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Comparison of high-intensity focused ultrasound for the treatment of internal and external adenomyosis based on magnetic resonance imaging classification

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ABSTRACT

Objective: To compare the safety and efficacy of high-intensity focused ultrasound (HIFU) treatment for patients with internal or external adenomyosis based on magnetic resonance imaging (MRI) classification.

Materials and methods: A total of 238 patients with internal adenomyosis and 167 patients with external adenomyosis who received HIFU treatment were enrolled. HIFU treatment results and adverse effects between patients with internal and external adenomyosis were compared.

Results: The treatment time and sonication time for patients with external adenomyosis were significantly longer than that for patients with internal adenomyosis. The total energy used and EEF for patients with external adenomyosis were higher than that for patients with internal adenomyosis ($p < 0.05$). The pre-HIFU median dysmenorrhea score in patients with internal or external adenomyosis was 5 or 8 points, the median score decreased to 1 or 3 points in these two groups at 18-month post-HIFU ($p < 0.05$). The relief rate of dysmenorrhea was 79.5% in patients with internal adenomyosis, and it was 80.8% in patients with external adenomyosis. The pre-HIFU median menorrhagia score in patients with internal or external adenomyosis was 4 or 3 points, the median score decreased to 1 point in both groups at 18-month post-HIFU with a relief rate of 86.2% and 77.1%, respectively ($p = 0.030$). No serious complication occurred in any of these patients.

Conclusions: HIFU is a safe and effective treatment either for patients with internal adenomyosis or external adenomyosis. It seemed that internal adenomyosis is easier to be treated with HIFU and with a higher relief rate of menorrhagia than external adenomyosis.

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Introduction

Adenomyosis is an estrogen-dependent uterine benign disease characterized by the invasion of endometrial glands and stroma into the myometrium [1]. The incidence rate of adenomyosis in patients who underwent hysterectomy over the last 50 years ranged from 8.8% to 61.5%, and the estimated prevalence of adenomyosis was about 10–50% in reproductive age women [2,3].

Clinically, around two-thirds of patients with adenomyosis are symptomatic and thus need to be treated [4]. The main symptoms of adenomyosis are dysmenorrhea and menorrhagia. This disease also has a great impact on the fertility of childbearing age women [5–7]. The diagnosis of adenomyosis is suspected by clinical evaluation and confirmed with ultrasound and magnetic resonance imaging (MRI). MRI offers the best soft tissue resolution and can clearly show

the appearance of adenomyotic lesions in internal or external layers of the myometrium. The typical MRI features of adenomyotic lesions include ill-defined low signal intensity areas with hyperintensity foci in the lesions on T2-weighted images (T2WI) [8–9]. Kishi et al. classified adenomyosis as four types based on the location of adenomyotic lesion and the relationship between the lesion and the endometrium, junction zone, myometrium, and the serosa of the uterus revealed by MRI: type I (intrinsic), type II (extrinsic), type III (intramural) and type IV (indeterminate) [10].

The treatment for adenomyosis is an intense challenge. Traditionally, treatments of adenomyosis include medical and/or surgical. Hysterectomy is still the only curative treatment for adenomyosis. However, hysterectomy is not suitable for patients who wish to have more children. As the margin of adenomyotic lesion is ill-defined, it is difficult to perform adenomyomectomy to remove the lesion

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completely and the recurrence rate is very high. Although medical treatment can effectively improve symptoms of patients, symptoms often return after medication withdrawal. Uterine artery embolization(UAE)has also been used in the treatment of adenomyosis, but it has a certain impact on ovarian function [11,12]. Therefore, it is an urgent task for gynecologists in clinical practice to explore and find a conservative treatment with less harm to patients.

High-intensity focused ultrasound (HIFU) ablation has been utilized in the treatment of adenomyosis for more than 10 years. Many studies have shown its safety and efficacy in the management of adenomyosis [13–19]. A previous study showed that the relief rate of dysmenorrhea was 84.7%, 84.7%, and 82.3%, respectively at 3 months, 1 year, and 2 years after HIFU treatment. The relief rate of menorrhagia was 79.8%, 80.7%, and 78.9%, respectively at 3 months, 1 year, and 2 years after HIFU treatment. In these patients, some reported complete relief of the symptoms, some reported obvious or partial relief [20]. However, it is not clear if the symptom relief is related to the types of adenomyosis. Recently, Gong et al. compared the results of HIFU treatment for different subtypes of adenomyosis and showed that the relief rate of menorrhagia was related to different subtypes [21]. However, no study was performed in comparing HIFU treatment for internal and external adenomyosis. The aim of this study was to objectively evaluate mid-term symptom improvement in patients with internal and external adenomyosis based on MRI classification after HIFU treatment.

