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The advantages of focused ultrasound ablation for uterine fibroids and the use of MRI in management

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Abstract: *uterine fibroids are extremely prevalent in women of reproductive age, and it not only causes abnormal vaginal bleeding, but may also trigger a variety of reproductive diseases, which seriously affect patients' health. High intensity focused ultrasound (HIFU) is a micro noninvasive procedure with the advantages of being noninvasive and preserving the uterus, providing a new option for women of reproductive age. However, HIFU has a high rate of long-term re intervention and carries a risk of recurrence, and the use of magnetic resonance imaging (MRI) to effectively assess the efficacy and safety of HIFU ablation of uterine fibroids can be used for preoperative safety assessment and efficacy prediction, intraoperative monitoring, postoperative efficacy assessment, and postoperative re intervention and local recurrence. In this article, the recent progress of magnetic resonance in the treatment of uterine fibroids with HIFU is reviewed.*

Keywords: *magnetic resonance imaging; Uterine fibroids; High intensity aggregation ultrasound*

1. Introduction

Uterus fibroids (UFs), benign monoclonal tumors, are benign lesions of the uterus that consist of smooth muscle cells and fibroblasts and are rich in the Extracellular matrix (ECM). It is the most common benign tumor in women of childbearing age and a common cause of abnormal vaginal bleeding and other reproductive disorders in women. Because in many women, the occurrence of uterine fibroids is asymptomatic or asymptomatic, so its incidence is difficult to accurately calculate, the estimated prevalence of women of reproductive age is about 25%, according to autopsy statistics can be as high as 50%[1]. The most common symptoms in women with uterine fibroids are excessive menstrual bleeding and prolonged periods, leading to social awkwardness, and can also cause iron deficiency anemia, fatigue, and pain. Other symptoms include non-periodic pain, abdominal swelling or pain during sex, enlarged fibroids that can press on the uterus, resulting in increased pelvic pressure, urinary symptoms (such as frequent urination, nocturia or urinary retention) or gastrointestinal symptoms (such as diarrhea or constipation), and fibroids that can be associated with reproductive problems. Including impaired fertility, pregnancy complications, and recurrent miscarriage[2], so for symptomatic fibroids patients, especially women of childbearing age, medical interventions that can adequately relieve symptoms are very important.

HIFU treatment can effectively alleviate clinical symptoms, reduce the size of fibroids, and can be repeated treatment, rapid recovery after surgery, and can preserve the uterus and fertility, providing a new choice for women with fertility needs. It has attracted much attention in tumor treatment, and is a non-invasive treatment method that has been studied and applied more in recent years[3].

Imaging plays an important role in the treatment of uterine fibroids, which have been visualized using several imaging techniques, including pelvic ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasound is the most commonly used imaging method for uterine fibroids, but it can be limited for large-volume fibroids, multiple fibroids, or fibroids in obese patients. In addition, differences between observers are one of the main limitations of ultrasound. Computed tomography is rarely used as an imaging technique for uterine fibroids because of its poor discrimination in soft tissue masses. MRI has become the main evaluation method before and after the treatment of uterine fibroids because of its high soft tissue resolution, no ionizing radiation, and multi-parameter multi-directional imaging. It is the most accurate imaging method for detecting and locating fibroids, showing good contrast between fibroids and the surrounding soft tissue, providing a superior view of the ribbon

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anatomy of the uterus, and having less impact on results from observer to observer variability than ultrasound[4].

2. HIFU treatment

2.1. Basic principles of HIFU therapy

Since Lynn et al[5]. first proposed the use of high-intensity focused beams in 1942, they have been explored for many different potential medical applications. Ultrasound is a kind of mechanical wave with good penetration in human tissues. The treatment principle of HIFU is based on such biological effect. Under the guidance of medical imaging equipment, ultrasonic transducer is usually concave and uses the ultrasonic transducer to accurately focus low-energy ultrasound in vitro from different directions on the site of fibroids in vivo. The temperature of the focal area rapidly rises to 60-100℃ in a short period of time, and the coagulation necrosis of uterine fibroids is induced through thermal effect, cavitation effect and mechanical effect, so as to inhibit the growth of fibroids, make them atrophy and necrosis and then disappear, and do not damage the surrounding normal tissues and vascular system[6]. Thus, HIFU can be thought of as a hot knife, but without the need for open surgery to remove tissue. HIFU ablation typically uses a frequency in the range of 0.8-4 MHz, an intensity between 400-10,000 W/cm2 (time average intensity) and a pressure amplitude of up to 10MPa, depending on the exact application and treatment regimen[7].

