Identification of an optimal magnetic resonance imaging-based classification for evaluating efficacy of ultrasound-guided high-intensity focused ultrasound

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September 29, 2022

Abstract

Objective: To identify an optimal magnetic resonance imaging-based classification for evaluating the efficacy of focused ultrasound ablation surgery (FUAS). Design:A retrospective cohort study. Setting: The Affiliated Nanchong Central Hospital of North Sichuan Medical College, Nanchong, Sichuan, China. Population: A total of 643 adenomyosis patients who received FUAS from June 2017 to December 2021. Methods: One-way ANOVA test and chi square test were used to identify an optimal classification for evaluating FUAS efficacy. Magnitude of the optimal classification relating to timing of recurrence in FUAS group was measured by cox regression with hazard ratio (HR) and 95% CI. K-M curve was applied to estimate the medium recurrence time of adenomyosis in the optimal classification. Main outcome measures: The identification of different classifications for FUAS efficacy and the factors contributing to recurrence after FUAS. Results: The rates of dysmenorrhea relief (χ2=10.079, P=0.018) and recurrence could be identified by classification 2 in FUAS group (χ2=10.582, P=0.014), but not in FUAS+ group (P¿0.05). Besides, the recurrence rate in FUAS group (22.2.0%) was higher than that in FUAS+ group (12.1%). Extrinsic subtype in classification 2 (HR=2.315, 95% CI 1.219 4.560, P=0.011) correlated to recurrence of adenomyosis in FUAS group. K-M curve showed that the medium recurrence time of extrinsic subtype (45.2 months) was shorter than that of other subtypes (52.0 months). Conclusions: Classification 2 was the optimal one to identify the rates of dysmenorrhea relief and recurrence. Extrinsic subtype was related to the earlier onset of recurrence after FUAS.

Introduction

Adenomyosis, a benign gynecological disease observed in women in their reproductively active years, is characterized by invasion of endometrial glands and stroma within the myometrium [1]. Current treatments for adenomyosis, especially uterine sparing therapy, have limited efficacy and high recurrence rates due to the estrogen-dependent nature[2]. Hence, hysterectomy is considered the optimal option for women with adenomyosis, except for those who would like to preserve fertility. As a non-invasive technique, focused ultrasound ablation surgery (FUAS) has become a popular option for patients with adenomyosis, especially for those who hope to preserve fertility[3]. Previous studies have shown that FUAS is a safe and effective treatment for adenomyosis[2-4]; however, dysmenorrhea and/or menorrhagia may relapse in 12 months after treatment[4]. Several predisposing factors, such as phenotypes and morphological characteristics, have been reported to

be potentially associated with either FUAS efficacy or symptom recurrence after FUAS, nevertheless few of them were proved to be clinically applicable[5-7].

Several phenotypes based on magnetic resonance imaging (MRI) classification were reported to be associated with clinical features of adenomyosis in recent years[5,7-9]. However, a consensus classification has yet to be reached, and data from previous studies are heterogeneous and not fully comparable. Thus, it is imperative to confirm a standard classification criterion MRI for evaluating FUAS efficacy.

We retrospectively reviewed a cohort of 643 adenomyosis patients treated with FUAS in our center over the past four years, aiming to identify an optimal MRI-based classification for evaluating the efficacy of FUAS, and to explore the factors associated with the recurrence of adenomyosis after FUAS.

Methods

Patients

This retrospective cohort study collected and analyzed the data of 643 adenomyosis patients with complete clinical data and follow-up in the Affiliated Nanchong Central Hospital of North Sichuan Medical College from June 2017 to December 2021.

Inclusion criteria were patients who had complete clinical data from medical record; performed MRI before FUAS; received ultrasound-guided FUAS; had willing to follow up after FUAS[3].

Exclusion criteria were patients who had incomplete clinical data from medical record; had no MRI before FUAS; refused ultrasound-guided FUAS; refused to follow up after FUAS[3].