Materials and methods

This retrospective study was approved by the ethics committee at our institutes (NO. SJZPH-2021002), and the requirement for an informed consent to do the research was waived.

Patients

From January 2016 to December 2020, a total of 1254 patients with adenomyosis were treated with HIFU at Shijiazhuang People's Hospital and Chongqing Haifu Hospital. Based on the inclusion and exclusion criteria, 405 patients with internal or external adenomyosis were enrolled in this study (Figure 1). The medical history of the patients was collected. All patients had a routine physical examination, routine laboratory tests, TCT, HPV, electrocardiogram, chest X-ray, ultrasound and MRI after their admission into hospital.

The inclusion criteria were as follows: (1) the initial diagnosis of adenomyosis was made by clinical evaluation, and confirmed with ultrasound and MRI; (2) patients presented dysmenorrhea and/or menorrhagia and were classified as internal or external adenomyosis; (3) patients completed HIFU ablation in one session and completed follow-up; (4) patients should take pre- and post-HIFU MRI examinations; (5) patients could communicate with the nurse or physician during the procedure of HIFU.

The exclusion criteria were as follows: (1) patients with suspected or confirmed uterine malignancy; (2) patients received hormone therapy after HIFU; (3) patients with internal or external adenomyosis and had uterine fibroids; (4) patients didn't complete the 18-month follow-up.

MRI evaluation

All patients underwent MRI examination within 1 week before and 1 day after HIFU treatment. A series of standard T1 weighted images (T1WI), T2WI, and contrast-enhanced MRI were performed on all patients. T1WI before and after administration of gadolinium and T2WI were obtained in three planes. The parameters used for T1WI were as below: TR 214ms/TE 10 ms, voxel size $1.13 \times 0.79 \times 5.0$ mm, slice

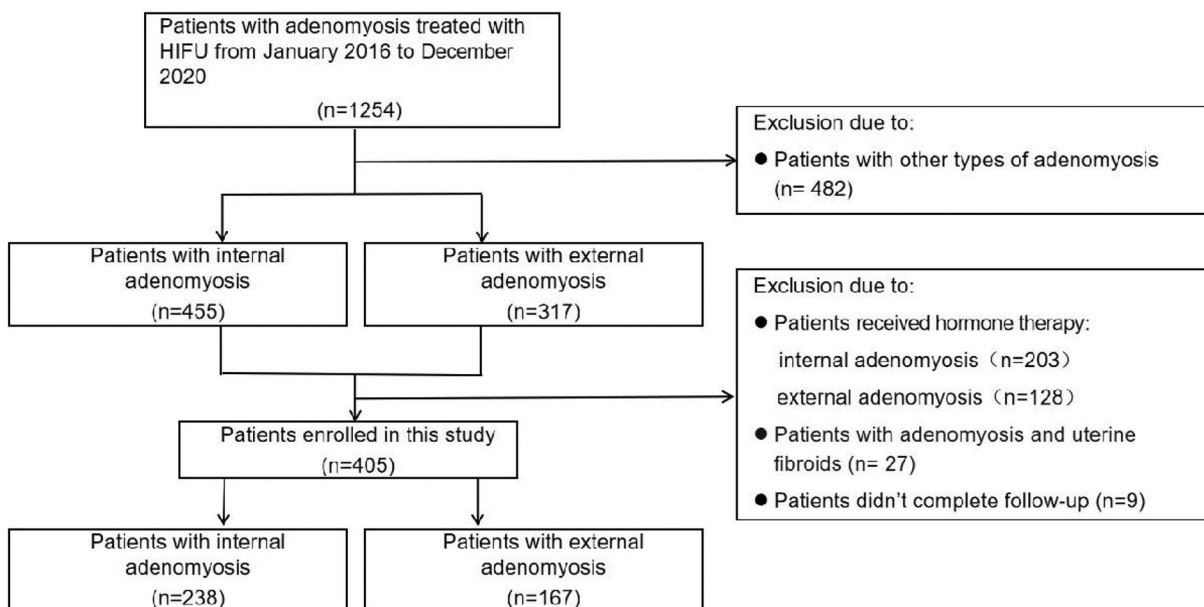


Figure 1. Flowchart of patient selection.

thickness 5 mm. The parameters used for T2WI were: TR 5300 ms/TE 88 ms, voxel size $1.7 \times 0.75 \times 5.0$ mm, slice thickness 5 mm. The parameters for contrast-enhanced images were: TR 3.94 ms/TE 1.84 ms, voxel size $1.62 \times 1.22 \times 4.0$ mm, slice thickness 4 mm. The MRI scanning sequences and parameters were consistent before and after HIFU treatment. The contrast agent used was gadolinium glucamine or gadolinium diamine.

