**High intensity focused ultrasound treatment of adenomyosis:
the relationship between the features of magnetic resonance
imaging on T2 weighted images and the therapeutic efficacy**

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Abstract

Objectives: To investigate the relationship between the features of magnetic resonance imaging (MRI) on T2 weighted images (T2WI) and the therapeutic efficacy of high intensity focused ultrasound (HIFU) on adenomyosis.

Materials and Methods: From January 2011 to November 2015, four hundred and twenty-eight patients with symptomatic adenomyosis were treated with HIFU. Based on the signal intensity and the number of hyperintense foci in the adenomyotic lesions on T2WI, the patients were classified into groups. The day after HIFU ablation patients underwent contrast-enhanced MRI and a comparison was made of non-perfused volume (NPV) ratio, energy efficiency factor (EEF), treatment time, sonication time, and adverse effects.

Results: No significant difference in terms of HIFU treatment settings and results was observed between the group of patients with hypointense adenomyotic lesions and the group with isointense adenomyotic lesions ($P>0.05$). However, the sonication time and EEF were significantly higher in the group with multiple hyperintense foci compared to the group with few hyperintense foci. The NPV ratio achieved in the lesions with multiple hyperintense foci was significantly lower than that in the lesions with few hyperintense foci ($P<0.05$). No significant difference was observed in the rate of adverse effects between the two groups.

Conclusions: Based on our results, the response of the adenomyotic lesions to HIFU treatment is not related to the signal intensity of adenomyotic lesions on T2WI. However, the number of the high signal intensity foci in the adenomyotic lesions on T2WI can be considered as a predictive factor to help select patients for HIFU treatment.

Keywords: High intensity focused ultrasound (HIFU); Magnetic resonance imaging (MRI); Adenomyosis; Signal characteristics; Ablative efficiency

1. INTRODUCTION

Adenomyosis is a common gynaecological disease in women of childbearing age, characterized by ectopic endometrial glands and stroma within the myometrium, and usually accompanied by hyperplasia of the adjacent smooth muscle. The reported prevalence of adenomyosis ranges from 8.8% to 31%, and almost two-thirds are symptomatic [1-3]. The treatment of adenomyosis is at present a substantial challenge in gynecological practice. Hysterectomy remains the most definitive treatment for adenomyosis, but it is not suitable for patients who wish to retain their uterus [4]. Other treatments for adenomyosis include endometrial ablative therapy (Novasure), uterine artery embolization (UAE), levonorgestrel-releasing intrauterine device (IUD), oral contraceptives, and gonadotropin-releasing hormone analogues (GnRHa). However, these treatments are limited due to adverse effects [5]. Therefore there is a need to explore new techniques in the treatment of adenomyosis. For the past ten years, ultrasound-guided high intensity focused ultrasound (USgHIFU) has been found to be safe and effective in the treatment of adenomyosis [6-11]. Based on the non-perfused volume (NPV) ratio immediately after USgHIFU, several studies showed that patients with larger NPV ratio had significantly greater symptom improvement, with higher probability of long-term sustained symptom relief [10,11]. Therefore, to achieve a large NPV ratio of adenomyotic lesion may be important for long-term success. In clinical practice it was found that the adenomyotic lesions vary in their response to HIFU treatment. However, to the best of our knowledge, no study has been conducted on the relationship between the magnetic resonance imaging (MRI) features of adenomyosis on T2-weighted imaging (T2WI) and HIFU ablative efficiency. Therefore, in this study, we intend to objectively evaluate the T2WI signal intensity of adenomyosis in predicting the ablative efficiency of USgHIFU.

2. MATERIALS AND METHODS

This retrospective study was approved by the ethics committee at our institution. Before HIFU treatment the details of the treatment were discussed with all patients, who then signed a consent form..

