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CLINICAL ARTICLE

Effective ablation therapy of adenomyosis with ultrasound-guided high-intensity focused ultrasound

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ABSTRACT

Objective: To evaluate the effects of ultrasound-guided high-intensity focused ultrasound (HIFU) on adenomyosis. **Methods:** In a retrospective analysis, data were reviewed from 202 patients with adenomyosis who underwent ultrasound-guided HIFU between November 2010 and June 2012 at Suining Central Hospital, Sichuan, China. Among these patients, 120 and 82 were classified as having focal adenomyosis and diffuse adenomyosis, respectively. All patients underwent pre-treatment and post-treatment magnetic resonance imaging by a standardized protocol to evaluate the treatment. All adverse effects were recorded. **Results:** All patients completed the ultrasound-guided HIFU treatment in 1 session. A non-perfused volume ratio of $71.6\% \pm 19.1\%$ was achieved. Compared with baseline data, the average menorrhagia severity score and the average dysmenorrhea severity pain score decreased significantly after ultrasound-guided HIFU (both $P < 0.001$). The proportion of women with complete relief of dysmenorrhea at the 3-month follow-up was significantly higher among women with focal adenomyosis than among those with diffuse adenomyosis ($P = 0.02$). No other significant differences were observed between the 2 patient groups. **Conclusion:** Ultrasound-guided HIFU was found to be an effective technique for treating both focal and diffuse adenomyotic lesions to alleviate the symptoms of menorrhagia or dysmenorrhea.

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1. Introduction

Adenomyosis is a common benign disease among women of reproductive age [1,2]. The prevalence of adenomyosis varies across race; it can range from 1% to 70% among women of reproductive age, and is frequently reported as 20%–30% [3–5].

Patients with adenomyosis often report menorrhagia and dysmenorrhea, and sometimes complain of pelvic pressure and frequent urination. In clinical practice, gynecologists can offer several treatment options to women with symptomatic adenomyosis. Among these options, hysterectomy is considered as the only definitive treatment for patients with adenomyosis. However, hysterectomy is only suitable for patients who are older than reproductive age and are not opposed to definitive surgical treatment. Conservative myomectomy is an option for patients who desire to preserve their uterus but, because of ill-defined boundaries between the

endometrium and myometrium, complete removal of the focal adenomyotic lesions is problematic.

In an attempt to find a treatment option with minimal impact on a patient's lifestyle, lower cost, and less invasiveness, several groups have tested the clinical value of uterine artery embolization, intrauterine devices, gonadotropin-releasing hormone analogs, oral hormonal medication, non-hormonal medication, and ultrasound-guided high-intensity focused ultrasound (HIFU) for the treatment of adenomyosis [6–10].

Ultrasound-guided HIFU is a non-surgical technique. Over the past 10 years, this non-invasive therapeutic modality has been applied to treat malignant solid tumors in the liver, breast, pancreas, and bone [11–13]. Although many studies have shown that ultrasound-guided HIFU ablation is a safe and effective treatment for uterine fibroids [14–16], only a few have examined the application of ultrasound-guided HIFU for treating patients with adenomyosis [9,10,17].

The primary aim of the present study was to evaluate the therapeutic effect of ultrasound-guided HIFU on adenomyosis-associated clinical symptoms, as defined by the symptom severity score (SSS) and the uterine fibroids symptoms quality of life (UFS-QOL) questionnaire. A secondary aim was to compare the alleviation of symptoms of pain and heavy periods between patients with focal adenomyosis and patients with diffuse adenomyosis.

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2. Materials and methods

In a retrospective study, data were analyzed from women who underwent ultrasound-guided HIFU for adenomyosis between November 1, 2010, and June 30, 2012, at Suining Central Hospital of Sichuan, China. The ethics committees at Suining Central Hospital of Sichuan and Chongqing Medical University approved the study protocol. All patients gave written informed consent for ultrasound-guided HIFU and for the future use of data collected.

The diagnosis of adenomyosis was confirmed by magnetic resonance imaging (MRI). The selection criterion for the study was the presence of symptomatic adenomyosis with an endometrial–myometrial junctional zone thickness of more than 3 cm for diffuse adenomyosis or a lesion diameter larger than 3 cm for focal adenomyosis.

