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INTERVENTIONAL

Safety and efficacy of US-guided high-intensity focused ultrasound for treatment of submucosal fibroids

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Abstract
Objectives To evaluate the safety and efficacy of US-guided high-intensity focused ultrasound (HIFU) ablation for the treatment of submucosal fibroids
Methods A total of 76 women with 78 submucosal uterine fibroids (68 type II fibroids, 10 type I fibroids) underwent US-guided HIFU ablation. The pretreatment fibroid diameter ranged from 2.4 to 13.5 cm (mean 5.7±2.3 cm). The fibroids were ablated using a power output of 420–520 W. During follow-up, the volume shrinkage of the ablated fibroids was continuously observed on contrast-enhanced MR and/or contrast-enhanced ultrasound (CEUS). The change of symptoms was evaluated by using the symptom severity score questionnaire.
Results HIFU ablation was well tolerated in all patients. No major complications occurred. The mean nonperfused ablation ratio was 80±12 % on CEUS. During follow-up, the ablated fibroids shrank significantly over time. The symptoms were alleviated significantly. No patients had amenorrhoea after treatment. Vaginal expulsion of necrotic tissue was seen in 58 % (44/76) of patients after HIFU ablation which disappeared after 2–4 menstrual cycles. Four patients received repeated HIFU ablation for enlarged residual fibroids.
Conclusions US-guided HIFU ablation may be a safe and effective treatment for submucosal fibroids. Further studies are warranted to observe its influence on fertility.
Key points
• *High-intensity focused ultrasound (HIFU) is a new minimally invasive therapeutic technique.*
• *HIFU ablation may be safe and effective for treatment of submucosal fibroids*
• *Treatment is minimally invasive and repeatable.*
• *Vaginal expulsion of necrotic tissue is common after treatment.*

Keywords Ultrasonography · High-intensity focused ultrasound · Submucosal · Uterine fibroids · Ablation

Introduction

Submucosal fibroids are the most common anatomical cause of abnormal uterine bleeding, dysmenorrhoea and infertility in women of reproductive age [1]. According to the European Society of Hysteroscopy classification, submucosal fibroids are classified into three types: type 0 (pedunculated fibroid without intramural extension), type I (sessile with an intramural extension less than 50 %) and type II(sessile with an intramural extension of at least 50 %) [2]. Type 0 submucosal fibroids can be easily excised at hysteroscopy. Management of type I and type II submucosal fibroids, however, may be technically challenging. Hysterectomy is an aggressive option which is not suitable for women who want to preserve their uterus. Myomectomy, via laparatomy or laproscopic approach, can preserve the uterus but it involves substantial operative risks, including haemorrhage, postoperative adhesion, and uterine rupture during pregnancy and labour [3]. Hysteroscopic myomectomy, in the last two decades, has become a less invasive surgical treatment for submucosal fibroids [4, 5]; however, it is associated with risks such as uterine perforation, fluid overload, ascending genitourinary infection, and iatrogenic adenomyosis. Hysterscopic resection of submucosal fibroids with deep intramural extension is

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difficult and multiple procedures may be necessary for complete resection [6].

High-intensity focused ultrasound (HIFU) ablation is an extracorporeal treatment which can yield coagulation necrosis of target lesions without surgical exposure. Under imaging guidance, a well-defined coagulative ablation area can be induced at depth in the focal area, through the intact skin. In the past decade, HIFU ablation, under magnetic resonance (MR) or ultrasound (US) guidance, has been used for the treatment of symptomatic uterine fibroids, yielding shrinkage of the ablated tumour and improvement of symptoms [7–14]. However, to our knowledge, no study had focused primarily on US-guided HIFU ablation of symptomatic submucosal fibroids. Therefore, this study evaluated the safety and efficacy of US-guided HIFU ablation for the treatment of submucosal fibroids.