2.1. Patients

Between January 2011 and November 2015, four hundred and twenty-eight symptomatic adenomyosis patients were treated with USgHIFU in our hospital. The diagnosis of adenomyosis was suspected by clinical evaluation and confirmed with MRI. The diagnostic criteria used in this study include focal or diffuse thickening of the uterine junctional zone or the presence of a low signal intensity myometrial mass with ill-defined borders [12, 13].

The inclusion criteria were as follows: (1). all patients had clinical symptoms and were 18 years or older; (2). patients could communicate with the nurse or physician during HIFU procedure; (3). patients agreed to take pre- and post-HIFU MRI examinations. Exclusion criteria: (1). the adenomyotic lesion could not be reached by the focused ultrasound beams or could not be visualized; (2). patients with suspected or confirmed uterine malignancy; (3). patients with contraindications to MRI.

2.2. MRI Evaluation

All patients underwent pre- and 1 day post-HIFU MRI examinations. MRI was conducted with a 1.5T Magnetom Symphony MR system (Siemens Healthcare, Erlangen, Germany). Conventional T1WI (TR/TE 500ms/13ms, section thickness 4mm, voxel size 1.7 x 1.3 x 5.0mm), T2WI (TR /TE 2300ms/100ms, section thickness 4mm, voxel size 1.0 x 1.0 x 4.0mm.) and contrast-enhanced MRI (TR /TE 6.23ms/2.91ms, section thickness 4mm, voxel size 1.7 x 1.2 x 4.0mm, flip angle 90°) were performed in every patient. Twenty seconds after intravenous injection of gadolinium, contrast-enhanced MRI commenced.

1 The size and location of both the adenomyotic lesion and the uterus were
2 evaluated on T2WI of MRI. Four hundred and twenty-eight patients with
3 symptomatic adenomyosis were classified into two types, based on the signal
4 intensity of the adenomyotic lesions on T2WI. Type one: the signal intensity of
5 the adenomyotic lesion was lower than that of the normal myometrium
6 (hypointense); type two: the signal intensity of the adenomyotic lesion was
7 similar to the normal myometrium (isointense)(Fig.1).

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15 Based on the number of hyperintense foci on T2WI the patients were
16 classified into two types: type one – few hyperintense foci (the number of
17 hyperintense points was less than 5 on a single slice) type two – multiple
18 hyperintense foci (the number of hyperintense foci was more than 5 on a single
19 slice) (Fig.2). The volume of the adenomyotic lesion and the non-perfused
20 volume (NPV) were measured on the contrast-enhanced T1WI using software
21 created by Chongqing Haifu Medical Technology Co.,_Ltd. , to contour
22 adenomyotic lesions, and the non-perfused area in every slice of MR imaging,
23 then calculated by the same program (Fig. 3).

2.3. HIFU ablation

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36 All patients received specific bowel and skin preparation prior to HIFU
37 treatment. Bowel preparation included ingesting liquid food for 3 days before
38 HIFU treatment, a 12 hour fast before treatment and a cleansing enema on the
39 morning of treatment. Skin preparation included shaving, degreasing and
40 degassing the skin of the anterior abdominal wall from the umbilicus to the
41 upper margin of the pubic symphysis. In order to optimize the therapeutic
42 acoustic pathway, a urinary catheter was inserted to control the size of the
43 bladder.

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USgHIFU ablation was performed under conscious sedation (Fentanyl at
0.8–1µg/kg administered at 30–40 min intervals; midazolam hydrochloride, at
0.02–0.03 mg/kg, administered at 30–40min intervals). The JC200 Focused
Ultrasound Tumor Therapeutic System (Chongqing Haifu Medical Technology

Co, Ltd, Chongqing, China) was used to perform the ablation. Real-time ultrasonographic imaging was used to monitor the adenomyotic lesions. The patients were required to report any discomfort during the procedure and the vital signs such as heart rate, blood pressure, respiration and oxygen saturation were monitored.