2.2. Advantages of HIFU in the treatment of uterine fibroids

At present, the main treatment options for uterine fibroids include surgery (abdominal surgery, hysteroscopic surgery, transvaginal surgery), uterine artery embolization, and uterine artery embolization. UAE), high-intensity focused ultrasound (HIFU), and drug therapy. Surgical treatment is the traditional treatment for uterine fibroids, and it is also the most important and thorough treatment for uterine fibroids at present. Although surgical methods are constantly improving, there is still a high risk of postoperative complications, which may affect the patient's fertility ability and normal pelvic structure, which not only causes harm to the patient's physical health, but also harms the patient's mental health， and it also adversely affect the quality of life[8]. Although drug therapy can reduce uterine blood flow, shrink the volume of uterine fibroids, and effectively improve the clinical symptoms of patients, drug therapy cannot completely remove fibroids, and most patients will relapse after stopping the drug. Long-term use may also increase the risk of endometrial cancer. For patients requiring surgical treatment of uterine fibroids, preoperative medication can significantly improve intraoperative bleeding and improve the success rate of surgery. Therefore, current drug therapy is mostly used for preoperative pretreatment, which can correct anemia and reduce the volume of uterus and fibroids[9]. With the development and progress of modern medical technology, more and more micro-non-invasive surgery has been used for the treatment of uterine fibroids. Ultrasound (US) guided high-intensity focused ultrasound (HIFU) is an effective non-invasive treatment strategy for uterine fibroid ablation that significantly reduces tumor volume, and the results of HIFU for uterine fibroids have been shown to be repeatable and a promising therapeutic alternative. It has the advantages of accuracy, non-inventiveness, rapid recovery, preservation of uterus and fertility[10-14].

Tonguc et al.[12] followed up 55 patients with symptomatic uterine fibroids after HIFU treatment at 6 weeks, 3, 6, 9 and 12 months, respectively. Clinical assessment was conducted according to uterine fibroid symptoms and health-related quality of Life Questionnaire (UFS-QOL), and imaging follow-up was conducted according to contrast-enhanced ultrasound (CEUS) and MRI. Significant reductions were found in both Symptom Severity Scale (SSS) and Health-related Quality of Life Questionnaire (HRQL) outcomes from 6 weeks to 12 months after HIFU treatment, and significant post-intervention improvements were observed in each of the HRQL subscales, while only mild, transient, and self-limiting side effects were observed in most patients, demonstrating that high-intensity focused ultrasound therapy can reduce clinical symptoms associated with uterine fibroids and improve health-related quality of life in patients with uterine fibroids.

Li Fang et al.[13] compared the pregnancy outcomes of three fertility preservation therapies, high intensity focused ultrasound ablation (HIFU), hysteromyomectomy, and uterine artery embolization (UAE), and conducted a meta-analysis of 54 studies involving 12,367 patients. In order to assess the blood flow impedance of bilateral uterine arteries before and after HIFU, A retrospective self-controlled study of 26 patients with uterine fibroids from May 2019 to December 2020 was conducted. The results

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showed that in the treatment regimen analysis, the pregnancy rate after HIFU was 0.18, which was significantly higher than that of UAE. The miscarriage rate after HIFU was 0.08, lower than 0.15 after myomectomy and 0.16 after UAE. In a subgroup analysis, it was found that women who underwent ultrasound-guided HIFU (USgHIFU) were more likely to have desirable pregnancy outcomes than those who underwent magnetic resonance image-guided HIFU, such as significantly higher right side pulse index and resistance index at 3 months after HIFU than before HIFU. HIFU may help improve pregnancy rates by increasing uterine blood flow impedance, and HIFU therapy, particularly USgHIFU, may be another method of fertility preservation for patients with uterine fibroids over 40 years of age.

3. Preoperative examination

3.1. Preoperative Diagnosis

Preoperative diagnosis of malignant uterine tumors is essential to prevent conservative treatment or surgery, because inappropriate treatment may crush the potentially malignant mass and lead to the spread of malignant tumors[15]. MRI has been recognized as a very useful method for diagnosing, locating, and managing uterine fibroids, with the Conventional Magnetic resonance imaging (cMRI) package capable of a comprehensive assessment of location, morphology, boundaries, blood vessels, and internal components. The effect is better after the application of paramagnetic contrast agent[16]. On MRI, ordinary fibroids without degeneration usually show a definite mass of the myometrium. On T1 and T2-weighted images, the mass is equal-signal and uniformly low-signal compared to muscle signals, and a high-signal T2 edge may be present, which may be attributed to edema, such as obstruction or dilation of peripheral lymphatic vessels and veins, which in most cases show uniform enhancement after intravenous gadolinium contrast agent. Low signals are typically seen on apparent coefficient diffusion (ADC) graphs and diffusion-weighted (DWI) images[17]. Although the imaging findings of uterine fibroids and uterine sarcomas overlap, the results of some studies showed that 90.9% of uterine sarcoma lesions showed ambiguous edges, which was significantly higher than that of uterine fibroids. 72.7% of uterine sarcomas showed high signal on T2WI, which was significantly higher than that of uterine fibroids. In addition, the proportion of uterine sarcomas without central enhancement was significantly higher than that of uterine fibroids[18].