The size and location of the adenomyotic lesions were evaluated on T2WI of MRI. In this study, internal adenomyosis was defined as the lesion had developed in the thickened junctional zone and that healthy muscular structures were preserved outside the adenomyosis (Figure 2(A)); external adenomyosis was defined as the lesion located in the outer myometrium of the uterine wall, the healthy muscular structures were preserved between the adenomyotic lesion and the junctional zone, and the junctional zone was kept intact without aberrancy (Figure 2(B)).

The uterine volume, adenomyotic lesion volume and NPV were obtained using the software program, which was programmed by the engineers from Chongqing MicroSea Software Development, to contour the uterine, adenomyotic

lesion and the nonperfused region in every slice of contrast enhanced MR images, then calculated using the same program [22]. The NPV ratio was calculated as the volume of nonperfused area after HIFU treatment/the volume of adenomyotic lesion before treatment $\times 100\%$ (Figure 3). Energy efficiency factor (EEF) was defined as the ultrasound energy delivered for ablating 1mm^3 of the adenomyotic lesion ($\text{EEF} = \eta P t / V$ (J/mm^3), where η indicates a focusing factor ($\eta = 0.7$), P indicates sonication power (W), t indicates sonication time, and V indicates NPV (mm^3) [23].

Preparation before HIFU ablation

Specific bowel preparation should be performed before HIFU treatment. The patients were asked to ingest semiliquid meal for 2 days, followed by ingestion of liquid food for 1 day, fasting for 12 h, and an enema before HIFU on the treatment day.

Skin preparation included shaving the hair of the abdominal wall between the umbilicus and the superior border of the symphysis pubis, then degreasing and degassing with 70% ethanol and degassed water.

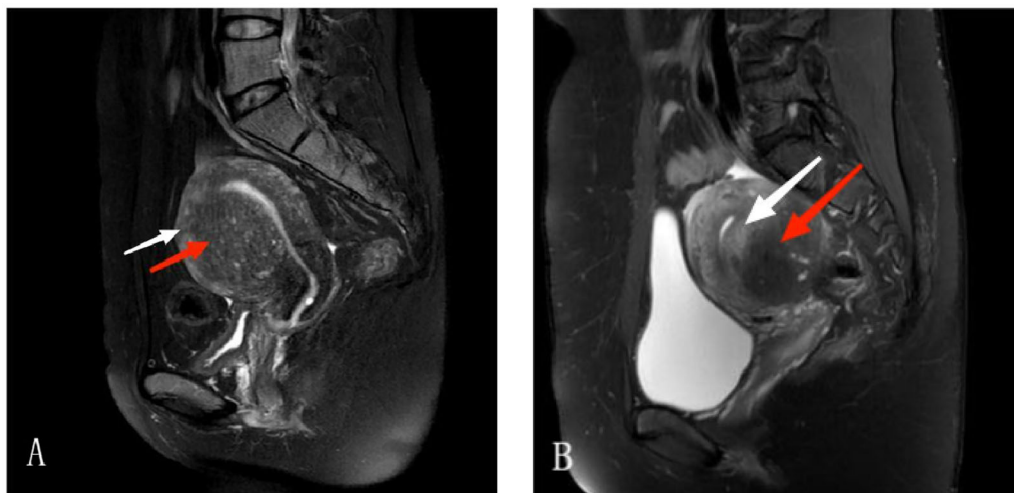


Figure 2. MRI features of internal and external adenomyosis. (A) Internal adenomyosis: a lesion with ill-defined margin located in the anterior wall of the uterus had developed in the thickened junctional zone (red arrow) and the myometrium outside the adenomyotic lesion was preserved. The thickness of the intact myometrium was 6 mm (white arrow). (B) External adenomyosis: a lesion with ill-defined margin (red arrow) located in the outer myometrium of the posterior wall of the uterus, the inner myometrium (the thickness was 8 mm, white arrow) between the adenomyotic lesion and the junctional zone was preserved, and the junctional zone was kept intact without aberrancy.