Assessments

Adenomyosis was diagnosed as the maximal junctional zone thickness (JZ_{max}) [?]12 mm, JZ_{max}/entire myometrium $> 40\%$ and the difference between the maximum and minimum > 5 mm thick based on MRI[7,10]. Adenomyosis-caused dysmenorrhea was defined as the clinically recorded patient-reported pain during the menstrual cycle[11]. Adenomyosis-caused menorrhagia was defined as the clinically recorded patient-reported heavy or prolonged menstrual bleeding[12]. The relief of dysmenorrhea and menorrhagia was defined as patient-reported symptom relief of dysmenorrhea and menorrhagia within 12 months after FUAS. The recurrence was defined as patient-reported dysmenorrhea and/or menorrhagia after 12 months following a period in which the symptomatic relief lasted for at least 3 months after FUAS. The uterine volumes and the lesion volumes of adenomyosis were calculated using the following formula: 0.52*length*anteroposterior diameter*transverse diameter[13].

MRI-based Classifications for adenomyosis

According to the typical classification (classification 1), adenomyosis was mainly classified as focal adenomyosis and diffuse adenomyosis. Adenomyosis is defined as focal when the lesion is surrounded by circumscribed adenomyomas in the inner one third of the myometriun, whereas diffuse adenomyosis is diagnosed when the lesion extends to the outer two thirds of the myometrium and up to gross involvement of the entire uterus[14]. According to Kishi et al[5] (classification 2), adenomyosis was divided into four groups based on different etiologies: subtype I (intrinsic), subtype II (extrinsic), subtype III (intramural), and subtype IV4 (indeterminate). Subtype I is characterized by the invagination of the basal endometrium into the myometrium without affecting the outer myometrial layer, while subtype II directly invades uterine serosa from peritoneal or pelvic endometriosis without affecting the inner myometrial layer[5]. According to Bazot and Daraï[7](classification 3), we defined adenomyosis as three subtypes: internal (similar to intrinsic), external (similar to extrinsic), and adenomyomas (similar to intramural adenomyoma). According to Kobayashi et al[8] (classification 4), we categorized patients into six subtypes on the basis of affected areas and volumes, i.e., subtype 1-3 (internal adenomyosis) and subtype 4-6 (external adenomyosis). Subtype 1 and subtype 4 represent the volumes $<1/3$ of uterine wall; subtype 2 and subtype 5 represent the volumes $<2/3$ of uterine wall; subtype 3 and subtype 6 represent the volumes [?]2/3 of uterine wall. According to Gong et al[9] (classification 5), adenomyosis could be classified as internal adenomyosis (asymmetric internal as subtype

1, symmetric internal as subtype 2), external adenomyosis (asymmetric external as subtype 3), intramural adenomyosis (subtype 4), and full thickness adenomyosis (asymmetric full thickness as subtype 5, symmetric full thickness as subtype 6).

FUAS procedure

Preparation before FUAS and during the FUAS procedure conformed to the guideline of Focused Ultrasound Tumor Therapeutic System (Model-JC200, Chongqing Haifu Medical Technology Co., Ltd.)[9,13]. The ablation volume and non-perfused volume (NPV) ratio of adenomyotic lesions were performed by contrast-enhanced ultrasound[15]. Treatment details including total ablation time, sonication time and average sonication power were recorded by computer. The ablation volume was calculated using the ellipsoid volume formula $V=4/3\pi ABC$[16], in which A, B and C represent the long diameter, wide diameter and thickness diameter of the lesion, respectively. The NPV ratio = NPV/adenomyotic lesion*100%[9]. All patients were kept under observation for 24h after FUAS.

Adjuvant therapy after FUAS and Follow-up

To consolidate the efficacy of FUAS in the treatment of adenomyosis, three to six cycles of gonadotropin-releasing hormone agonist (GnRH-a) were suggested for patients whose uteri were greater than 10 weeks of gestation or the length of the uterine cavity were more than 9 cm. Then mirena was recommended for patients without fertility requirement when the uterus volume were suitable[15]. Accordingly, patients were included in FUAS group and FUAS+ (combined with GnRH-a/mirena) group based on the therapeutic regimen.

