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## **A contrastive study on the clinical efficacy and safety of laparoscopic myomectomy and high intensity focused ultrasound in the treatment of uterine fibroidsn the treatment of uterine fibroids**

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**A contrastive study on the clinical efficacy and safety of laparoscopic myomectomy and high intensity focused ultrasound in the treatment of uterine fibroids**

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**ABSTRACT**

**Objectives:** This study intended to compare the safety and clinical efficacy between two treatments of uterine fibroids: laparoscopic myomectomy (LM) and high intensity focused ultrasound (HIFU).

**Material and methods:** Clinical data were collected from 587 uterine fibroid patients who were treated in The People's Hospital of Nanchuan, Chongqing from January 1, 2018 to December 31, 2019. Among the patients, 287 cases were treated with HIFU (observation group), and 300 cases were treated with LM (control group). The progression-free survival (PFS) was taken as the primary endpoint. The secondary endpoints included operation results (including operative time, intraoperative blood loss, and intraoperative fluid replacement), complications, hemoglobin level one month after surgery and clinical efficacy. In addition, the fibroid volume of the

observation group before treatment and 3, 6, and 12 months after treatment were also analyzed.

**Results:** The operative time of observation group was evidently shortened compared to the control group, and the intraoperative blood loss and intraoperative fluid replacement of observation group were also considerably reduced (all  $p < 0.05$ ), but there was no significant difference in the hemoglobin level between the two groups one month after surgery ( $p > 0.05$ ). In terms of curative effect, the total effective rate of HIFU group and LM group was 98.6% (283/287) and 95.3% (286/300) respectively, with statistically significant difference ( $p < 0.05$ ). In terms of complications, the incidence of bleeding and infection in HIFU group was obviously lower than that in LM group (both  $p < 0.05$ ), while no significant differences were observed in the remaining complications (all  $p > 0.05$ ). Fibroid volume comparisons before treatment and 3, 6 and 12 months after operation in observation group showed that fibroid volume decreased significantly (all  $p < 0.05$ ). The median follow-up time was 30.6 months. The mean PFS of patients in the observation group and control group was 29.71 months (95% CI 28.24–29.75) and 26.74 months (95% CI 26.49–28.33), respectively (HR 0.47; 95% CI, 0.29 to 0.76; Log-rank  $p = 0.002$ ).

**Conclusions:** HIFU could improve the intraoperative efficacy and reduce the complications of patients with uterine fibroids and has excellent performance in improving clinical efficacy and prolonging PFS. HIFU can be used as an alternative to surgical treatment.

**Key words:** laparoscopic myomectomy; uterine fibroids; high intensity focused ultrasound; clinical efficacy; safety

## INTRODUCTION

Uterine fibroids rank the top among benign tumors in reproductive tract in women of reproductive age<sup>1</sup>. Its prevalence rate increases with the rising of age, until menopause, with estimates ranging from 50% to 77% [2]. About 30–40% of uterine

fibroid patients require treatment because of their symptoms, which include dysmenorrhea, menorrhagia, pelvic pressure, abnormal uterine bleeding and infertility [3, 4]. A previous study has shown that infertility and miscarriage rates of women with fibroids are 10% and 20–30%, respectively [5]. At present, the therapies of uterine fibroids mainly include drug treatment, routine surgery, emerging high intensity focused ultrasound (HIFU) and uterine artery embolization (UAE) [6]. Among them, surgical treatment can be classified into myomectomy (MY) and hysterectomy (HY). The treatment of uterine fibroids should consider the size and location of the tumors as well as the age, symptoms, and desire to preserve fertility of patients. However, there is uncertainty about the most effective treatment due to the lack of comparison of long-term outcomes between different treatments.