Materials and methods

Patients

The inclusion criteria for HIFU ablation were as follows: (1) women at child-bearing age who had no desire for future fertility; (2) type I or type II submucosal fibroids with a diameter of at least 2 cm; (3) not received other treatment for uterine fibroids before HIFU ablation. The exclusion criteria were as follows: (1) pregnancy; (2) presence of bowel in the proposed pathway of the energy beam; (3) unable to lie in the prone position; (4) contraindication to contrast-enhanced MR or contrast-enhanced ultrasound (CEUS). To prevent thermal damage to the endometrium, intrauterine devices have to be removed before HIFU ablation. This prospective study was approved by the institutional ethics committee. Written informed consent was obtained in all patients at enrolment.

From October 2006 to October 2009, 76 premenopausal women with 78 symptomatic submucosal uterine fibroids underwent US-guided HIFU ablation in our hospital. The age of the patients ranged from 24 to 52 years (mean 38.2± 6.4 years). Of these, 74 patients had one submucosal uterine fibroid and 2 patients had two submucosal uterine fibroids. According to contrast-enhanced MR before treatment, 10 fibroids were classified as type I and 68 fibroids were classified as type II. The largest fibroid diameter ranged from 2.4 to 13.5 cm (mean 5.7±2.3 cm). The pretreatment fibroid volume ranged from 4.6 to 695.6 cm^3 (mean 140.3± 137.6 cm^3). All patients had heavy and/or prolonged menstrual bleeding, 69 patients (90.8 %) had reduced intervals between menstrual periods and 35 patients (46.1 %) were anaemic. The patients' quality of life was naturally influenced by the symptoms caused by submucosal fibroids. The Uterine Fibroid Symptom and Quality of Life (UFS-QOL) score [15] was 26.0± 4.5 before HIFU ablation.

Equipment

A HIFU system (model JC; Chongqing Haifu Technology, Chongqing, China) was used in this study. The instrument was composed of three parts: a therapeutic transducer located in a degassed water tank, an imaging system comprising a US probe coupled with a sterotaxic localizing arm, and a computer-controlled system for firing energy and moving the therapeutic transducer in three dimensions. The energy is produced from a 20-cm-diameter therapeutic transducer with a focal length of 150 mm operating at a frequency of 0.9 MHz. The focal region is 9.8 mm along the beam axis and 1.3 mm in the transverse direction. In the centre of the HIFU transducer, a 3.5- to 5.0-MHz convex diagnostic US probe is mounted to provide real-time imaging for targeting. Through computer control, the therapeutic transducer can be moved smoothly in six directions, i.e. three orthogonal directions (x, y and z), rotation along the US beam axis (θ), and rotation along the long (γ) or short (φ) axis of the bed.

Pretreatment preparation and imaging workup

Before HIFU ablation, patients underwent careful bowel preparation including low residue diet for 3 days, fasting for 12 h before treatment, administration of cathartics in the evening the day before treatment, and an enema in the early morning on the treatment day. A catheter was inserted into the bladder and connected to degassed sterile water through an infusion set for the purpose of properly filling the bladder during HIFU ablation. Degassed water balloons of different size were used to compress and push away the bowel from the acoustic pathway during treatment when necessary.

Pretreatment imaging examinations included contrast-enhanced MR and CEUS. Contrast-enhanced MR was performed in all patients at 1.5 T (Signa Echo-Speed, GE Healthcare, Milwaukee, USA). The fibroid's vascularity and its anatomical relationship to adjacent structures were observed for planning of HIFU ablation.

CEUS was performed using a Sequoia 512 US system (Acuson, Mountain View, CA, USA). A 1.0- to 2.0-ml bolus of US contrast agent (SonoVue, Bracco, Milan, Italy) was injected via the cubital vein, which was followed by a 5-ml saline flush. The size and vascularity of the target fibroids were observed.

HIFU ablation procedures

Treatment was performed under conscious sedation (fentanyl and midazolam) by one doctor (W.W.) with more than 10 years' experience in HIFU ablation. During treatment, the

patients were carefully placed in the prone position, with the abdominal skin in contact with the degassed water. The fibroids were divided into sections with 5-mm separation on US. HIFU energy exposures of 1–3 s separated by 2–3 s were applied to ablate one target spot. An acoustic power of 420–520 W was used in this study. If the echogenicity of the target spot did not change after firing energy, the energy exposure was repeated until the echogenicity of the target spot became increased on US. To avoid thermal damage to adjacent structures such as bowel, bladder and endometrium, the focus of the energy beam was kept at least 1 cm away from the tumour margin. After ablation of one spot, the transducer was moved, and a nearby spot was treated similarly. This process was repeated section by section, from the deep to shallow regions until the planned target areas were ablated.

