a significantly higher clinical success rate and a lower re-intervention rate than those shown by patients with NPV ratio less than 80%. Park et al. [41] demonstrated that fibroids with immediate NPV ratios greater than 80% showed a volume reduction ratio of 43% at the 3-month follow-up, which was significantly greater than that of

fibroids with NPV ratios less than 80%. These results are comparable to those reported in studies on uterine artery embolization with the same follow-up durations.

8 Hormone pretreatment

Gonadotropin-releasing hormone agonists (GnRHa) are used for medical treatment of uterine fibroids. GnRHa pretreatment before HIFU ablation decreases the volume and vascularity of uterine fibroids, which reduces the treatment time and increases tissue susceptibility to HIFU.

GnRHa pretreatment before HIFU is performed in the same manner as usual medical treatments, and consists of three subcutaneous injections every 4 weeks; the last injection should be administered 2–3 weeks prior to the scheduled date of HIFU therapy [42]. Volume reduction ratios after GnRHa pretreatment differ among patients, with the mean ratio being approximately 25%.

9 Conclusion

HIFU ablation has great clinical implications in terms of providing a new non-surgical therapeutic option for patients suffering from uterine fibroids. Owing to its noninvasiveness, HIFU therapy carries virtually no risk of complications such as bleeding or infections; moreover, this technique can be performing on an outpatient basis, which has resulted in its rapid adoption worldwide. However, compared with other therapeutic modalities, the range of the patients with uterine fibroids that can be benefited from HIFU ablation is restricted, and clinical outcomes are subject to appropriate patient selection and the operator's experience.

The most critical factors in order to achieve clinical success are appropriate selection of patients based on the aforementioned conditions, via MR imaging, and achievement of complete or near-complete ablation of the target fibroids as long as the safety conditions are met. In addition, although the frequency and severity of complications is lower in HIFU when compared with other modalities, serious complications such as bowel perforation could occur.

Compliance with ethical standards

Conflict of interest Kim Y-S declares that he has no conflicts of interest in relation to the work in this article.

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