To evaluate FUAS efficacy, patients were suggested for regular follow-up. From August 2021 to December 2021, 643 patients completed the questionnaire either on the spot or by telephone if they could not come back to our cohort.

Statistical methods

Continuous data are summarized by the mean ± standard deviation and count data are summarized by proportion. One-way ANOVA test and chi square test were used to examine the differences in baseline characteristics (age, the rates of dysmenorrhea, menorrhagia and endometriosis, uterus position, adenomyosis location, subcutaneous fat thickness, uterus volume, adenomyosis volume) between FUAS group and FUAS+ group, and to identify the differences in baseline characteristics among subtypes in the optimal classification. Chi square test was used to examine the ability of the classification for differentiating pain relief after FUAS, among which the one that produced the largest chi square value was identified as the optimal classification. The cox regression logistic mode was used to analyze the correlation of baseline characteristics (age, the rates of dysmenorrhea, menorrhagia and endometriosis, uterus position, adenomyosis location, subcutaneous fat thickness, uterus volume, adenomyosis volume), FUAS parameters (total ablation time, sonication time, average sonication power, sonication energy, sonication volume, NPV ratio) and recurrence rate after FUAS. Magnitude of classification relating to timing of recurrence was measured by cox regression with hazard ratio (HR) and 95% CI. K-M curve was applied to estimate the median recurrence time of the optimal classification subtypes for adenomyosis. All analyses were performed in FUAS group and FUAS+ group separately. Statistical analysis was completed with SPSS 22.0 (IBM, Armonk, NY), and $p<0.05$ was defined as statistically significant.

Results

Clinicopathological features

Baseline characteristics and FUAS parameters of the 643 patients enrolled in this study are summarized in Table 1. The median follow-up time were 29 (2-62) months. 288 (55.2%) patients were included in FUAS group, while 355 (44.8%) patients were included in FUAS+ (combined with GnRH-a and/or mirena) group. The rates of endometriosis in FUAS group (18.7%) was higher than that in FUAS+ group (12.7%) (P¡0.05),

whereas there were no significant differences between two groups in terms of baseline characteristics and FUAS parameters (P¿0.05, Table S1).

Evaluating efficacy of FUAS based on different classifications

The rates of dysmenorrhea relief (χ2=10.079, P=0.018) and recurrence could be identified by classification 2 in FUAS group (χ2=10.582, P=0.014), but not in FUAS+ group (P¿0.05). In addition, other classifications (i.e., classification 1, 3, 4 and 5) could not identify the rates of dysmenorrhea relief and recurrence in both groups (P¿0.05, Table 1). The rates of menorrhagia relief could be identified by classification 4 in FUAS group (χ2=16.529, P=0.005), rather than in FUAS+ group. And other classifications (i.e., classification 1, 2, 3 and 5) could not identify the rates of menorrhagia relief (P¿0.05, Table 2). Besides, the recurrence rate in FUAS group (22.2.0%) was higher than that in FUAS+ group (12.1%). Furthermore, the poor dysmenorrhea relief rate (17.0%) and the highest recurrence rate (33.0%) were both shown in subtype II of FUAS group based on classification 2, which were significantly higher than those in other subtypes (Table 2, P¡0.05).

Clinicopathological features of FUAS group based on classification 2

Accordingly, 138 patients, 68 patients, 48 patients and 34 patients were included in subtype I, subtype II, subtype III and subtype IV4, respectively. The rates of retrote-verted uterus in subtype II was significantly higher than those in other subtypes (P¡0.001). And the rates of posterior adenomyosis (67.6%) and endometriosis (45.6%) were significantly higher in subtype II than those in other subtypes (Table S2, P¡0.001). Besides, uterus volume and adenomyotic lesions volume in subtype I and subtype IV were higher than those in other subtypes (Table S2, P¡0.05).