The patients were carefully positioned on the HIFU treatment table in the prone position, with the lower abdomen in contact with degassed water. A cold degassed water balloon was placed on the abdominal wall to compress and push the bowel away from the acoustic pathway. Treatment began from the deep to the shallow aspect of the lesion and from the foot side to head side, and the focal point was at least 1.5 cm away from the endometrium and 1cm from the margin of the adenomyotic lesion. During the treatment the ultrasonic energy was adjusted based on both patient feedback and changes in gray scale on ultrasonographic imaging. This process was repeated on a section-by-section basis until the entire target lesion was covered by hyperechoic changes or the contrast-enhanced ultrasound showed no blood supply.

2.4. Statistical Methods

Statistical analysis was completed using SPSS17.0 (SPSS Inc., Chicago, IL, USA). Normal distribution data was indicated as mean $\pm$ SD. The abnormal distribution data was reported as median and interquartile range. One-way ANOVA analysis was applied when comparing variables between the two groups. The Wilcoxon test and chi-square test were applied for the analysis of the quantitative and enumerated data. *P* value of less than 0.05 was defined as statistically significant.

3. RESULTS

3.1. Patients and Lesions

The average age of the 428 patients was 38.2 ± 6.4 years (range, 23–53

years) with a median body mass index (BMI) of 24 (interquartile range: 13.0-38.0) kg / m².

Based on the T2 signal intensity of the adenomyotic lesions on MRI, 197 were classified as hypointense and 231 were classified as isointense. Table 1 shows the average age was 38.3±4.9 years in the patients with hypointense adenomyotic lesions and it was 36.7±5.1 years in the patients with isointense adenomyotic lesions. The mean BMI of patients with hypointense adenomyotic lesions and isointense adenomyotic lesions was 22.3±2.5 kg/m² and 22.1±2.9 kg/m², respectively. The average volume of the hypointense lesions was 117.6±90.3 mm³, while the average volume of the isointense lesions was 118.6±87.1 mm³ (Fig.1). No significant difference was observed in baseline characteristics between the two groups ($P>0.05$).

Based on the number of T2WI high signal intensity foci, the adenomyotic lesions were classified into two groups; one group of 265 patients with none or few scattered hyperintense points (less than 5), and another group of 163 patients with multiple hyperintense points (more than 5 on one slice of MRI) (Fig. 2). Table 2 shows the average age was 38.1±4.9 years in the group of patients with none or a few scattered hyperintense foci and it was 36.7±5.4 years in the patients with multiple hyperintense foci. The mean BMI in the two groups was 22.1±2.6 kg/m² and 22.4±3.1 kg/m², respectively. The average volume of the lesions in the two groups was 117.7±83.4 mm³, and 118.8±96.5 mm³ respectively (Fig.2). No significant difference was observed between the two groups with regard to baseline characteristics ($P>0.05$).

3.2. Intra- and Post-HIFU procedure evaluation

As shown in Table 3, in HIFU treatment settings and procedures, no significant difference was seen between patients with hypointense lesions and those with isointense lesions ($P>0.05$). Both the hypointense and isointense groups were treated using similar sonication power, sonication time, sonication time/hour and treatment time. No significant difference was noted in the NPV

ratio, where $54.9 \pm 20.7\%$ was achieved in the adenomyotic lesions with hypointense signal and $60.1 \pm 21.2\%$ was achieved in the group with isointense signal on T2WI ($P < 0.05$). The NPV ratio was defined as the NPV divided by the volume of the target lesion. In a comparison of the energy efficiency factor (EEF) (which is defined as the amount of energy needed to ablate 1 cubic millimeter (mm^3) of the adenomyotic lesion), no significant difference was observed between the two groups ($P > 0.05$).