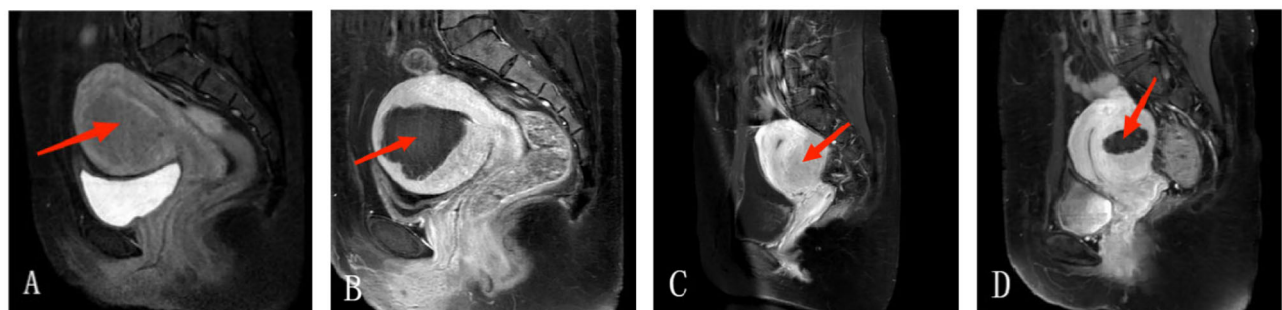


Figure 3. HIFU treatment for internal and external adenomyosis. (A) Pre-HIFU enhanced MRI showed an internal adenomyotic lesion located at the anterior wall of the uterus (arrow); (B) A contrast enhanced MR image obtained 1 day after HIFU showed the internal adenomyotic lesion was ablated (arrow). The NPV ratio was 89.5 %. (C) Pre-HIFU enhanced MRI showed an external adenomyotic lesion located at the posterior wall of the uterus (arrow); (D) A contrast enhanced MR image obtained 1 day after HIFU showed the external adenomyotic lesion was ablated without damaging to the serosa of the uterus (arrow). The NPV ratio was 44.1%.

An urinary catheter was inserted into the bladder and the bladder volume was adjusted by infusing warm normal saline (30 °C) to obtain a safe acoustic pathway.

HIFU ablation

The procedure of HIFU treatment for adenomyosis was performed under conscious sedation (Fentanyl at 0.8–1 µg/kg administered at 30–40 min intervals; midazolam hydrochloride, at 0.02–0.03 mg/kg, administered at 30–40 min intervals) using a Focused Ultrasound Tumor Therapeutic System (Model-JC200, Chongqing Haifu Medical Technology Co., Ltd., Chongqing, China) equipped with an ultrasound imaging probe (MyLab 90, Esaote, Genova, Italy), which was used for real-time monitoring during treatment. Therapeutic ultrasound was generated by a transducer with a frequency of 0.8–1.0 MHz, a focal length of 15 cm, and a diameter of 20 cm. The patients were carefully positioned prone on the HIFU treatment table, with the anterior abdominal wall in contact with degassed water. A degassed water balloon was placed between the abdominal wall and the transducer, which was used to push the bowel away from the acoustic pathway by adjusting its size and tension to prevent bowel injury.

Sagittal ultrasound scanning mode was selected. The treatment plan was made by dividing the adenomyotic lesion into different slices with a distance of 5 mm between slices. Point scanning was selected and the sonication power used was between 300 W and 400 W. The treatment began from the innermost slice, and the focus was kept at least 1.5 cm away from the endometrium and 1 cm from the boundary of the adenomyotic lesion. During the procedure, HIFU therapeutic power was adjusted based on patient feedback and changes in grayscale of the treated area on ultrasonographic imaging. HIFU treatment was terminated when the increased grayscale covered the adenomyotic lesion or the enough energy was delivered as planned. Contrast-enhanced ultrasound was then performed to evaluate the ablation volume of adenomyotic lesions. The patients were asked to report any discomfort during the procedure and the vital signs of heart rate, blood pressure, respiration and oxygen saturation were monitored.

Follow-up

The scores for dysmenorrhea and menorrhagia during menstruation were recorded before HIFU. After HIFU ablation, the patients were followed up at 1-, 3-, 6-, 12- and 18-month to assess improvement of symptoms.

The visual analog scale (VAS) was used to evaluate the degree of the dysmenorrhea [24]. The VAS scoring criteria was as follows: 0 points represent 'no pain' while 10 points, represent the 'most severe pain imagined', 1–3 points represent mild pain, 4–6 points represent moderate pain and 7–9 points represent severe pain.

The menorrhagia was categorized by a 5-point categorical scale [25]. In this categorical scale, 1 point indicated a small amount of menstruation volume; 2 points indicated a

moderate amount of menstruation volume; 3 points indicated a large amount of menstruation volume; 4 points indicated a very large amount of menstruation volume; 5 points indicated an extremely large amount of menstruation volume.