Magnitude of classification 2 impacting symptom recurrence of FUAS group

In the cox regression, age (HR=0.935, 95% CI 0.888 0.984, P=0.010) and classification 2 (subtype II vs. other subtypes) (HR=2.315, 95% CI 1.219 4.560, P=0.011) were associated with the recurrence of adenomyosis in FUAS group (Table 3). However, no significant associations were found in uterus volume, lesion volume, uterus position, lesion position, subcutaneous fat thickness, the rates of endometriosis, and FUAS parameters (total ablation time, sonication time, average sonication power, sonication energy, sonication volume, NPV ratio) (P¿0.05). K-M curve showed medium recurrence time in extrinsic subtype of FUAS group (45.2 months) was shorter than that in other subtypes of FUAS group (52.0 months) (Figure 1, P=0.032).

Discussion

Main findings:

Extrinsic subtype with FUAS alone might inform earlier recurrence of adenomyosis after FUAS.

In this retrospective cohort study, we established that classification 2 was the optimal one to identify the dysmenorrhea relief and recurrence of adenomyosis. The extrinsic subtype of classification 2 correlated to an earlier onset of recurrence after FUAS alone. However, there was no association between classifications based on MRI and FUAS efficacy combined with GnRH-a/mirena. Besides, our study also informed that FUAS combined with GnRH-a/mirena might be a good choice to decrease the recurrence rates of adenomyosis after FUAS.

Our results were in agreement with the results of Kishi et al[5], suggesting that extrinsic subtype was more prone to suffering from dysmenorrhea and higher chance of concomitant endometriosis, especially in the posterior lesion of myometrium in patients with adenomyosis. We found no significant differences in age among four subtypes, and age was considered an independent factor for the relapse of adenomyois after FUAS. Our results were also in consistent with the finding of Kobayashi et al[17], suggesting that patients in external and diffuse subtypes had more chance of dysmenorrhea and coexistence with endometriosis. Subsequently, Gong et al[9] tried to explore the FUAS efficacy based on MRI, finding that there were significant differences between menstrual pain scores and menstrual blood volume scores before and 18 months after FUAS among different subtypes, while there were no significant differences among subtypes in menstrual pain 18 months after FUAS. The results were partially different from our results of the relief rates of dysmenorrhea for the

the usage of union MRI classification criterion in evaluating FUAS efficacy. In our study, we compared five common criteria MRI for their ability to evaluate FUAS efficacy, found that classification 2 was the optimal one for evaluating FUAS efficacy, and identified that extrinsic subtype of classification 2 correlated to an earlier onset of symptomatic recurrence after FUAS alone.

Strengths and limitations

We found an optimal classification for evaluating FUAS efficacy with a relatively large sample size and identified a promising subtype of classification for the recurrence of adenomyosis after FUAS, which might be of interest to clinicians to make strategy and researchersto explore the association between standard classification based on MRI and FUAS efficacy. Nonetheless, there are some limitations in our study. First, patients in our study were all under FUAS treatment, which limited our interpretation of the results for the general patient population although our analysis confirmed that classification 2 was related to the rates of dysmenorrhea relief and recurrence after FUAS. Besides, our study informed that FUAS combined with GnRH-a/mirena might be a good choice to decrease the recurrence rates after FUAS. Future validation studies are needed for patients with adenomyosis under other treatments. Second, the retrospective study only focused on clinical symptom improvement, rather than the volume changes of uterus and lesions after FUAS for patients lived far away from our center, and chose to visit local hospital for follow up. Third, dysmenorrhea and menorrhagia were not recorded by the pain severity level of Numerical Rating Scale, but collected from patients-self-reported recurrence of dysmenorrhea and/or menorrhagia as yes or no, which may lead to recall bias. However, as commonly used in the routine clinic visit in the follow-up of adenomyosis patients, the patients-self-reported outcome can also reflect the efficacy of FUAS to some extent. A multicenter study is needed to provide more evidence.