Although there was no significant difference in baseline characteristics between the patients with few hyperintense foci and the patients with multiple hyperintense foci in the adenomyotic lesions, Table 4 showed significant differences between the two groups in sonication time, sonication time/hour, EEF and NPV ratio ($P < 0.05$). With the utilization of similar sonication power to ablate the adenomyotic lesions, the average sonication time used for the group with few hyperintense foci of adenomyotic lesions was significantly shorter than that for the group with multiple hyperintense foci of lesions (19.9 ± 11.5 min vs. 23.9 ± 14.3 min, $P < 0.05$). The average NPV ratio achieved in the group with few hyperintense foci was significantly higher than that of the group with multiple hyperintense foci ($63.1 \pm 20.5\%$ vs. $54.1 \pm 20.1\%$, $P < 0.05$). The average EEF was 5.1 J/mm^3 (interquartile range, $0.5\text{--}980.0 \text{ J/mm}^3$) for the group of patients with few hyperintense foci, while it was 8.0 J/mm^3 (interquartile range, $0.7\text{--}1225.0 \text{ J/mm}^3$) for the group of patients with multiple hyperintense foci. ($P < 0.05$). We further sub-classified these patients as hypointense with few hyperintense foci, hypointense with multiple hyperintense foci, isointense with few hyperintense foci, isointense with multiple hyperintense foci. The NPV ratio achieved in these four groups was $64.1 \pm 19.8\%$, $55.7 \pm 16.5\%$, $62.2 \pm 21.4\%$, and $53.1 \pm 22.3\%$, respectively. The median EEF in the four groups was 5.0 J/mm^3 , 7.7 J/mm^3 , 5.3 J/mm^3 , and 8.6 J/mm^3 , respectively. The significant difference was also only observed between the two groups with few hyperintense foci and with multiple hyperintense foci.

3.3. Adverse effects and complications

During the procedure the common adverse effects included transient leg pain, sciatic or buttock pain, skin discomfort, lower abdominal pain and groin pain. These pains were mild and often disappeared after sonication was terminated. We compared the incidence rate of adverse effects between the two groups. No significant difference was observed (Table 5&6)($P>0.05$).

After HIFU treatment, mild pain in the treated region and sacrum was observed in some cases; the pain subsided within 3 days. No major post-HIFU complications were observed in any of these patients.

4. DISCUSSION

MRI offers a highly accurate diagnosis of adenomyosis. The appearance of adenomyotic lesions on MRI varies according to the amounts of fibrous tissue and smooth muscle density in the lesions. The previous studies on MRI suggested a relationship between the signal intensity on T2WI and the biological characteristics of adenomyotic lesions. The hypointense adenomyotic lesion on T2WI represents numerous nuclear areas, higher smooth muscle density and lower extracellular matrix per unit volume [14,15]. However, it is difficult to follow the signal intensity of T2WI to select patients for HIFU treatment because of the wide variety of histopathological features of adenomyosis [3]. Based on the principle of HIFU ablation, tumors with more fibrous tissue and less water are more sensitive to HIFU, thus less energy deposition is required at the focal point. Previous studies have shown that uterine fibroids with hypointense or isointense signal on T2WI respond more effectively to HIFU treatment than those with hyperintense signal because hyperintense fibroids on T2WI contain more water and less fibrous tissue [16,17]. However no significant difference was found in HIFU procedure settings, NPV ratio, or EEF in patients with hypointense and isointense adenomyotic lesions. Thus the MRI indicators are not successful in predicting

treatment results.