The clinical relief ratio of dysmenorrhea and menorrhagia, defined as (pre-HIFU score-post-HIFU)/pre-HIFU score, was compared between the two types. The degree of symptom relief was evaluated using the following criteria: (1) partial relief: the relief ratio is less than 50%; (2) clinical obvious relief: the relief ratio is over 50%; (3) clinical complete relief: complete relief of symptoms; (4) clinical ineffective: post-HIFU scores increase or equal to pre-HIFU. Clinical relief included partial relief, obvious relief and complete relief [21].

Statistical analysis

SPSS 21.0 software was used for statistical analysis. Shapiro–Wilk test was performed to verify whether the data is normal distribution. Normal distribution data were expressed as mean ± standard deviation (mean ± SD). Non-normally distributed data were presented as median and interquartile range. The student t test and nonparametric unpaired Mann–Whitney *U*-test were used for comparison between groups, and the nonparametric Wilcoxon signed-rank test was used for intra-group comparison. The Chi-square test was applied for the analysis of the enumerated data. $p < 0.05$ was considered as statistically significant.

Results

Baseline characteristics

The baseline characteristics of the 405 patients were summarized in Table 1. Among them, 238 patients had internal adenomyosis, 167 patients had external adenomyosis.

The average age of patients with external adenomyosis was significantly younger than that of patients with internal adenomyosis (39.3 ± 5.7 vs. 42.3 ± 6.3 years, $p = 0.000$). The average BMI of patients with external adenomyosis was slightly lower than that of patients with internal adenomyosis (23.5 ± 3.3 vs. 24.1 ± 3.3 kg/m², $p = 0.043$). Both the internal and external adenomyotic lesions were more often seen in the posterior wall of the uterus, but the percentage of adenomyotic lesions in the posterior wall of the uterus over all adenomyotic lesions was significantly higher in patients with external adenomyosis than that of patients with internal adenomyosis ($p < 0.05$). The volume of the uterus and adenomyotic lesion was significantly lower in patients with external adenomyosis than the patients with internal adenomyosis ($p < 0.05$). Ovarian endometrial cysts were seen in 5% of patients with internal adenomyosis and 41.3% of patients with external adenomyosis ($p < 0.05$). There were no significant differences in either rectus abdominis thickness or subcutaneous fat thickness between the two groups.

Table 1. Comparison of baseline characteristics of patients with internal and external adenomyosis.

Variables	Internal adenomyosis (n = 238)	External adenomyosis (n = 167)	p
Age (years)	42.3 ± 6.3	39.3 ± 5.7	0.000
BMI (kg/m ²)	24.1 ± 3.3	23.5 ± 3.3	0.043
Rectus abdominis thickness(mm)	9.7 ± 3.6	10.1 ± 3.7	0.326
Subcutaneous fat thickness(mm)	18.7 ± 7.6	19.4 ± 8.3	0.379
Location of the lesions(A/P/F)	88/131/19	16/140/11	0.000
Volume of the uterus (cm ³)	223.9 (155.2, 302.5)	197.3 (135.8, 274.0)	0.038
Volume of lesion (cm ³)	86.2 (55.9, 148.7)	70.7 (33.4, 121.2)	0.001
Endometriosis cyst of ovary (%)	12 (5.0)	69 (41.3)	0.000

Notes. A: anterior wall of the uterus; P: posterior wall of the uterus; F: fundus.

Table 2. Comparison of HIFU treatment results between patients with internal and external adenomyosis.

Variables	Internal adenomyosis (n = 238)	External adenomyosis (n = 167)	p
Power (W)	357.0 ± 48.8	360.7 ± 51.0	0.462
Treatment time(min)	58.5 ± 31.1	70.9 ± 43.9	0.001
Sonication time(s)	526.8 ± 321.8	597.4 ± 396.2	0.049
Treatment intensity(s/h)	545.5 (428.6, 664.1)	534.0 (398.0, 623.5)	0.361
Total energy(KJ)	190.5 ± 124.6	224.4 ± 159.2	0.017
NPV ratio (%)	48.0 (29.0, 69.0)	43.0 (26.0, 59.0)	0.054
EEF(J/mm ³)	2.9 (1.5, 6.9)	5.2 (2.5, 11.5)	<0.001

HIFU ablation results

All patients completed HIFU ablation for adenomyotic lesions in one session. As shown in Table 2, using similar sonication power for treating patients with internal adenomyosis or external adenomyosis, similar NPV ratio was achieved in both groups ($p > 0.05$). However, the treatment time and sonication time of patients with external adenomyosis were significantly longer than that of patients with internal adenomyosis. The total energy used and EEF for patients with external adenomyosis were significantly higher than those for patients with internal adenomyosis ($p < 0.05$).