Post-treatment follow-up

After HIFU ablation, patients were carefully observed for 1–3 h for possible complications before discharge. Oral antibiotics were prescribed for 7 days to prevent infection. CEUS was performed immediately after HIFU ablation to observe the therapeutic response. If a significant fraction of fibroids still had blood perfusion, additional HIFU ablation was performed immediately. Otherwise, patients entered the follow-up protocol which consisted of contrast-enhanced MR and/or CEUS at 1, 3 and 6 months and every 6 months thereafter. If the residual fibroids enlarged significantly and symptoms recurred during follow-up, further HIFU ablation was planned.

The size of the fibroid and the nonperfused ablation area was measured in three orthogonal directions on CEUS. The volume was simply calculated using the ellipsoid formula: (length × width × height) × 0.523 [16]. The measurements were made by consensus of two experienced physicians (W.W. and Y.W.). The ablation ratio was defined as the volume of the nonperfused area divided by the volume of the fibroid. Changes in the severity of symptoms were assessed by the score of the UFS-QOL questionnaire during follow-up. The Student *t* test was used to determine whether the scores after HIFU ablation were significantly different from the pretreatment score. The statistical analyses were performed by using Stata software (version 7.0; Stata Corporation, College Station, Tex). A *P* value of less than 0.05 was considered statistically significant.

Results

HIFU ablation was performed successfully in all patients. During HIFU ablation, all patients complained of a mild burning sensation in the abdominal skin, requiring no termination of treatment. The treatment time (calculated from the start of the first energy exposure until the end of the last energy exposure) ranged from 27 to 196 min (mean 85±43 min). Right after HIFU ablation, a nonperfused ablation area with clear margins was observed in all patients on CEUS or contrast-enhanced MR (Fig. 1). The nonperfused ablation ratio was 80±12 % (range 70–100 %) on CEUS. No major complications such as bowel perforation and nerve damage were encountered in this study.

The patients were continuously followed up until January 2011. In a median follow-up of 30 months (range 15–52 months), the ablated fibroids shrank significantly over time (Fig. 2). The average volume shrinkage at 3, 6, 12 and 24 months was 46.7 %, 68.2 %, 78.9 % and 90.1 % on CEUS, respectively.

No patients developed amenorrhoea after HIFU ablation. The volume of menstrual bleeding decreased significantly ($P<0.05$) the first menstrual period after HIFU ablation in 55.3 % (42/76) of patients. It also decreased significantly ($P<0.05$) in 71.1 % (54/77) and 89.5 % (68/76) of patients at 3 and 6 months after HIFU ablation. No patients had heavy menstrual bleeding and anaemia at 12 months after HIFU ablation. Symptoms of abnormal mentrual bleeding were relieved significantly in all patients. The UFS-QOL score decreased to 16.0±3.7 at 6 months after HIFU ablation and tended to decrease further thereafter: it was 13.3±3.5 and 11.0±3.0 at 12 and 24 months after HIFU ablation, respectively. Enlargement of residual fibroid was observed in four patients. Three of these patients received one additional HIFU ablation and one patient received two additional HIFU ablations. Because the patients' quality of life was significantly improved, no patients received other treatments for submucosal fibroids during follow-up.

Expulsion of necrotic ablated tissue from the vagina was observed in 44 patients. Intermittent mild pain was felt prior to the onset of vaginal discharge and was alleviated after vaginal discharge. The expulsion disappeared after 2–4 menstrual cycles. In two patients, the treated fibroids were completely expelled from the vagina 1 and 3 months after HIFU ablation, respectively. The two fibroids were relatively small, with a largest pretreatment diameter measuring 2.4 cm and 3.5 cm, respectively.