We further noted a difference in the number and size of hyperintense foci in the adenomyotic lesions. Reinhold et al. have shown that hyperintense foci may represent ectopic endometrial tissue, endometrial cysts or hemorrhage on histology [18]. In this study, the results show that the adenomyotic lesions with multiple hyperintense foci were more difficult to treat than the group with fewer hyperintense foci. Using similar sonication power and less sonication time, the NPV ratio achieved in the group with fewer hyperintense foci was significantly higher than that of the group with multiple hyperintense foci. The EEF in the group with fewer hyperintense foci significantly lower than that of the group with multiple hyperintense foci (Table 4). A further analysis of the four groups of patients (hypointense with fewer hyperintense foci, hypointense with multiple hyperintense foci, isointense with fewer hyperintense foci, isointense with multiple hyperintense foci) revealed an NPV ratio of $64.1 \pm 19.8\%$, $55.7 \pm 16.5\%$, $62.2 \pm 21.4\%$, and $53.1 \pm 22.3\%$, respectively. The median EEF in the four groups was 5.0 J/mm^3 , 7.7 J/mm^3 , 5.3 J/mm^3 , and 8.6 J/mm^3 , respectively. A significant difference was only observed between the two groups with fewer hyperintense foci and multiple hyperintense foci. The results further indicated that the number of hyperintense foci on T2WI, and not the signal intensity of the adenomyotic lesion, can be used to predict the response of the adenomyotic lesions to HIFU. This finding may be the result of repeated bleeding in the adenomyotic lesions during menstruation; this leads to structural changes in the lesion which in turn affects the deposition of ultrasound energy. At the same time the existence of numerous, scattered, small, hyperintense foci could result in structural inhomogeneities, which can increase absorption, reflection, and scattering of ultrasound beams and reduce the energy deposition of ultrasound at the focus point.

Safety is always a main concern during HIFU treatment for adenomyosis. HIFU treatment was performed under conscious sedation, and the most

common adverse effects reported included transient leg pain, sciatic/buttock pain, lower abdominal pain, burning sensation of the skin, and groin pain. (Table 5&6). These adverse effects were transient and mild and most disappeared immediately after HIFU treatment. A comparison was made between the incidence rate of adverse effects among the two groups and no significant difference was found. Therefore, HIFU is a safe treatment in the management of adenomyosis.

This study is limited because it is a retrospective study and the non-randomization of patients may cause result bias. A further limitation of this research is that the classification is only based on T2WI MR imaging and the hyperintense foci are only counted on one slice of the sagittal view image that contains the highest number of hyperintense foci; this may also cause a bias in the results because of the variations in distribution of the hyperintense foci that may occur on different slices. A prospective study with randomized, enrolled patients and a range of slices is required.

5. CONCLUSIONS

In summary, the results show that the signal intensity of adenomyosis on T2WI is not related to the response of the adenomyosis to HIFU treatment. However, the adenomyotic lesions with fewer hyperintense foci were easier to treat with HIFU. Based on the results, the number of hyperintense foci in the adenomyotic lesions on T2WI can be considered as a predictive factor to assist in the selection of patients for HIFU treatment.

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Table and Figure legends

Table 1. Comparison of baseline characteristics of patients with hypointense adenomyotic lesions and isointense adenomyotic lesions

Variables	With hypointense adenomyotic lesion (N=197)	With isointense adenomyotic lesion (N=231)	<i>P Value</i>
Age (years)	38.3±4.9	36.7±5.1	0.179
BMI(Kg/cm ²)	22.3±2.5	22.1±2.9	0.551
Volume of uterus (mm ³)	316.7±157.2	327.7±167.4	0.597
Volume of adnomyosis (mm ³)	117.6±90.3	118.6±87.1	0.926
Location of adnomyosis (A/P/AP/F)	56/110/16/15	42/130/31/1628	0.136
Location of uterus (A/M/R)	124/12/61	151/9/71	0.680

Table 2. Comparison of baseline characteristics of patients with few hyperintense foci and mutiple hyperintense foci on T2WI.