We further compared the treatment results of patients with adenomyosis located in the posterior wall of the uterus between patients with internal and external adenomyosis. As shown in Table 3, a larger NPV ratio was achieved in patients with internal adenomyosis than that in patients with external adenomyosis using similar treatment time, sonication time, treatment intensity, and total energy. EEF was significantly less for internal adenomyosis than that of external adenomyosis.

Comparison of adverse effects and complications

All patients tolerated HIFU treatment well. The most common intraoperative adverse effects included treated area pain, skin burning sensation, sciatic or buttock pain, transient leg pain and groin pain. These pains were generally transient and usually disappeared when sonication was terminated. We compared the incidence rate of adverse effects between the two groups. The percentage of sciatic or buttock pain in patients with external adenomyosis was significantly higher than that in patients with internal adenomyosis (56.3% vs. 40.8%, $p < 0.05$). The incidence of skin burning sensation in patients with internal adenomyosis was significantly higher

Table 3. Comparison of baseline characteristics and HIFU treatment results between patients with internal and external adenomyosis in the posterior wall of the uterus.

Variables	Internal adenomyosis (n = 131)	External adenomyosis (n = 140)	p
Age (years)	42.1 ± 6.7	39.2 ± 5.6	0.000
BMI (kg/m ²)	24.1 ± 3.0	23.4 ± 3.4	0.079
Rectus abdominis thickness(mm)	9.8 ± 3.7	9.9 ± 3.7	0.737
Subcutaneous fat thickness(mm)	18.2 ± 7.1	18.8 ± 8.2	0.471
Volume of the uterus (cm ³)	220.4 (154.7, 299.1)	193.8 (132.4, 268.6)	0.038
Volume of lesion (cm ³)	81.7 (55.7, 121.1)	72.0 (33.5, 123.4)	0.024
Power (W)	362.6 ± 29.3	360.2 ± 49.8	0.685
Treatment time(min)	60.1 ± 34.9	66.8 ± 42.6	0.162
Sonication time(s)	532.9 ± 350.4	540.9 ± 338.7	0.849
Treatment intensity(s/h)	545.5 (429.0, 649.5)	526.0 (391.3, 606.0)	0.328
Total energy(KJ)	198.0 ± 138.0	204.3 ± 136.5	0.705
NPV ratio (%)	49.0 (30.0, 71.0)	42.0 (25.0, 58.8)	0.008
EEF(J/mm ³)	2.9 (1.4, 8.0)	5.2 (2.4, 11.1)	0.003

Table 4. Comparison of adverse effects between patients with internal and external adenomyosis during HIFU treatment.

Variables	Internal adenomyosis (n = 238)	External adenomyosis (n = 167)	p
Leg pain	33 (13.9%)	26 (15.6%)	0.737
Sciatic or buttock pain (n, %)	97 (40.8%)	94 (56.3%)	0.003
Skin burning sensation (n, %)	93 (39.1%)	48 (28.7%)	0.041
Treated area pain	138 (58.0%)	104 (62.3%)	0.445
Groin pain	6 (2.5%)	4 (2.4%)	1

Table 5. Comparison of dysmenorrhea before and 18 month after HIFU between the two groups.

Variables	Internal adenomyosis (n = 205)	External adenomyosis (n = 161)	p
Pre-HIFU pain score	5.0 (3.0, 7.0)	8.0 (7.0, 9.0)	0.000
Post-HIFU pain score	1.0 (0.0, 3.0)	3.0 (2.0, 5.0)	0.000
p	0.000	0.000	

than that in patients with external adenomyosis (39.1% vs. 28.7%, $p < 0.05$). No significant difference was observed in incidence of leg pain, treated area pain and groin pain between the two groups ($p > 0.05$) (Table 4).

After HIFU treatment, the patients reported these pains were mild and no severe post-HIFU complications occurred in either group of these patients.

Improvement of dysmenorrhea

Among the 405 patients, 366 patients had dysmenorrhea before HIFU treatment, including 205 patients with internal adenomyosis, 161 patients with external adenomyosis. As shown in Table 5, the pre-HIFU dysmenorrhea score in patients with internal adenomyosis was significantly lower than that in patients with external adenomyosis ($p < 0.05$). After HIFU treatment, the pain score significantly decreased in both groups. The symptom relief sustained over 18 month after HIFU treatment. The patients with internal adenomyosis had the lower dysmenorrhea score than patients with external adenomyosis at 18 months after HIFU ($p < 0.05$). The clinical effectiveness rate of HIFU treatment for patients with internal and external adenomyosis in alleviating dysmenorrhea at 18-month follow-up was 79.5% and 80.8%, respectively. Statistical analysis showed that complete relief rate of

Table 6. Comparison of symptom improvement in patients with dysmenorrhea 18 month after HIFU between the two groups.