All patients were asked to take liquid food for 3 days. Mandatory enema was performed on the morning of the treatment day after a 12-hour fasting period. To avoid bowel injury during treatment, the bowel loops in the acoustic pathway were pushed away or compressed by placing a degassed water balloon on the abdominal wall of the patient.

A JC 200 HIFU system (Chongqing Haifu Technology, Chongqing, China) was used to perform ultrasound-guided HIFU. Equipped with a transducer of 20 cm in diameter, a focal length of 15 cm, and a frequency of 0.8 MHz, this system produced therapeutic focused ultrasound energy and was paired with an ultrasound imaging device (My-Lab70; Esaote, Genoa, Italy) as a real-time imaging unit to guide the HIFU procedure.

The HIFU ablation procedure was performed after conscious sedation of patients with a single- or multidose injection of fentanyl (range, 50–400 µg), and midazolam hydrochloride (range, 1–4 mg). During treatment, patients were requested to report any discomfort, and the vital signs of heart rate, respiration rate, and blood pressure were monitored. The HIFU ablation was terminated after an indistinct increase in the grayscale area in the adenomyotic lesion was observed (Fig. 1).

All patients were asked to undergo contrast-enhanced MRI before and 1 day after the HIFU treatment. Diffused thickening of the endometrial–myometrial junctional zone on the T2-weighted image was considered as diffuse adenomyosis. Focal adenomyosis was observed as a localized region on the T2-weighted image. This image was used to measure the adenomyotic lesion volume, and the contrast-enhanced T1-weighted image was used to measure the non-perfused volume (NPV) in the treated adenomyotic lesion (Figs. 2 and 3). The volume with no enhancement on the contrast-enhanced T1-weighted image

of the post-treatment MRI was recognized as the lesion coagulation volume, which was defined as NPV (Figs. 2C and 3C). HifuMars (Chongqing Haifu) software program was used to contour the uteri, adenomyotic lesion, and the area with no enhancement in the treated lesion slice by slice. The same program was then used to calculate the uterine volume, the adenomyotic lesion volume, and the NPV.

In accordance with institutional guideline for follow-up observations, a nurse was requested to call the patients daily during the first 3 days, and the patients were requested to come back 1, 3, 6, and 12 months after ultrasound-guided HIFU to check for adverse effects, symptoms, and MRI evaluation. Both menorrhagia and dysmenorrhea were evaluated via the SSS and the UFS-QOL questionnaire using a 5-point categoric scale (1, not affected; 2, a little affected; 3, somewhat affected; 4, greatly affected; 5, very greatly affected) [18].

The degree of dysmenorrhea alleviation after ultrasound-guided HIFU was assessed as follows: complete relief, dysmenorrhea completely disappeared; partial relief, dysmenorrhea was not resolved completely, but the pain score decreased by 2 points or more; minor relief, dysmenorrhea was present, but the pain score decreased by 1 point; ineffective, no change in pain score; exacerbated, the pain score increased after treatment.

Data were reported as the mean $\pm$ SD score. Data analysis was carried using SPSS version 18 (IBM, Armonk, NY, USA). A 1-sample *t* test was used to compare the menorrhagia and dysmenorrhea scores between the baseline and different follow-up times after ultrasound-guided HIFU. A 1-sample *t* test was also used for comparisons of adenomyotic lesion volume and NPV ratio between focal adenomyosis and diffuse adenomyosis. The changes in frequency of menorrhagia and dysmenorrhea after ultrasound-guided HIFU treatment (focal versus diffuse adenomyosis) were compared via χ^2 test. A significant difference was defined as a *P* value of less than 0.05.

3. Results

During the study period, 202 patients with adenomyosis were treated by ultrasound-guided HIFU. The mean $\pm$ SD age of the patients at treatment was 41.7 ± 4.9 years (range 26–54 years) (Table 1). A point scan with 300–400 W of power was used for HIFU treatment. Each patient tolerated and completed the procedure. The median room time was 102 minutes, and the mean time for sonication was 20 minutes 11 seconds.