Drug treatments are known to be effective at alleviating symptoms and reducing tumor size, but they cannot completely remove fibroids. Once the drug is stopped, fibroids may reappear, and symptoms may recur. Therefore, drugs are usually used as preoperative adjuvant therapy. Overwhelming evidences in evidence-based medicine have proved the effectiveness of surgical removal of fibroids in reducing miscarriage rate and increasing live birth rate [7]. However, patients may be at risk for hypofertility after surgery [8]. Currently, laparoscopic myomectomy (LM) is the most common method to treat fibroids, but patients are faced with a high risk of recurrence [9]. Therefore, alternatives to surgery are necessary to be explored and evaluated with the goal of preserving fertility. HIFU is a new type of non-invasive technique for tumor ablation. In the past two decades, HIFU has been widely applied in the treatment of uterine fibroids [10]. HIFU is a non-invasive technique guided by magnetic resonance imaging (MRI) or ultrasound, which can achieve myoma ablation without damaging adjacent structures [11]. Numerous previous studies have confirmed the efficacy and safety of HIFU, with rapid symptom relief, short recovery time and reduced risk of complications [12–15]. A recent literature review also shows that HIFU is a relatively safe treatment, with only about 10% of patients experiencing mild complications [16]. Nevertheless, few studies have conducted to compare the

clinical safety and efficacy of HIFU and LM.

Based on the results of previous studies, we carried out a retrospective analysis on 587 patients with uterine fibroids to compare the clinical efficacy and safety of HIFU and LM in patients with uterine fibroids.

## **MATERIAL AND METHODS**

### **Clinical data**

This study enrolled 587 patients with fibroids treated in The People's Hospital of Nanchuan, Chongqing from January 1, 2018 to December 31, 2019. All patients were diagnosed as uterine fibroids by B ultrasound and cervical cytology examination. According to the classification system for uterine fibroids of International Federation of Gynecology and Obstetrics (FIGO) [17], myomas attached to the endometrium with a narrow stalk are classified as type 0; type 1 requires  $< 50\%$  intramural myomas; type 2 requires  $\geq 50\%$  intramural myomas; myomas contact endometrium but 100% intramural are type 3; totally intramural myomas are type 4; subserous and  $\geq 50\%$  intramural myomas are type 5; subserous and  $< 50\%$  intramural myomas are type 6; subserous pedunculated myomas are type 7; myomas completely unrelated to the myometrium, such as ligamentous and cervical lesions, are type 8; myomas that impact both the endometrium and serosal layer are hybrid fibroids. Uterine fibroids were classified into mucosa-associated types (type 1, type 2, type 3 and hybrid) and non-mucosa-associated types (other types) according to the relationship between the fibroids and endometrium. In this study, patients with incomplete clinical data or confirmed malignant tumor were excluded. The included subjects were divided into HIFU group (observation group;  $n = 287$ ) and LM group (control group;  $n = 300$ ). The Medical Ethics Committee of The People's Hospital of Nanchuan, Chongqing has approved this study, and the clinical data were used for research purpose only. Before HIFU or LM operation, informed consent was obtained from each patient.

### **HIFU procedures**

JC200 focused ultrasound tumor therapy system (Chongqing Haifu Medical Technology Co., Ltd., China) was used for HIFU with a focal area of  $1.5 \times 1.5 \times 10$  mm of ultrasonic transducer. The diameter of the transducer was 20 cm, the focal length was 15 cm, and the operating frequency was 0.8-1 MHz. My-Lab70 ultrasound equipment (Bisound Esaote Group, Italy) was used for real-time monitoring. All patients underwent intestinal preparation of three days before HIFU treatment. Patients had a light diet on day one and had only semi-liquid foods without milk on day two and day three. For luminal laxation, patients were given the compound polyethylene glycol electrolyte solution. Clysis was performed for the patients on the morning of treatment day to further cleanse the intestine. Skin preparation was needed 1 h before HIFU treatment, including shaving from the umbilical region to the superior margin of the pubic symphysis and degreasing and deaeration with 75% ethanol and de-aerated water, respectively. Before surgery, a catheter was introduced to control intraoperative bladder volume.

To compress and push the intestine away from the acoustic pathway, the anterior abdominal wall of the patient was made to contact the de-aerated water, and a de-aerated water balloon was placed between the abdominal wall and the transducer. HIFU treatment was performed when the patient was in conscious sedation. For conscious sedation, midazolam hydrochloride (0.02–0.03 mg/kg) and fentanyl (0.8–1  $\mu$ g/kg) were administered intravenously. The conscious sedation was maintained at level 3 or 4 (patients respond to commands or show rapid responses to taps or loud noises) in accordance with the Ramsay Sedation Scale. The drug was administered every 30–40 min to ease pain and avoid unnecessary physical movement.