Variables	Internal adenomyosis (n = 205)	External adenomyosis (n = 161)	p
Partial relief (n, %)	23 (11.2)	22 (13.7)	0.496
Obvious relief (n, %)	86 (42.0)	95 (59.0)	0.148
Complete relief (n, %)	54 (26.3)	13 (8.1)	0.003
Clinical effective rate (n, %)	163 (79.5)	130 (80.8)	0.086

Table 7. Comparison of menorrhagia scores before and 18 month after HIFU between the two groups.

Variables	Internal adenomyosis (n = 209)	External adenomyosis (n = 140)	p
Pre-HIFU menstruation volume score	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	0.000
18-month post-HIFU score	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.856
P	0.000	0.000	

patients with internal adenomyosis was significantly higher than that of patients with external adenomyosis, but no significant difference was observed in partial relief rate, obvious relief rate, and clinical effectiveness rate between the two groups ($p > 0.05$) (Table 6).

Improvement of menorrhagia

Among the 405 patients who had completed 18-month follow-up, A total of 349 had varying degrees of menorrhagia before HIFU treatment, including 209 patients with internal adenomyosis, and 140 patients with external adenomyosis. As shown in Table 7, the patients with internal adenomyosis had a higher median pre-HIFU menstruation volume score than that of patients with external adenomyosis ($p < 0.05$). The median pre-HIFU menstruation volume score was 4 points in the group of patients with internal adenomyosis, and it was 3 points in the group of patients with external adenomyosis. The scores in both groups decreased to 1 point at 18-month after HIFU. The obvious relief rate in patients with internal adenomyosis was significantly higher than that of patients with external adenomyosis (43.1% vs 12.8%, $p < 0.05$). The clinical effectiveness rate of HIFU treatment at 18-month after HIFU was 86.2% in the group of patients with internal adenomyosis, as compared with 77.1% in the group with internal adenomyosis (Table 8). Patients with external adenomyosis had a significant lower median relief rate than that of the patients with internal adenomyosis ($p < 0.05$).

Discussion

A previous study with a small number of subjects has shown that internal adenomyosis (Kishi type I) accounted for 38.8%, external adenomyosis (Kishi type II) accounted for 33.6% [10]. In present study, we observed internal adenomyosis in 36.3%, and external adenomyosis in 25.3% of the total patients. Kishi et al. reported that anterior wall involvement of adenomyosis is more frequently seen in internal adenomyosis, external adenomyosis is frequently seen in posterior

Table 8. Comparison of treatment efficacy in patients with menorrhagia 18 month after HIFU between the two groups.

Variables	Internal adenomyosis (n = 209)	External adenomyosis (n = 140)	p
Partial relief (n, %)	32 (15.3)	28 (20.0)	0.524
Obvious relief (n, %)	90 (43.1)	18 (12.8)	0.000
Complete relief (n, %)	58 (27.8)	62 (44.3)	0.920
Clinical effective rate (n, %)	180 (86.2)	108 (77.1)	0.030

wall of the uterus [10]. In this study, we found that whether patients with internal adenomyosis or external adenomyosis, the adenomyotic lesion was more common seen in the posterior wall of the uterus, but the percentage of adenomyotic lesions located in the posterior wall of the uterus in patients with external adenomyosis was significantly higher than that of patients with internal adenomyosis ($p < 0.05$) (Table 1). We also found that patients with external adenomyosis were younger than that of patients with internal adenomyosis, which were consistent with the results from Bourdon M, et al. [26]. In this study, we found that the adenomyotic lesion volume and uterine volume were significantly larger in patients with internal adenomyosis than that of patients with external adenomyosis. We could not explain this phenomenon clearly. Is this difference related to its pathological characteristics and pathogenesis or onset of illness?