The adenomyotic lesion was clearly displayed on the T2-weighted image of MRI. The NPV, which is induced by ultrasound-guided HIFU ablation, was clearly observed on the contrast-enhanced T1-weighted image of

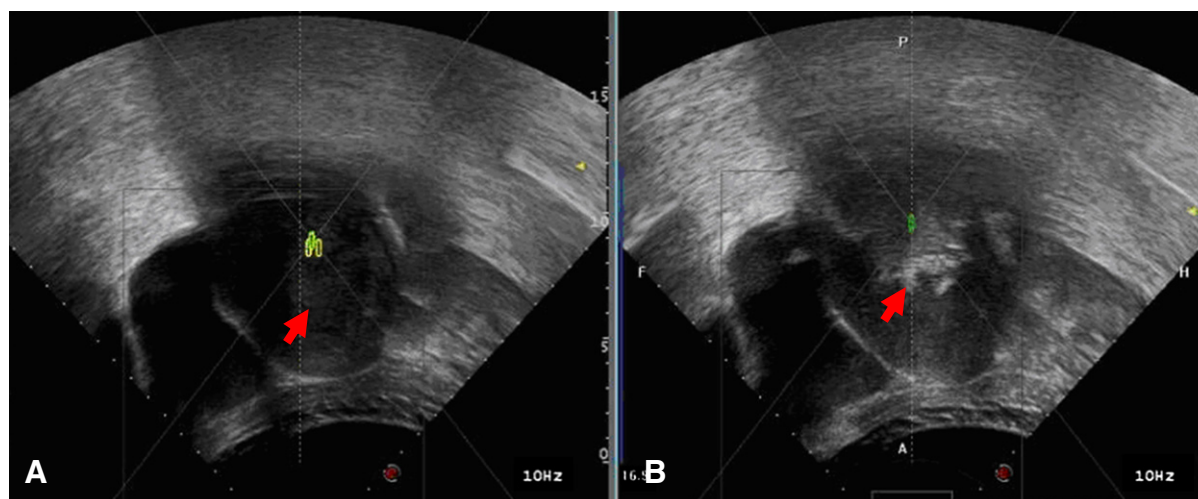


Fig. 1. Real-time ultrasound images from a 44-year-old woman with focal adenomyosis. (A) Pre-treatment ultrasound image shows a focal adenomyotic lesion at the posterior wall of the uterus (arrow). (B) Intra-procedure ultrasound image shows massive grayscale changes in the adenomyotic lesion (arrow).

