Ultrasound-guided microwave ablation for symptomatic adenomyosis: More areas of concern for more uniform and promising outcomes

**Abstract**

Adenomyosis is a common gynecological disease in reproductive women, which causes serious dysmenorrhea, menorrhagia, anemia, and infertility, and has a serious impact on the physical and mental health of women. Considering that the efficacy of the traditional medication and surgical treatment is not ideal, an increasing number of patients are searching for more effective and less invasive therapies. Ultrasound (US)-guided microwave ablation (MWA) has emerged as a new effective and minimally invasive alternative treatment for symptomatic adenomyosis, and it is widely being used in clinical settings. Several studies have proven that it is an efficient and safe treatment modality for symptomatic adenomyosis, but a significant variance in clinical outcomes reported in previous studies was also observed. Herein, we have analyzed the potential causes of this problem from the aspects of the diagnosis of adenomyosis, symptom evaluation before ablation, steps of US-guided ablation treatment, and outcome evaluation after ablation. Simultaneously, the clinical problems existing in the ablation treatment of adenomyosis are discussed, and the directions of future research are pointed out.

1. Introduction

Adenomyosis is a common gynecological disease in women aged 30–50 years. According to a previous report, its incidence rate varies significantly between 7% and 88%. The pathological characteristics include the presence of ectopic endometrial epithelial cells and stroma in the myometrium, hyperplasia, and hypertrophy of the surrounding uterine smooth muscle cells. It causes severe dysmenorrhea, menorrhagia, secondary anemia, infertility, enlarged uterus, and pelvic compression, which have a serious impact on the physical and mental health of patients.

Ultrasound (US)-guided microwave ablation (MWA) has shown significant advantages over traditional long-term medication and surgical treatments, such as better efficacy, shorter post-treatment hospital stay, and lower cost. In a meta-analysis which included 38 studies of 15,908 patients with symptomatic adenomyosis from the year 2000–2020, MWA showed better efficacy than radiofrequency ablation (RFA) and high intensity focused ultrasound, when the evaluation criteria for local treatment response included non-perfused volume ratio and the volumetric reduction rate of the uterus and lesion.

The mechanism of MWA involves the insertion of a microwave antenna into the adenomyosis foci under the guidance of real-time US imaging and the subsequent introduction of heat energy through the rapid movement of the polar molecules in the electromagnetic field. When the temperature reaches 60°C, significant protein coagulation and tissue necrosis can be induced, causing lesion shrinkage and gradual disappearance, while the surrounding tissues and organs are well preserved. Compared with other thermal ablation methods, US-guided MWA has several advantages, such as higher effectiveness, less time consumption, and fewer complications.

The first report on the application of RFA in the treatment of adenomyosis was published in 2006. In 2011, Zhang et al. first reported that US-guided percutaneous MWA (PMWA) was applicable in the treatment of symptomatic adenomyosis, which indicated that PMWA was effective in relieving symptoms, and no major complications were observed. In the past 10 years, several studies have reported similar results regarding the efficacy and post-procedural complications of this treatment. In general, US-guided MWA has shown good potential in the treatment of adenomyosis and is expected to benefit patients as a new minimally invasive alternative treatment in the future, especially for patients who fail to respond to other conservative treatments or have poor adherence to long-term medication therapy. Similar indications have been reported in previous studies: symptomatic adenomyosis in patients of reproductive age, adenomyosis diagnosed both by pre-ablation US and magnetic resonance imaging (MRI), patients who refused surgery or other interventional therapy, and patients who had no medication history in the past 3 months before ablation.