Interpretation

Numerous classifications for adenomyosis based on MRI have been proposed in recent years[5,7-9], whereas, there is no standard classification criterion for FUAS efficacy of adenomyosis. Our study identified that classification 2 was the optimal one for evaluating FUAS efficacy of adenomyosis by comparing five common classification criteria. Firstly, we confirmed a potential classification criterion, which might be conducive to the evaluation of FUAS efficacy, long-term strategic management and research in adenomyosis. Secondly, the optimal classification for evaluating FUAS efficacy may be helpful to understand the theories of adenomyosis. Our study showed that patients with extrinsic subtype of optimal classification had high rates of dysmenorrhea and endometriosis, especially in young women with high estrogen levels, which was consistent with the potential mechanism that adenomyosis is caused by the migration and differentiation of endometrial and stromal stem cells arising from Müllerian remnants after retrograde menstruation through the invasion from the outside of the uterus[18,19]. Thirdly, the optimal classification identifying the evaluation of FUAS efficacy may help clinicians to make the best strategy for adenomyosis. Our research preliminarily showed that FUAS combined with GnRH-a and/or mirena may reduce the recurrence rates of adenomyosis, and the influence of different subtypes of classification on FUAS efficacy. Hence, no matter what subtypes of classification based on MRI, FUAS combined with GnRH-a and/or mirena might be an optimal choice to decrease the recurrence rates and preserve fertility, which was in consistent with the results of Yang X, et al[15] and Li X, et al[13].

Conclusions

In summary, our results preliminarily showed that classification 2 was the optimal one to identify the rates of dysmenorrhea relief and recurrence after FUAS. Furthermore, extrinsic subtype of classification 2 was related to an earlier onset of recurrence after FUAS. Besides, FUAS combined with GnRH-a/mirena might decrease the recurrence rates after FUAS.

Conflict of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Author contributions

YT, HQH, and QLS designed the study. SY collected the data. JX, MBW, BS, ZJJ and MTY performed the analyses. All authors drafted the first manuscript with the help of QLS and FX. All authors have given approval of the final version prior to submission..

Ethics approval

This study was approved by the Ethics Committee of the Affiliated Nanchong Central Hospital of North Sichuan Medical College (permit number. 2021/104). Consent was not required because of the retrospective nature of the study. However, a notice about study design and contact information was posted at a public location in our hospital.

Funding

This work was supported by National Natural Science Foundation of China (No. 81872506), Foundation of State Key Laboratory of Ultrasound in Medicine and Engineering (Grant No. 2020KFKT003, 2021KFKT022) and the Project of Nanchong Science and Technology Bureau (No. 20SXQT0320, 22SXQT0254, 22SXQT034).

Acknowledgements

The authors thank Xue Li, a scholar majoring in medical translation of Chongqing Medical University, for her thorough review and correction of the English of this paper.

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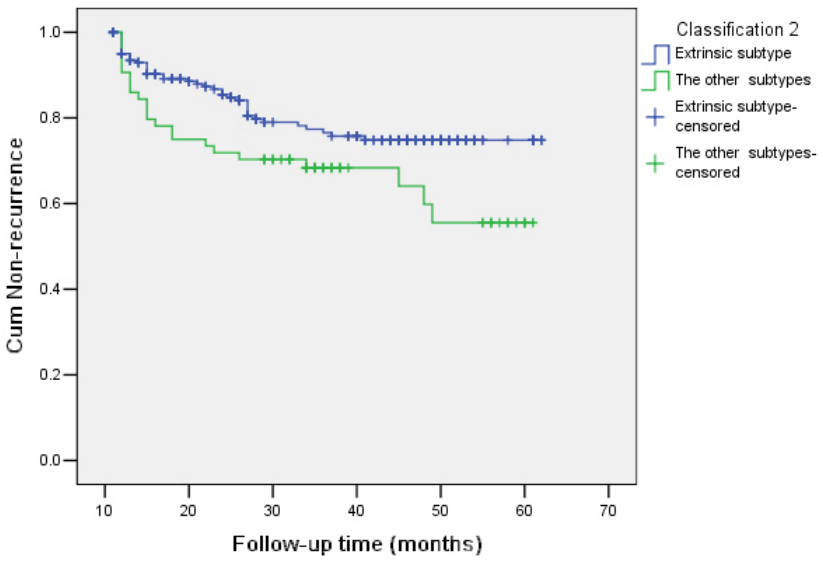

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