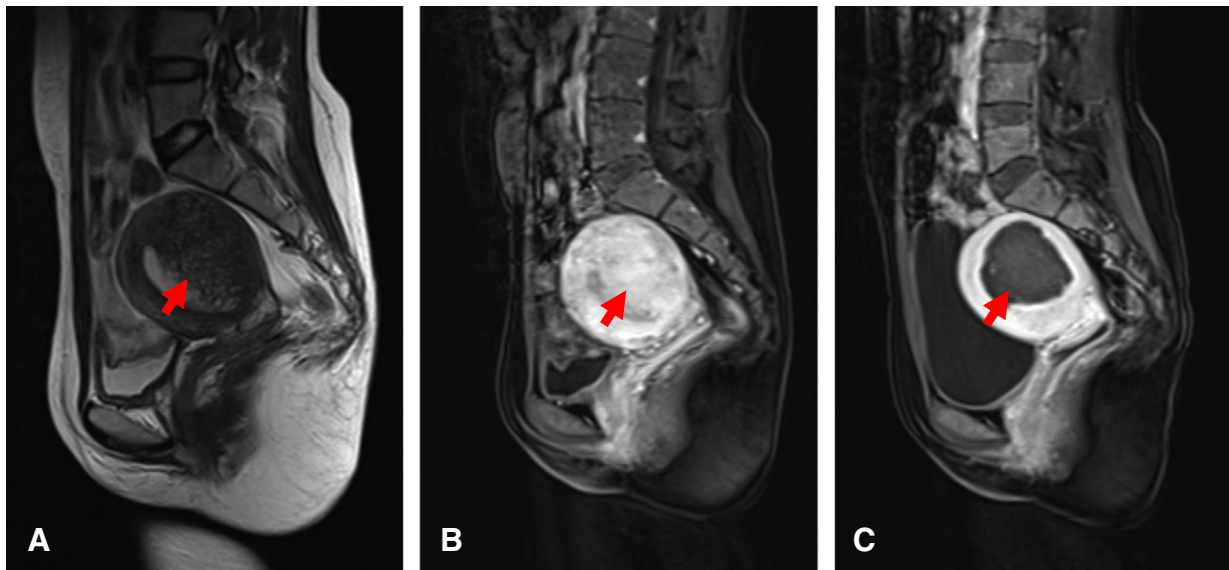


Fig. 2. Sagittal view of magnetic resonance images from a 37-year-old woman with focal adenomyosis. (A) Pre-treatment T2-weighted image shows a focal adenomyotic lesion at the posterior wall of the uterus (arrow). (B) Pre-treatment T1-weighted contrast-enhanced image shows perfusion of the adenomyotic lesion (arrow). (C) Post-treatment T1-weighted contrast-enhanced image shows that the non-perfused volume ratio was 85.0% (arrow).

MRI (Figs. 2 and 3). The pre-procedure uterus volume and the adenomyotic lesion volume were $226.4 \pm 93.2 \text{ cm}^3$ and $40.0 \pm 34.2 \text{ cm}^3$; the average NPV obtained from MRI 1 day after ultrasound-guided HIFU was $31.0 \pm 29.9 \text{ cm}^3$ and the average NPV ratio was $71.6\% \pm 19.1\%$ among the 202 patients.

On the basis of MRI, 120 patients were found to have focal adenomyosis (Fig. 2) and 82 patients to have diffuse adenomyosis (Fig. 3). Among the 120 patients with focal adenomyosis, the pre-procedure uterus volume and the adenomyotic lesion volume were $210.5 \pm 80.8 \text{ cm}^3$ and $44.9 \pm 32.9 \text{ cm}^3$, respectively; the average NPV was $29.0 \pm 24.8 \text{ cm}^3$; and the mean NPV ratio was $71.7\% \pm 19.3\%$. Among the 82 patients with diffuse adenomyosis, the average volume of the pre-procedure uterus and the adenomyotic lesion were $250.4 \pm 105.4 \text{ cm}^3$ and $46.8 \pm 29.4 \text{ cm}^3$, respectively; the average NPV was $33.5 \pm 35.1 \text{ cm}^3$; and the average NPV ratio was $71.6\% \pm 19.1\%$. The size of the uterus was larger among patients with diffuse adenomyosis than among patients with focal adenomyosis; however, no significant

difference was observed in adenomyotic lesion volume, NPV, or NPV ratio between the 2 patient groups (Table 1).

Among the 202 patients with symptomatic adenomyosis, 139 patients had menorrhagia and 177 patients had varying degrees of dysmenorrhea. As of the end of September 2012, 121 of the 139 patients with menorrhagia had attended their 1-month follow-up, and 119 had attended their 3-month follow-up. Among 103 patients who had been treated with ultrasound-guided HIFU 6 months earlier, 88 had returned for their 6-month follow-up; and, among the 58 patients who had been treated 12 months earlier, 47 had returned for their 12-month follow-up; lastly, 23 of 29 patients with menorrhagia had attended their 18-month follow-up. Table 2 shows the average score of menorrhagia at baseline and at different follow-up times after HIFU: there was a significant difference in menorrhagia score between baseline and every follow-up time (all $P < 0.001$).

Among the 177 patients with varying degrees of dysmenorrhea, 154 had completed their 1-month follow-up and 152 had attended