Some advanced MRI techniques, such as diffusion-weighted MRI (DWI), can complement the physiological and functional information obtained by traditional imaging and are more helpful in distinguishing benign leiomyomas from malignant uterine sarcomas. In a recent study, Abdel et al.[19] developed a DWI-based algorithm to distinguish between benign atypical leiomyomas and malignant uterine sarcomas. Some scholars have systematically studied the characteristics of cMRI and found that irregular morphology, unclear edge definition, and high signal on T2WI are the most valuable features that can significantly distinguish uterine fibroids from uterine sarcomas or degenerative fibroids. Combining cMRI characteristics with the ADC values obtained from DWI, optimal sensitivity and specificity can be achieved in distinguishing these tumors[20], improving diagnostic accuracy to 92%[21].In a recent meta-analysis, scholars validated that high signal intensity and low ADC values on T1 weighted images can improve the accuracy of distinguishing between leiomyosarcoma and benign leiomyoma[22].

3.2. Preoperative Prediction

Fibroids with different signal characteristics have different sensitivity to HIFU treatment, different efficacy during ablation, different surgical risks and complications, and corresponding treatment plans will also be changed and adjusted accordingly. Studies have shown that factors such as uterine fibroids > 50mm in diameter, anterior uterine fibroids, low T2WI signal intensity and low T1WI enhancement can affect the effectiveness of high-intensity focused ultrasound treatment. Therefore, preoperative MRI examination has certain value in predicting the efficacy and safety of HIFU ablation of uterine fibroids.

Current predictive models tend to be based on traditional T2-weighted imaging (T2WI), which is highly sensitive in assessing the histological features of uterine fibroids before treatment[23]. For example, rich cell content, high water content, or uterine fibroid degeneration can lead to high signal strength on T2WI, whereas high T2 signal fibroids are difficult to treat with HIFU, and heterogeneous fibroids are more difficult to treat with HIFU than homogeneous fibroids. A retrospective study[24] analyzed the clinical data of 172 cases of MRI-T2WI and ultrasound-guided high-intensity focused ultrasound (USgHIFU) in the treatment of different appearance of uterine fibroids. According to the signal intensity of MRI-T2WI, uterine fibroids were divided into three types: low intensity, equal intensity and high

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intensity. To evaluate the clinical safety and effectiveness of different types of fibroids ablation, it was found that the percentage of non-perfusion volume and ablation efficiency of high-intensity fibroids were lower than those of equal-intensity and low-intensity fibroids, possibly because fibroids in the high-intensity T2 signal group had more abundant tissue cells and higher proliferation rate. Another study[25] divided 401 patients with isolated uterine fibroids treated with HIFU into four groups, including very low-intensity, low-intensity, isostrong, and high-signal fibroids, while each group was further divided into two subtypes based on the signal homogeneity of the fibroids: Comparing the treatment dose and long-term follow-up results, it was found that the treatment time of patients with heterogeneous fibroids was significantly longer than that of patients with homogeneous fibroids with equal strength.

In addition to high signal on T2WI, significant enhancement of contrast enhanced T1-weighted imaging (CE-T1WI) can indicate abundant blood supply, which is another important factor limiting the rate of HIFU ablation of uterine fibroids[26]. The theoretical basis of this resistance is that uterine fibroid cells are composed of abundant smooth muscle cells with high water content, sparse collagen fibers and low acoustic impedance. At the same time, the blood supply can absorb HIFU energy and leave the treatment area with circulating movement, resulting in low energy deposition efficiency. Therefore, the absorption of ultrasonic energy and the subsequent tissue warming effect are reduced, thus reducing the ablation effect.