According to the latest published review, the ablation rate reported in previous studies ranged from 79.7% to 91.34%, and the common clinical outcomes of 12 months of follow-up after ablation included significant relief of dysmenorrhea and menorrhagia, significant decrease in serum CA125 level, significant improvement of serum hemoglobin (Hb) level, and significant volumetric reduction of the uterine body and adenomyosis lesion within 3 months after treatment. However, the symptomatic relief rates of different studies varied greatly: the symptomatic relief rate of dysmenorrhea ranged from 50 to 81.7%, the improvement
rate of menstrual disorder was 39.1–80.2%, and the significant decrease in symptomatic severity score (SSS), which represented the severity of menorrhagia, differed from 20.9% to 60.2%. US-guided MWA showed good safety owing to lesser trauma than other invasive treatments. Common minor complications after ablation include lower abdominal pain, fever, vaginal discharge, and slight vaginal bleeding. Generally, no additional invasive treatment is required, and post-ablation discomfort usually disappears within a short time. However, the incidence rate of lower abdominal pain and vaginal discharge varied significantly in previous studies, ranging from 43.9% to 100% and 7.1%–88.2%, respectively. Therefore, the potential reasons underlying the various outcomes of the US-guided MWA treatment for adenomyosis are worth discussing from several aspects, including pre-ablation evaluation, surgical skills of MWA treatment, post-ablation evaluation, and follow-up. Furthermore, the clinical problems existing in the current clinical practice need to be pointed out so that effective improvement methods can be found in future research work.

2. Evaluation of symptoms of adenomyosis

Dysmenorrhea is the most common symptom of adenomyosis, with an incidence rate of over 65%. The visual analog scale (VAS) is the most commonly used pain evaluation method, which ranges from 0 to 10, with 0 indicating no pain at all and 10 indicating intolerable pain similar to labor pain. Dysmenorrhea is usually defined as pain with a VAS score >4. However, some experts believe that this score does not reflect long-term chronic pain in terms of time dimension, and the comparison between before and after treatment is not perfect for patients with chronic pelvic pain. Nevertheless, it is regarded as a convenient and practical dysmenorrhea assessment tool during pre-ablation evaluation and follow-up.

Menorrhagia is another common symptom of adenomyosis, with an incidence rate of 40–60%. Different methods have been used to quantify the severity of menorrhagia in different studies. Among these, the SSS score had been widely used in thermal ablation treatment for adenomyosis. It can be calculated based on the score of the uterine fibroid symptom and quality of life (UFS-QOL) questionnaire, which was originally developed by Spies12 for quantification of the severity of abnormal uterine bleeding caused by uterine fibroid. This scale minimized the impact of the subjective randomness of patients’ symptom evaluation on the accuracy of evaluation results and facilitated the comparison before and after treatment to evaluate the treatment effectiveness. However, it was not helpful for preoperative screening of patients with menorrhagia who needed treatment, because its accuracy is affected by the subjectivity of the patients’ evaluation, dietary habits, and previous history of hormone and iron drug treatment. The use of serum hemoglobin levels as an indicator of efficacy evaluation also has a similar problem, because not all patients with menorrhagia show low Hb levels before ablation.

A pictorial blood-loss assessment chart (PBAC) is also frequently used in clinical research and practice for the treatment of adenomyosis-related menorrhagia. Many researchers have adopted it as a quantitative assessment of menstrual bleeding volume in patients with uterine fibroids and adenomyosis.13 It was first developed by Higham14 in 1999 to quantify menstrual blood loss volume by recording the number of sanitary napkins used during menstruation and the range of blood immersion of the sanitary napkins. Two years later, Wyatt et al.15 found that extraneous blood loss and clots in the toilet during menstruation were also an important part of menstrual blood loss; they then modified the PBAC scale accordingly. Since then, PBAC has been used by an increasing number of researchers, and various versions of the PBAC have also been created.16,17 After scrutinizing previous literature on the conservative treatment of adenomyosis, the version of the used PBAC was found to be unclear sometimes, and the threshold of the PBAC score defining menorrhagia varied from 80 to 150.13 When we focused on the literature on the treatment of adenomyosis with MWA or RFA, we found that PBAC evaluation was not carried out in most cases, which compromised the accuracy of the pre-ablation evaluation of menorrhagia. A clear, unified, and practical version of the PBAC scale is required for future clinical work and research programs.

The difference in evaluating the symptoms before and after treatment could directly cause variance in the symptomatic relief rate. A unified evaluation system should be used for potential cooperation between different research centers in the future.