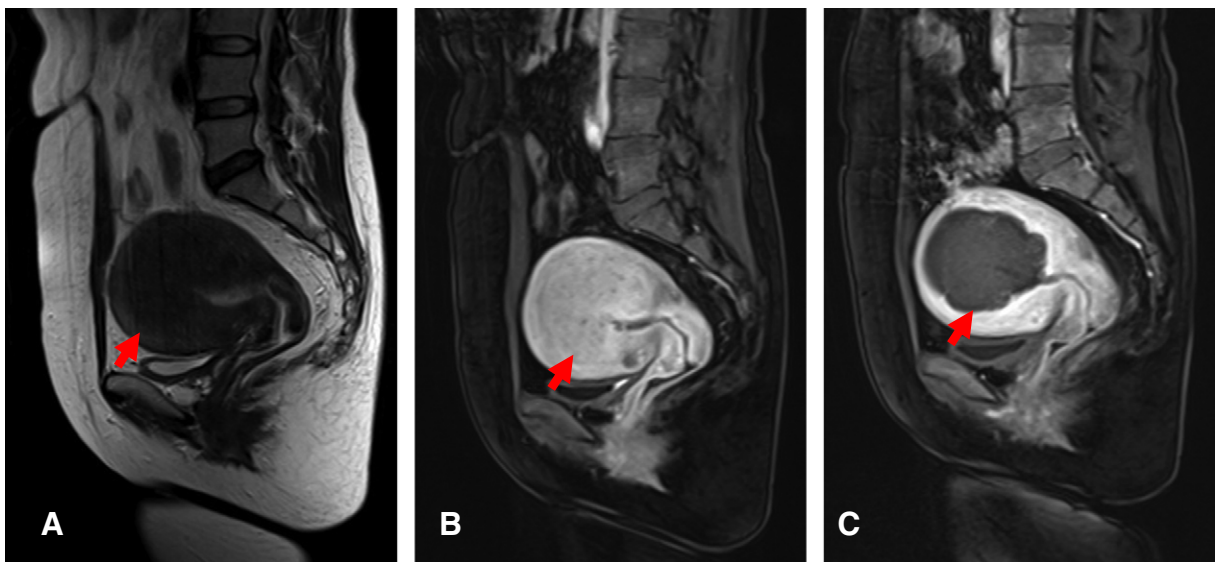


Fig. 3. Sagittal view of magnetic resonance images from a 47-year-old woman with diffuse adenomyosis. (A) Pre-treatment T2-weighted image shows that the invading endometrium causes a generalized expansion of the uterine walls. (B) Pre-treatment T1-weighted contrast-enhanced image shows perfusion of the adenomyotic lesion (arrow). (C) Post-treatment T1-weighted contrast-enhanced image shows that the non-perfused volume ratio was 83.5% (arrow).

Table 1
Characteristics of the 202 study patients with focal or diffuse adenomyosis.^a

Variable	Focal adenomyosis (n = 120)	Diffuse adenomyosis (n = 82)	P value
Age, y	41.5 ± 5.0	41.9 ± 4.9	0.200
Volume of uterus, cm ³	210.5 ± 80.8	250.4 ± 105.4	0.007
Volume of adenomyotic lesion, cm ³	44.9 ± 32.9	46.8 ± 29.4	0.384
Non-perfused volume, cm ³	29.0 ± 24.8	33.5 ± 35.1	0.178
NPV ratio, % ^b	71.7 ± 19.3	71.6 ± 19.1	0.313

^a Values are given as mean ± SD unless stated otherwise.^b Non-perfused volume divided by baseline adenomyotic lesion volume.

their 3-month follow-up as of the end of September 2012. Among these patients, 132 patients had been treated with ultrasound-guided HIFU 6 months earlier and 115 of them had completed their 6-month follow-up; among 85 patients who had been treated 12 months earlier, 73 had attended their 12-month follow-up; lastly, 30 of 37 patients had completed their 18-month follow-up. Table 3 shows the average menstrual pain score of these patients at baseline and at each follow-up time after HIFU: there was a significant reduction in menstrual pain score between baseline and every follow-up time (all $P < 0.001$).

Treatment efficacy was determined on the basis of the post-treatment relief of dysmenorrhea. At 1, 3, 6, 12, and 18 months after treatment, the percentage of women with complete relief of dysmenorrhea was 42.2%, 48.7%, 47.8%, 46.5%, and 46.6%, respectively; that of women with significant relief was 14.2%, 15.2%, 14.7%, 19.1%, and 26.6%, respectively; and that of women with partial relief was 25.9%, 21.0%, 14.7%, 13.6%, and 6.6%, respectively. The rate of overall relief of dysmenorrhea at 1, 3, 6, 12, 18 months was 82.3%, 84.9%, 77.2%, 79.2%, and 79.8%, respectively.

Clinical outcome was compared between patients with focal adenomyosis and those with diffuse adenomyosis. The rate of complete relief of dysmenorrhea at 3 months after ultrasound-guided HIFU was significantly higher among patients with focal adenomyosis than among patients with diffuse adenomyosis (Table 4). However, no other differences in the menorrhagia score, dysmenorrhea score, or other symptom relief rates were observed between the 2 groups at either 3 months or 12 months after HIFU treatment (Tables 4 and 5).