4. Intraoperative monitoring

According to the different guidance methods, the focused ultrasound ablation therapy currently provides comprehensive treatment plan, real-time control (spatial and temperature guidance) and evaluation mainly through ultrasound (US-HIFU) and magnetic resonance imaging (MR-HIFU) in clinical practice. Each of these two guidance methods has its advantages and limitations. MR-HIFU is based on MRI images with clear anatomical detail and high contrast of soft tissue for ultrasound planning. At the same time, MR Thermometry provides near-real-time temperature maps during ultrasonic treatment to track heating patterns in focal points and surrounding tissues, which can be used as feedback for HIFU sensors. In addition, contrast-enhanced T1 scanning opens up the possibility of subsequent treatment evaluation, where non-perfusion volume (NPV) is calculated by contrast-MR imaging measurements after surgery to evaluate the ablation effect[27]. MR Thermometry provides a near real-time temperature map that feeds back to the HIFU transducer to ensure a defined heat dose is deposited in the target tissue or that hyperthermia is maintained at a constant temperature for a long period of time. The responsible radiologist has access to all anatomical images as well as superimposed temperature maps, and can plan each ultrasound treatment through a planning console embedded with sophisticated software for optimal energy configuration. Using electron beam steering can heat tissue volumes of different sizes, and even larger volumes can be achieved by moving or tilting the transducer with the help of a moving robot[28]. In a meta-analysis, researchers compared the efficacy and safety of MR-HIFU and US-HIFU in the treatment of symptomatic uterine fibroids <300cm^3. The average non-perfusion volume ratio (NPVR) of the US-HIFU group was higher than that of the MR-HIFU group at 3, 6 and 12 months after surgery. In addition, the incidence of postoperative abdominal pain and abnormal vaginal secretions in the US-HIFU group was lower than that in the MRI-HIFU group. However, postoperative skin burn and sciatic nerve pain were more common in the US-HIFU group than in the MRI-HIFU group. The one-year re-intervention rate after MR-HIFU was 13.4%, higher than 5.2% in the US-HIFU group. Overall, US-HIFU is likely to demonstrate better efficacy and safety than MR-HIFU in the treatment of symptomatic fibroids <300cm^3[29].

5. Postoperative evaluation

The basic principle of the treatment of uterine fibroids is to convert high-intensity ultrasound energy into thermal energy of the target area. The non-enhanced area on enhanced magnetic resonance imaging is basically the same as the pathological necrotic area, showing high signal on T1WI and low signal on T2WI in conventional nuclear magnetic resonance imaging. Histopathologically, uterine fibroids with high T2WI signal had more cells, more blood vessels and more degeneration than those with low signal. The difference of histopathological features is an important factor that causes the difference in the treatment effect of HIFU ablation on different uterine fibroids. The ablation rate is negatively correlated with the content of collagen fibers, but positively correlated with the content of smooth muscle cells[30]. Cun Jiangping et al. [31]divided the T2WI signal intensity in the non-perfusion area of fibroids into 4 groups of low, moderate, mixed and high signal on the 3rd day after surgery, compared the difference in

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the residual volume of fibroids at the 3rd and 6th month after surgery, and found that the residual volume of fibroids in the high-signal group was higher than that in the other 3 groups. This is consistent with the view of foreign scholars that the ablation effect of high T2 signal and heterogeneous fibroids after HIFU treatment is not good[24, 25]. However, recent studies have shown that compared with HIFU alone, pretreatment of HIFU with GnRH-a can enhance the treatment effect of heterogeneous high-signal fibroids[32]. In addition, researchers[33] measured the apparent diffusion coefficient (ADC) and DWI signal values before and after surgery, compared the DWI signal change area and enhanced the volume of fibroid necrosis area after surgery, and found that the average ADC and DWI signal values before HIFU treatment were higher than that after surgery, 78.09% of fibroid DWI showed complete regular or irregular high-signal rings. In combination with preoperative T2WI and postoperative DWI, non-enhanced MRI can effectively evaluate the ablation rate in most patients with uterine fibroids. Adequate blood supply can prevent ultrasonic energy deposition of uterine fibroids and reduce heat sink, thus affecting the ablation effect. Dynamic contrast enhanced MRI can reflect the blood flow of uterine fibroids. Studies have shown that dynamic contrast-enhanced MRI for mild and irregularly enhanced high-signal fibroids in arterial phase is more suitable for US-HIFU treatment[34].

6. Conclusion

Modern medicine is focused on developing personalized treatment approaches and techniques that minimize patient intervention and length of stay, and HIFU fits very well with this philosophy. Thermal ablation therapy offers a minimally invasive approach to cancer treatment that is rapidly gaining clinical acceptance, and HIFU is the least invasive of existing ablation techniques and therefore should be the most attractive. With its own advantages, MRI has become an indispensable examination and evaluation means for HIFU treatment of uterine fibroids in all aspects, and the imaging principles, advantages and applications of different sequences are different, which can provide different aspects of clinical information. However, in the application of intraoperative monitoring, ultrasound-guided HIFU treatment is more widely used than MRI, and there are few studies on MRI in long-term efficacy evaluation and relapse re-intervention, most of which are early and medium-term evaluation, and long-term efficacy evaluation needs to be explored by more researchers and scholars. It is hoped that better functional MRI imaging technology will be developed in the future to present better images for patients, provide more useful information for clinicians, and contribute to preoperative and postoperative evaluation and curative effect prediction.

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