3. Histological and imaging diagnosis of adenomyosis

The diagnosis of adenomyosis is an integrated clinical and imaging approach based on the patient’s medical history, symptoms, signs, transvaginal ultrasound (TVUS), and magnetic resonance imaging (MRI) examination results.18 For now, the “gold standard” for the diagnosis of adenomyosis is still surgical pathology. The positive rates of US-guided puncture biopsy and hysteroscopic guided tissue biopsy have been reported to be 28%19 and 55.47%,20 respectively in previous studies. Their diagnostic value for adenomyosis is limited by the biopsy site and the sample size.

With the continuous development of the imaging quality of TVUS and MRI in the past 20 years, the application of these two imaging methods provides new non-invasive diagnostic tools for adenomyosis, which could increase the detection rate of adenomyosis and make a new epidemiological investigation scenario possible.21 TVUS has been widely used as the first-line imaging method because it is convenient, fast, and cost-effective. Presently, MRI is the second line and most widely recognized imaging method for the diagnosis of adenomyosis, because it has high diagnostic accuracy and low operator dependence and is able to provide multi-dimensional and multi-parametric information. MRI facilitates the classification of lesion type which is the basis of treatment planning. We agree that both TVUS and MRI should be performed in the pre-ablation evaluation of adenomyosis. However, there is still no unified diagnostic standard, including ultrasound and MRI, for adenomyosis worldwide. This has resulted in great heterogeneity in the patients in different studies, which have used a common inclusion criterion of “imaging diagnosis of adenomyosis”. Researchers worldwide have made great efforts to explore imaging and molecular markers for the noninvasive diagnosis of adenomyosis, while great progress had been achieved in the study of the US and MRI characteristics. Therefore, we have summarized the imaging features of adenomyosis mentioned in the guidelines and previous literature for reference.

The main US manifestations of adenomyosis include (1) uterine enlargement, (2) asymmetry of uterine wall thickness, (3) heterogeneous myometrial areas or myometrium with fan-shaped shadowing, (4) intra-myometrial cysts or hyperchogenic islands, (5) hyperchogenic sub-endometrial striation lines or nodules, (6) irregular endometrial-myometrial interface, and (7) interrupted, poorly defined or thickened junction zone (JZ).22

The typical MRI features of uterine adenomyosis include an ill-demarcated low-signal-intensity area, intra-myometrial cysts, and small high-signal-intensity spots on T2-weighted images (T2WI).23 The shape and thickness of JZ on T2WI also contribute to the diagnostic: (1) thickness >12 mm seems to be highly predictive of adenomyosis; (2) thickness between 8 and 12 mm, the ratio of maximum JZ thickness to the total myometrial thickness over 40%, and the difference between the maximum and minimum thickness of the JZ (JZmax–JZmin) of >5 mm are linked to adenomyosis; (3) JZ < 8 mm generally allows the exclusion of adenomyosis.24–26

Adenomyosis represents a spectrum of lesions, ranging from an increased thickness of the junctional zone to focal or diffuse lesions involving the entire uterine wall. Based on the complexity and diversity of imaging manifestations, many classification methods have been proposed using US and MRI findings from previous studies.25–31 Generally, according to the imaging characteristics and the extension of the lesion involvement, adenomyosis can be divided into diffuse and focal types. The focal type includes adenomyoma and cystic adenomyosis. However, this preliminary typing method is far from meeting clinical needs. Several
classification methods have been proposed regarding the location, severity, and etiological origin of adenomyotic lesions by imaging examination. Bosch reported a new US typing and severity grading system according to different uterine layers involved (type 1, only JZ involved; type 2, middle myometrium involved; and type 3, outer myometrium involved) and the percentage of affected myometrium (mild <25%, moderate 25–50%, and severe >50%). The most commonly used classification method based on MRI was proposed by Kishi in 2012, which divided adenomyosis into type I (intrinsic), type II (extrinsic), type III (intramural), and type IV (advanced). Evidence shows that diffuse adenomyosis and intrinsic adenomyosis are correlated with heavy menstrual bleeding and infertility, whereas extrinsic adenomyosis and coexistence of deep infiltrating endometriosis cause pelvic pain. Although none of these classifications has been widely accepted and applied, they have a positive clinical value in mapping lesions and grading disease severity. The absence of baseline classification information in previous clinical studies leads to difficulties in comparing the results of different studies. Simultaneously, further research should be carried out to establish a powerful and practical classification method based on the pathological characteristics, ability to reflect the severity of the disease, ease of operation, and usefulness for the treatment plan and prognosis prediction.