Immediately after ultrasound-guided HIFU, 64.2% and 70.7% of patients with focal adenomyosis and diffuse adenomyosis, respectively, complained of mild lower abdominal pain; 20.0% and 19.5% complained of sciatic or buttock pain; and 54.2% and 51.2% reported vaginal discharge; One patient with focal adenomyosis (0.8%) and 2 patients with focal adenomyosis (2.4%) had skin redness or blisters in the anterior abdominal wall. One patient with focal adenomyosis had a fever after treatment; however, their temperature was below 38 °C. No patient reported leg pain after HIFU treatment.

Table 2
Comparison of menorrhagia severity score before and after HIFU among 139 patients with menorrhagia.^a

Follow-up time	No. of patients ^b	Pre-HIFU score	Post-HIFU score	P value
1 month	121	2.8 ± 0.7 (2–5)	1.6 ± 0.7 (1–4)	<0.001
3 months	119	2.8 ± 0.7 (2–5)	1.5 ± 0.7 (1–4)	<0.001
6 months	88	2.9 ± 0.7 (2–5)	1.3 ± 0.6 (1–4)	<0.001
12 months	47	2.9 ± 0.6 (2–5)	1.3 ± 0.6 (1–4)	<0.001
18 months	23	3.0 ± 0.5 (2–5)	1.2 ± 0.4 (1–3)	<0.001

Abbreviation: HIFU, high-intensity focused ultrasound.

^a Values are given as number or mean ± SD (range) unless stated otherwise.^b As of September 2012, all patients had attended their 1- and/or 3-month follow-up; 15 of 103 patients had not attended their 6-month follow-up; 11 of 58 patients had not attended their 12-month follow-up; and 6 of 29 patients had not attended their 18-month follow-up.**Table 3**
Comparison of dysmenorrhea severity pain scores before and after HIFU in 177 patients with dysmenorrhea.^a

Follow-up time	No. of patients ^b	Pre-HIFU score	Post-HIFU score	P value
1 month	154	3.0 ± 0.7 (2–5)	1.7 ± 0.8 (1–4)	<0.001
3 months	152	3.0 ± 0.7 (2–5)	1.6 ± 0.7 (1–4)	<0.001
6 months	115	3.0 ± 0.7 (2–5)	1.7 ± 0.9 (1–4)	<0.001
12 months	73	3.2 ± 0.7 (2–5)	1.7 ± 0.8 (1–4)	<0.001
18 months	30	3.5 ± 0.7 (2–5)	1.8 ± 0.9 (1–4)	<0.001

^a Values are given as number or mean ± SD (range) unless stated otherwise.^b As of September 2012, all patients had attended their 1- and/or 3-month follow-up; 17 of 132 patients had not attended their 6-month follow-up; 12 of 85 patients had not attended their 12-month follow-up; and 7 of 37 patients had not attended their 18-month follow-up.

4. Discussion

A few small studies have suggested that ultrasound-guided HIFU is a feasible and safe technique for treating adenomyosis, and that most patients experience symptomatic relief through 2 years of follow-up [9,10]. Wang et al. [17] performed ultrasound-guided HIFU ablation on 12 patients using various acoustic intensities to achieve different necrotic volumes, and showed that better pain relief was achieved with a larger volume of necrosis [17].

In the present study of 202 symptomatic patients, the score of menorrhagia or the score of dysmenorrhea had decreased significantly after 1 month, and remained lower for 18 months, after ultrasound-guided HIFU with an average NPV ratio of 71.6% ± 19.1%. The present results showing complete relief are consistent with earlier studies, and suggest that ultrasound-guided HIFU is effective in relieving menorrhagia and dysmenorrhea. Furthermore, the score of menorrhagia and the score of dysmenorrhea decreased and remained lower among patients with either focal or diffuse adenomyosis over different follow-up periods. No significant difference in the score of menorrhagia or the score of dysmenorrhea was observed between patients with focal adenomyosis and those with diffuse adenomyosis; however, a significantly higher rate of complete relief of dysmenorrhea was achieved among patients with focal adenomyosis at 3 months after ultrasound-guided HIFU treatment. Although there was no significant difference in complete relief rate at other follow-up times, some trends were observed (Tables 4 and 5). These phenomena might be explained by the fact that focal adenomyosis is a circumscribed adenomyotic lesion in the myometrium (Fig. 2); as a result, a higher NPV ratio and a higher rate of complete relief of dysmenorrhea can be achieved.