Variables	With few hyperintense foci (N=265)	With mutiple hyperintense points (N=163)	<i>P Value</i>
Age (years)	38.1±4.9	36.7±5.4	0.095
BMI(Kg/cm ²)	22.1±2.6	22.4±3.1	0.394
Volume of uterus (mm ³)	324.4±171.1	319.8±148.4	0.833
Volume of adnomyosis (mm ³)	117.7±83.4	118.8±96.5	0.925
Location of adnomyosis (A/P/AP/F)	56/157/28/24	37/77/19/30	0.145
Location of uterus (A/M/R)	(171/82/12)	(103/51/9)	0.960

Table 3. HIFU treatment results in patients with hypointense adenomyotic lesion or isointense adenomyotic lesion

Variables	With hypointense adenomyotic lesion (N=197)	With isointense adenomyotic lesion (N=231)	<i>P value</i>
Sonication power (w)	400 (381-400)	400 (342-400)	0.652
Treatment time (min)	118.0±65.0	116.4±55.7	0.829
Sonication time (min)	20±12.5	21.8±12.4	0.376
Sonication time/hour (s/h)	599.9±214.1	663.7±197.1	0.444
EEF (J / mm ³)	6.5 (1-673.1)	6.0 (0-1225)	0.889
NPV ratio (%)	54.9±20.7	60.1±21.2	0.864

Note: EEF: energy efficiency factor; NPV: non-perfused volume

Table 4. Comparison of HIFU treatment results between patients with few hyperintense foci in adenomyotic lesions and patients with multiple hyperintense foci on T2WI.

Variables	With few hyperintense foci (N=265)	With mutiple hyperintense points (N=163)	<i>P Value</i>
Average sonication power (w)	400 (305-402)	400 (381-400)	0.197
Treatment time (min)	112.9±58.3	128.4±62.9	0.052
Sonication time (min)	19.9±11.5	23.9±14.3	0.044
Sonication time/hour (s/h)	638.2±213.6	656.9±187.7	0.487
EEF (J / mm ³)	5.1 (0.5-980.0)	8.0 (0.7-1225)	0.004
NPV ratio (%)	63.1±20.5	54.1±20.1	0.001

Note: EEF: energy efficiency factor; NPV: non-perfused volume

Table 5. The incidence rate of adverse effects in patients with hypointense or isointense adenomyotic lesion during HIFU treatment

Variables	With hypointense adenomyotic lesion (N=197)	With isointense adenomyotic lesion (N=231)	<i>P</i> Value
Leg pain (%)	28.6 (56)	25.6 (59)	0.351
Sciatic pain or buttock pain (%)	48.2 (95)	45.3 (105)	0.865
Discomfort on skin (%)	44.6 (88)	40.2 (93)	0.656
Lower abdominal pain (%)	42.9 (85)	45.3 (105)	0.916
Groin pain (%)	23.1 (45)	7.1 (16)	0.523

Table 6. The incidence of adverse effects in patients with the number of hyperintense foci less than 5 or more than 5 in one slice of MRI image during HIFU treatment.

Variables	With few hyperintense foci (N=265)	With mutiple hyperintense points (N=163)	<i>P</i> Value
Leg pain (% , n)	23.0 (61)	25.8 (42)	0.646
Sciatic pain or buttock pain (% ,n)	43.4 (115)	48.4 (79)	0.509
Burning on skin (% , n)	38.8 (103)	41.9 (68)	0.687
Lower abdominal pain (% , n)	43.4 (115)	47.3 (77)	0.597
Groin pain (% , n)	9.2 (24)	7.5 (12)	0.815

Fig.1. Signal intensity of the adenomyotic lesion on T2WI: A. Hypointense: the signal intensity of the adenomyotic lesion is lower than myometrium (arrow); B. Isointensity: the signal intensity of the mass is similar to normal myometrium (arrow).

Fig. 2. Sagittal T2-weighted MR images obtained from patients with adenomyosis. A. The poorly defined mass without foci of high signal intensity located at posterior of the uterus (arrow); B. The poorly defined iso-signal intensity mass with numerous foci of high signal intensity located at the posterior of the uterus (arrow).

Fig. 3. Measurement of the volume of the adenomyotic lesion and the non-perfused volume (NPV). A. The adenomyotic lesion was outlined on every slice of the contrast-enhanced MR images using software. B. The non-perfused area was also outlined on every slice of the contrast-enhanced MR images using the same software.