4. US-guided MWA procedure

Standard operating procedures of US-guided MWA include intra-procedural analgesia and anesthesia, routine disinfection and sterile towel laying, preoperative B-mode US imaging and contrast-enhanced ultrasound (CEUS) examination, microwave antenna placement, ablation under the guidance of real-time US imaging, and intra-procedure evaluation of ablation range with CEUS. This procedure can be performed under general anesthesia or intravenous sedation and analgesia. The common complaints of discomfort during MWA under intravenous sedation and analgesia are significant lower abdominal pain, anal distending pain. Sometimes, serious intra-procedural pain may lead to early termination of ablation treatment, which may cause a small ablation range and failure to reach the predetermined goal. Disappointingly, this issue has not been discussed in any previous study. The optimal anesthesia scheme used for the ablation of adenomyosis remains unknown, and further prospective research is needed.

The main goal of US-guided MWA is to completely damage the adenomyosis lesions without hampering the adjacent organs. The ablation range can be monitored under the guidance of real-time B-mode ultrasound imaging, and the actual range of tissue necrosis can be quickly evaluated by observing the non-perfused area on intra-procedural CEUS. If residual lesions are observed on CEUS, supplementary ablation is performed under its guidance. Similar to conservative resection, the clinical efficacy of US-guided MWA is negatively correlated to the percentage of the residual lesion. Therefore, most researchers regard the ablation rate as the technical efficacy evaluation parameter. The Chinese guidelines and recommendations of US-guided PMWA treatment for adenomyosis published in 2015 suggest that the ablation rate for efficient ablation treatment of adenomyosis should exceed 70% in principle, and good clinical outcomes can be achieved when the ablation rate is >90%.

To obtain a sufficient ablation range and minimize accidental injury to the normal uterine smooth muscle tissue during the ablation procedure, it is necessary to formulate a reasonable ablation termination standard in the ablation plan and perform an ablation operation following this standard. However, the termination criteria adopted in previous studies were not uniform, and individual research centers implemented their own standards. Different versions that can be observed include “the hyperechoic cloud covered the entire lesion”, “>80–90% of the entire lesion” “3–5 mm from the margin of the lesion and ‘reached 0.3 cm to the serosa inferior margin or covered more than 1/2 of the lesion range’. To prevent potential thermal damage to the adjacent organs, it is recommended that the distance from the ablative margin to the serosal surface should be at least 3 mm, which is one of the safety boundary standards for ablation of adenomyosis. However, it is still controversial whether a safe distance between the ablation zone and endometrial-myometrial junction should be set. Hai et al. reported that the minimum distance from the ablative margin to the endometrium was significantly correlated to the incidence and duration of vaginal discharge after ablation. While the safe distance between the ablative margin was not mentioned at all in some other studies, it might contribute to the significant variance of the incidence rate of vaginal discharge. Overall, the non-unified standard of terminating the ablation procedure may contribute to the significant difference in the clinical outcomes of patients in different studies. Additionally, although adenomyosis classification has a positive value in disease severity classification, lesion location, and prognosis prediction, as shown in previous studies, we did not set different ablation targets according to different classifications of adenomyosis. The effective use of the classification system to formulate an individualized ablation treatment plan to improve the effectiveness and safety of US-guided MWA treatment is worthy of further exploration.

5. Post-ablation evaluation

Post-ablation evaluation mainly includes technical efficacy, clinical efficacy, and safety. For the clinical efficacy evaluation, dysmenorrhea score, UFS-QOL scale, and PBAC score are commonly used to assess symptomatic relief. In addition, CA125 and Hb levels are also used to evaluate clinical effectiveness.