The present study also demonstrated that ultrasound-guided HIFU ablation of adenomyosis is safe. The incidence of adverse effects was similar to that reported in previous studies, including studies of ultrasound-guided HIFU treatment for uterine fibroids [10,19]. After treatment with ultrasound-guided HIFU, patients often complained of

Table 4
Comparison of clinical outcome between patients with focal adenomyosis and those with diffuse adenomyosis 3 months after HIFU.^a

Variable	Focal adenomyosis (n = 120)	Diffuse adenomyosis (n = 82)	P value
Menorrhagia severity score ^b	1.34 ± 0.61	1.42 ± 0.73	0.423
Dysmenorrhea severity pain score ^b	1.48 ± 0.69	1.69 ± 0.76	0.481
Complete relief of menorrhagia	62.1	57.1	0.709
Clinically effective alleviation of menorrhagia ^c	82.3	79.5	0.814
Complete relief of dysmenorrhea	56.0	36.0	0.02
Clinically effective dysmenorrhea alleviation ^c	87.9	81.9	0.351

Abbreviation: HIFU, high-intensity focused ultrasound.

^a Values are given as percentage or mean ± SD unless stated otherwise.^b In total, 133 patients with menorrhagia (74 with focal and 49 with diffuse adenomyosis) and 152 patients with dysmenorrhea (91 with focal and 61 with diffuse adenomyosis) completed the 3-month follow-up.^c Complete, partial, and minor relief were determined as clinically effective.

Table 5

Comparison of clinical outcome between patients with focal adenomyosis and those with diffuse adenomyosis 12 months after HIFU.^a

Variable	Focal adenomyosis (n = 120)	Diffuse adenomyosis (n = 82)	P value
Menorrhagia severity score ^b	1.19 ± 0.40	1.50 ± 0.83	0.064
Dysmenorrhea severity pain score ^b	1.67 ± 0.88	1.72 ± 0.88	0.715
Complete relief of menorrhagia	71.8	59.2	0.409
Clinically effective menorrhagia alleviation ^c	90.4	81.4	0.450
Complete relief of dysmenorrhea	50.0	40.0	0.475
Clinically effective dysmenorrhea alleviation ^c	78.5	80.0	>0.99

Abbreviation: HIFU, high-intensity focused ultrasound.

^a Values are given as percentage or mean ± SD.

^b In total, 59 patients with menorrhagia (32 with focal and 27 with diffuse adenomyosis) and 72 patients with dysmenorrhea (42 with focal and 30 with diffuse adenomyosis) completed the 12-month follow-up.

^c Complete, partial, and minor relief were taken to be clinically effective.

mild lower abdominal local pain owing to inflammation and uterine contraction; sciatic or buttock pain was also a frequent adverse effect when the lesions were located at the posterior wall of the uterus, but such pain was mild. Without specific treatment, the pain ceased in 1 to 3 days. Skin burn is a complication unique to HIFU. In the present study, 3 patients had skin blisters immediately after ultrasound-guided HIFU. In accordance with the institutionally approved protocol, all patients were required to have routine bowel preparation before the procedure; as a result, no bowel injury occurred in any patient. There were no reports of abdominal cramping or nerve injury.

The study has a few limitations. It was a retrospective study, all of the women were from a single center, and the duration of the follow-up varied considerably; thus, only a small number of patients completed the 12- or 18-month follow-up. There were no differences in the baseline characteristics of the patients with focal or diffuse adenomyosis except for uterine volume; however, the difference in uterine size might have affected the results. Future studies, such as multicenter clinical studies or prospective randomized controlled trials (myomectomy versus ultrasound-guided HIFU) might help to address whether ultrasound-guided HIFU can be used to treat patients with adenomyosis safely and effectively.

In conclusion, the present study has demonstrated that ultrasound-guided HIFU is a promising technique for treating patients with adenomyosis. Although further studies are needed for optimization of indications, the present results show that ultrasound-guided HIFU might be used to treat both focal and diffuse adenomyosis safely in order to alleviate the symptoms of menorrhagia and dysmenorrhea.

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Conflict of interest

L.Z. worked as a consultant at Chongqing Haifu. The other authors have no conflicts of interest.

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