Discussion

Because surgical treatments are associated risks such as bleeding and infection, require a long recovery period and often necessitate general anaesthesia, several minimally invasive uterus-preserving techniques have been developed for the treatment of symptomatic uterine fibroids, e.g. transarterial embolization [17, 18], pecutaneous ablation using cryoprobes [19], laser [20], and radiofrequency [21, 22], and high-intensity focused ultrasound (HIFU) [8–13]. Embolization

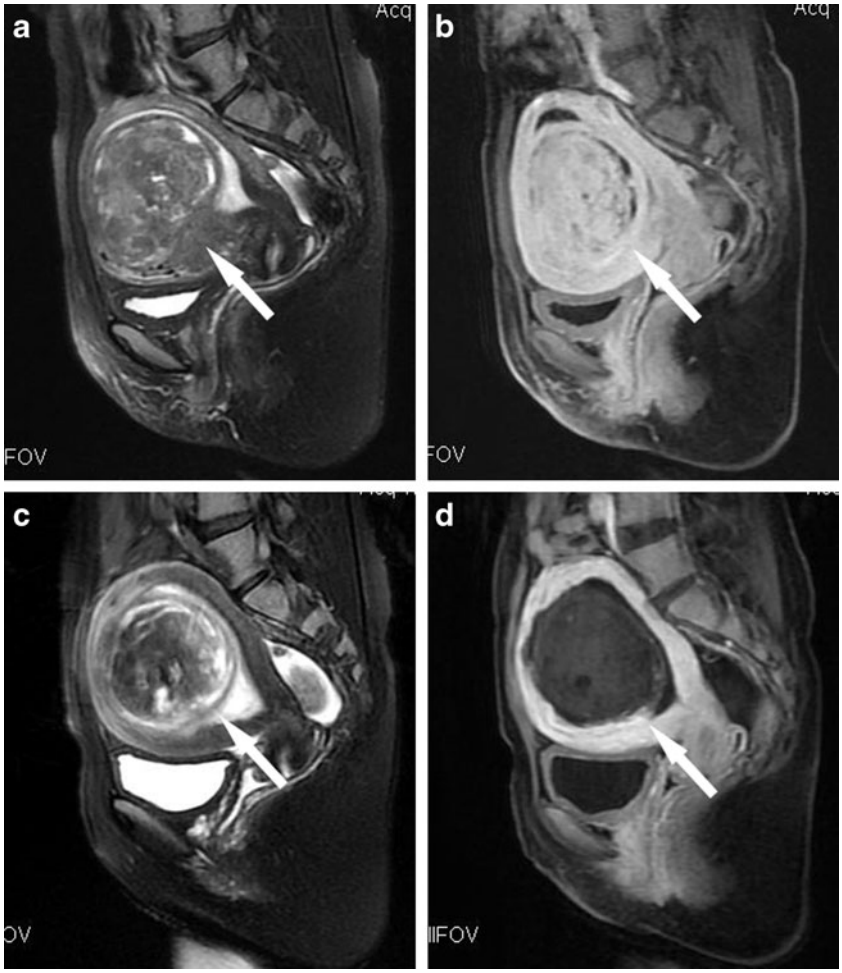

Fig. 1 Sagittal contrast-enhanced MR in a 40-year-old woman receiving US-guided HIFU ablation of submucosal uterine fibroid. **a** Before HIFU ablation, T2-weighted MR showed the relationship between the submucosal fibroid and the endometrium. **b** Before HIFU ablation, the fibroid showed enhancement on contrast-enhanced MR. **c** Immediately after HIFU ablation, T2-weighted MR showed the relationship between the submucosal fibroid and the endometrium. **d** Immediately after HIFU ablation, the ablated fibroid showed no enhancement on contrast-enhanced MR

can occlude the blood supply to the fibroids, resulting in tumour shrinkage and relief of symptoms, but it is associated with side effects like severe pelvic pain and complications such as premature menopause and ovarian failure. All percutaneous ablation techniques require insertion of needle-like applicators. It may be difficult to find a safe puncture route for placement of applicators in deeply located fibroids.