MRI is more reliable and preferable than other imaging modalities for the evaluation of technical efficacy. The most commonly used local treatment response evaluation parameter of MWA is the ablation rate, which is equal to the non-perfused volume (NPV) ratio calculated on the contrast-enhanced MRI. During the follow-up period, the volumetric reduction rates (VRR) of the uterine body and lesion and the change in the uterine muscle wall thickness are also used as efficacy evaluation parameters (Fig. 1). Therefore, the accuracy of the ablation rate and VRR of the uterine body or lesion are worthy of discussion. The volumetric measurement of the adenomyotic lesion, uterine body, and NPV were all calculated with the traditional ellipsoid analog volume formula (V = π/6 × height × length × width), based on the hypothesis that the shape of the lesion, uterine corpus, and non-perfused area is close to an ellipsoid. In reality, the shape of adenomyosis lesions is sometimes irregular, and the accuracy of the volumetric measurement of the lesion or NPV is doubtful in these cases. The bias in these parameters may reduce the accuracy of local efficacy evaluation results and cause inconsistency between the symptom relief rate and the ablation rate in the same patient. Although this is the most commonly used method, no previous studies have focused on the accuracy of this method. Several three-dimensional (3D) reconstruction technologies of MRI or US imaging have been recently developed. Zhang et al. used a new 3D ablation planning and evaluation system to measure the volume of the submandibular gland accurately in the MWA treatment of submandibular gland hyperfunction. This volumetric measurement method seems promising for solving this problem; however, the value of its clinical application remains unclear.

6. Adjuvant medication therapy after ablation

Postoperative adjuvant medication therapy can reduce the risk of relapse and improve the symptomatic relief rate in the conservative surgical treatment of adenomyosis. Gonadotropin-releasing hormone agonist (GnRHa) is often used for consolidation treatment after conservative surgery, and its value is unanimously recognized worldwide. A meta-analysis showed that drug treatment for 6 months immediately
after conservative surgery improved the remission rate of postoperative clinical symptoms and effectively reduced the recurrence rate. In other words, conservative invasive treatment combined with drug therapy can significantly improve the clinical outcomes of patients and prolong the recurrence cycle.

US-guided thermal ablation combined with medication therapy is a new approach for the long-term management of patients with symptomatic adenomyosis. Adjuvant medication therapy is expected to become an effective supplementary treatment for patients with recurrence or poor curative effect after ablation. Hai et al. found that the improvement rate of clinical symptoms reached 98% in 3 years in patients with a significantly enlarged uterus (average uterine volume of 307 ml) after RFA treatment combined with levonorgestrel-releasing intrauterine device (LNG-IUD) implantation, which was significantly better than simple ablation treatment. The study provided clinical evidence that post-ablation adjuvant medication therapy was useful in improving the long-term outcomes of patients with adenomyosis treated with thermal ablation.

However, all medications have side effects, and common adverse effects of GnRHα are menopausal symptoms and bone loss caused by hypoestrogenicity, while spot bleeding, breast pain, and depression are commonly seen in patients who consumed oral contraceptives. To the best of our knowledge, no relevant study has investigated the long-term efficacy of US-guided MWA combined with GnRHα or oral contraceptives in the treatment of adenomyosis. Further prospective randomized controlled studies are needed to determine the best adjuvant medication for treatment after ablation.

7. Conclusion and prospect

US-guided MWA has proven to be an effective minimally invasive alternative treatment for symptomatic adenomyosis, and an increased number of patients have been benefited. However, a significant difference in the symptom relief rate and incidence of post-ablation complications has been observed in previous studies. The potential reasons include variance in the pre-ablation evaluation, non-uniform ablation procedures, and bias caused by the use of traditional post-ablation imaging evaluation. Many clinical problems remain unsolved in this field, and more high-quality prospective multicenter studies are needed to optimize the therapeutic effect and further standardize the ablation procedure. Simultaneously, systematic training and promotion of novice interventional doctors are very important. It is gratifying that the original 2015 MWA clinical application guidelines for the treatment of adenomyosis are being revised and updated by relevant experts and will be available shortly. We are looking forward to seeing new progress and the transformation of new research results to better promote the clinical application and promotion of this technology.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this editorial titled “Challenge and opportunities of ultrasound-guided microwave ablation in the treatment of symptomatic adenomyosis”.

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