A study has demonstrated that the symptom relief is related to NPV ratio [27]. Although the adenomyotic lesion volume in patients with external adenomyosis was smaller than that of patients with internal adenomyosis, we spent more treatment time, sonication time, and delivered more energy to treat external adenomyosis than internal adenomyosis to achieve the similar NPV ratio. Therefore, the EEF for external adenomyosis was significantly greater than that for internal adenomyosis ($p < 0.05$) (Table 2). This higher EEF indicated that it needed more acoustic energy to ablate the same volume of external adenomyotic lesion than that for internal adenomyotic lesion. Since the contrast-enhanced MRI did not show a significant difference in enhancement in the lesions between the two types of adenomyosis and the external adenomyotic lesions were not adjacent to major blood vessels, so we think there was no difference in blood flow between the two types of adenomyotic lesions and 'heat sink effect' did not contribute to this phenomenon. One possible explanation for this phenomenon was that the proportion of external adenomyotic lesions located in the posterior wall of the uterus was more than that of internal adenomyosis in this study, thus the average distance from abdominal skin to adenomyotic lesion was longer in patients with external adenomyosis than that of patients with internal adenomyosis (Table 1). During HIFU treatment, ultrasound energy attenuation occurs since ultrasound beams go through the skin and other intermediate tissue layers before reaching adenomyotic lesion at posterior wall of the uterus. Thus, if the distance from the abdominal wall to the target region is longer, the more energy is lost [28]. This phenomenon might be also related to the small volume of adenomyotic lesion and can be explained by the 'damage-damage interference effects', because the necrotic area in the treated lesion changed the 'acoustic environment' of the

adenomyotic lesion and promote the deposition of ultrasound energy [28]. We further compared the treatment results between the two types with the adenomyotic lesions in the same location. In this study, the adenomyotic lesion located in posterior wall of the uterus was seen in 131 patients with internal adenomyosis, and 140 patients with external adenomyosis. The results showed a significant larger NPV ratio achieved in internal adenomyotic lesions than that in external adenomyotic lesions using the similar treatment time, sonication time, treatment intensity, and similar total energy. The EEF was significantly lower in internal adenomyotic lesions than that of external adenomyotic lesions ($p < 0.05$) (Table 3). It also indicated that external adenomyosis was more difficult to treatment with HIFU than internal adenomyosis. Therefore, the different pathological characteristics of the two types may affect the efficacy of HIFU ablation.

Our results indicated that HIFU can be safely used to treat patients with either internal adenomyosis or external adenomyosis. In this study, patients often complained of mild treated area pain owing to uterine contraction caused by sonication. Sciatic or buttock pain was also a frequent adverse effect, the incidence rate of sciatic or buttock pain was significantly higher in the group of patients with external adenomyosis than that of patients with internal adenomyosis because of the location of adenomyotic lesions ($p < 0.05$) (Table 1). No any other significant difference was observed between the two groups and no any major complication occurred in this study.

In this study, we found that the pre-HIFU dysmenorrhea score was lower in patients with internal adenomyosis than that in patients with external adenomyosis, but the menorrhagia score was higher. This may be related to the internal adenomyosis is less associated with pelvic endometriosis, and the symptoms of menorrhagia often accompanied by internal adenomyosis. Previous studies have shown that external adenomyosis is frequently coexist with endometriosis, especially with deep infiltrating endometriosis, compared to internal adenomyosis [29–30]. Based on the MRI scans in this study, ovarian endometrial cysts were detected in 5% of patients with internal adenomyosis and 41.3% of patients with external adenomyosis (Table 1). Our results also indicated that patients with external adenomyosis are more often associated with endometriosis than those with internal adenomyosis. Patients with deep infiltrating endometriosis are more likely to experience severe pain [31]. During follow-up period after HIFU, the dysmenorrhea score and menorrhagia score all significantly decreased in patients with internal or external adenomyosis. In terms of the relief rate of dysmenorrhea, there was no significant difference in partial relief rate, obvious relief rate, and clinical effective rate between the two groups. However, the complete relief rate in patients with internal adenomyosis was significantly higher than that of patients with external adenomyosis because internal adenomyosis was less associated with endometriosis than external adenomyosis. Regarding the relief rate of menorrhagia, a higher partial relief rate and a higher clinical relief rate were found in patients with internal

adenomyosis at 18-month after HIFU treatment when compared with patients with external adenomyosis. This phenomenon may be due to the fact that patients with external adenomyosis mainly manifested as dysmenorrhea while the symptom of menorrhagia is not obviously before treatment (Tables 4 and 6). Therefore, our results indicated that the different type of adenomyosis maybe another important factor that influencing the clinical efficacy of HIFU.

This study is limited because it is a retrospective study and the patients were not enrolled randomized, therefore, some bias may have occurred. In the future, multicenter or prospective randomized controlled trials with a large number of subjects are needed to confirm the findings of this study.

Conclusions

HIFU is an effective treatment in the management of patients with internal or external adenomyosis, without any severe adverse effects or complications. HIFU treatment can significantly improve symptoms of dysmenorrhea and menorrhagia. Based on the results from this study, HIFU seems to be more effective in relieving menorrhagia in patients with internal adenomyosis than patients with external adenomyosis.

Disclosure statement

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