In this study, most of the submucosal fibroids had deep intramural extension and were considered difficult for complete resection. However, US-guided HIFU ablation yielded an encouraging therapeutic outcome. A high percentage of ablation necrosis was observed in all patients on CEUS. The mean nonperfused volume ratio was about 80 %. Previous studies had shown that the nonperfused volume ratio is predictive of long-term reduction in tumour volume and relief of symptoms for at least 24 months. A higher nonperfused volume ratio correlates with marked reduction in symptom severity and a significant decrease in the number of patients undergoing other fibroid treatments 12 and 24 months after MRI-guided HIFU ablation [11, 12]. Because the nonperfused volume ratio obtained in this study was significantly larger than that of previous studies, the alleviation of symptoms was more significant and sustainable. Enlargement of residual fibroid was only found in four patients during follow-up and was readily treated by additional HIFU ablations.

Unlike other minimally invasive techniques, HIFU ablation requires no insertion of applicators. The procedure can be easily repeated and large ablation areas can be induced under imaging guidance in one treatment session. These properties make it more advantageous for the treatment of submucosal fibroids with deep intramural extension. Further studies are warranted to compare HIFU ablation with other minimally invasive techniques in the treatment of submucosal fibroids.

Safety is a major concern for HIFU ablation of symptomatic fibroids as the uterus is in close proximity to important structures, such as the bowel, bladder and lumbosacral plexus. To avoid thermal damage of these structures, the focus of the energy beam was kept at least 1 cm away from the tumour margin and the ablation area did not extend beyond the tumour margin. Because HIFU ablation was performed under conscious sedation, the patients can tell the doctor immediately about any abnormal sensations during energy exposures. If pain was reported in the posterior thigh or leg, the focus of the energy beam was moved away from the target spot to

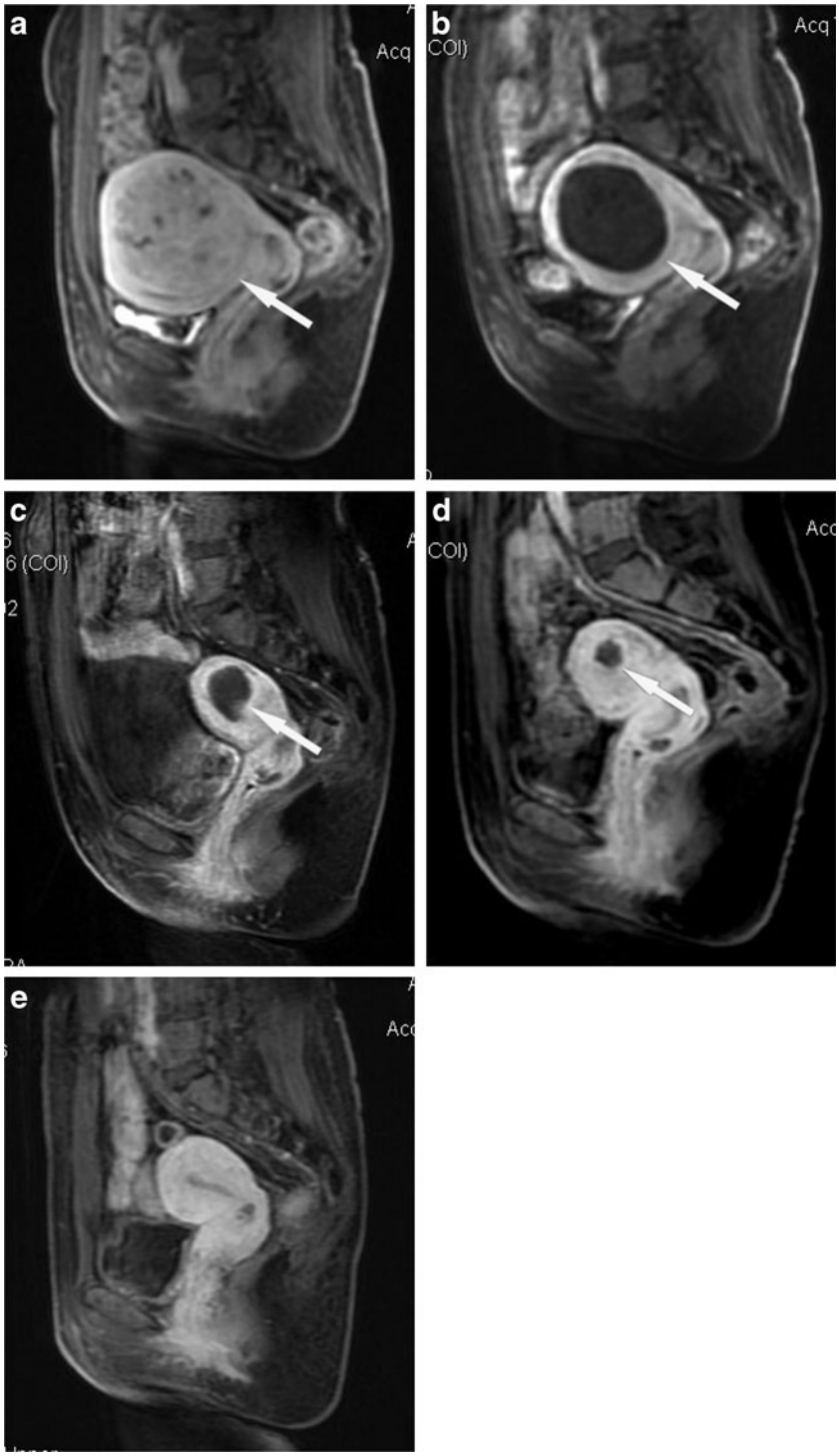

Fig. 2 Sagittal contrast-enhanced MR in a 50-year-old woman receiving US-guided HIFU ablation of submucosal uterine fibroid. **a** Before HIFU ablation, the submucosal fibroid showed enhancement on contrast-enhanced MR. **b** One week after HIFU ablation, a well-defined nonperfused ablation area was shown on contrast-enhanced MR. **c** Six months after HIFU ablation, the ablated fibroid shrank significantly on contrast-enhanced MR. **d** One year after HIFU ablation, the ablated fibroid shrank further on contrast-enhanced MR. **e** Two years after HIFU ablation, the ablated fibroid was completely absorbed and was undetectable on contrast-enhanced MR

minimize the risk of nerve damage. By taking these precautions, no major complications were observed in this study.

Irreversible thermal damage to the endometrium is a potential risk for HIFU ablation of submucosal fibroid which may cause amenorrhoea and infertility. Therefore we only enrolled patients having no desire for future fertility. However, we tried to protect the endometrium during HIFU ablation in this study. The focus of the energy beam was kept at least 1 cm away from the endometrium. No patients had amenorrhoea after HIFU ablation in this study. The results suggested that by careful control of the focal region, HIFU ablation may not cause irreversible thermal damage to the endometrium, the endometrium may repair itself and patient's fertility may be preserved. Further studies are warranted to observe the influence of HIFU ablation on patient fertility.

In this study, expulsion of necrotic fibroid tissue from the vagina was a common finding after US-guided HIFU ablation. As it was associated with minor accompanying symptoms and required no medication, it was not regarded as a complication. Expulsion of submucosal fibroids was also observed after uterine artery embolization [23]. The extent and length of vaginal expulsion after US-guided HIFU ablation were similar to the results reported for transarterial embolization of submucosal fibroids. However, the rate of complete expulsion seemed to be much lower for HIFU ablation, only two fibroids (2.6 %) were completely expelled after HIFU ablation. In our opinion, the expulsion of necrotic tissue may be a normal reaction after HIFU ablation of submucosal fibroid and doctors should inform patients about the possibility in order to avoid unnecessary anxiety. However, certain risk may still exist. If a large fibroid was expelled, it may obstruct the cervix and require hysteroscopic removal.

In conclusion, US-guided HIFU ablation may be a safe and effective minimally invasive technique for the treatment of submucosal fibroids. Further studies are warranted to observe its influence on fertility.

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