HIFU treatment was operated with the guidance of real-time ultrasound. Spot scanning was used, and the power was 400 watts. The length from the endometrium to the focus was at least 1.5 cm, and that from the focus to the subcutaneous surface of the uterus was 1 cm. The treating energy was modulated according to the feedback of the patient and the change of gray scale on the ultrasound image. This process was repeated until no blood supply was seen. The application of ultrasonography and

contrast agent (SonoVue, Bracco, Italy) can display the non-perfused volume (NPV) ratio of fibroids after treatment, which reflected the effect of immediate ablation. The patient was kept in prone position for 2 h after operation.

### **LM treatment**

LM was operated using standard laparoscopic equipment (Storz Xenon NOVA 300, Germany). The surgical procedure for LM was determined by the attending gynecologist. Preoperative evaluation included a detailed review of the patient's medical records, pelvic examination and ultrasound results. Prophylactic antibiotics were administered before laparoscopic surgery. All patients underwent meticulous intestinal and skin preparation before LM. Intestinal preparation included fluid diet 1 d before surgery, fasting for 6 to 8 h before surgery, and coloclisis at 2 h before surgery. The shaving area was the same with HIFU. A catheter was also introduced.

LM procedures: LM was operated under general anesthesia. The lithotomy position was adopted. An arc incision was cut at the upper margin of the umbilicus to form pneumoperitoneum. Trocar was used to puncture the abdomen. It was placed under laparoscopy throughout the treatment to avoid visceral organ injury. Then, 6-12 U of vasopressin was diluted and injected under the fibroid pseudocapsule on the protruding surface. After the target fibroids were removed, the incision was sutured.

### **Observation indicators and efficacy evaluation**

The operative time, intraoperative blood loss, intraoperative fluid replacement, postoperative complications and hemoglobin level one month after surgery were recorded. All patients underwent MRI scans before operation, including T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). Evaluation indicators included uterine fibroid volume reduction, symptom severity score (SSS), uterine fibroid symptoms — quality of life questionnaire (UFS-QOL) score [18, 19]. The curative effect was highly significant when one of the following conditions was met three months after ablation: uterine fibroid volume reduction was > 50%; SSS reduction



was > 50%; UFS-QOL score increase was > 50%. The therapeutic effect was significant when one of the following conditions was met three months after ablation: uterine fibroid volume reduction was 20–49%; SSS reduction was 30–49%; UFS-QOL score increase was 30–49%. The treatment was effective when one of the following conditions was met three months after the ablation: uterine fibroid volume reduction was 10–19%; SSS reduction was 10–29%; UFS-QOL score increase was 10–29%. The treatment was ineffective when one of the following conditions was met three months after the ablation: uterine fibroid volume reduction was < 10%; SSS reduction was < 10%; UFS-QOL score increase was < 10%.

### **Follow-up**

The fibroid volume of the observation group was recorded before treatment and 3, 6 and 12 months after treatment. Follow-up time was defined as the period from the date of surgical treatment to the occurrence of observed events or the last follow-up, and the maximum follow-up time was 36 months. Observed events were defined as: (1) progression of disease; (2) death due to cancer; (3) distant metastasis. The first observed event was recorded. The progression-free survival (PFS) of two groups was analyzed.

### **Statistical analysis**

SPSS 26.0 (SPSS, Inc.) was applied for statistical analysis. Median and interquartile range (IQR) [M (P25, P75)] were used to express the data that did not conform to normal distribution with. Enumeration data were expressed in percentage (%). The fibroid volume before and after HIFU was analyzed by repeated measure one-way ANOVA. Mann-Whitney U test was performed to compare measurement data between two groups. The Fisher's exact test or Chi-square test was used for the comparison of enumeration data. Kaplan-Meier curve was used for log-rank test in PFS analysis. Cox regression analysis was performed to calculate the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Difference was considered

significant when  $p < 0.05$ .

## **RESULTS**

### **Baseline characteristics**

This study included 587 patients with uterine fibroids, among which 287 received HIFU (observation group) and 300 received LM (control group). The median age was 42 years (range: 24–54) and 41 years (range: 33–49) in the observation group and control group, respectively (Tab. 1). Before treatment, no significant differences were observed between the two groups in age, Eastern Cooperative Oncology Group performance status (ECOG PS) score, body mass index (BMI), fibroid type, T1WI signal character, T2WI signal character, number of fibroids, maximum diameter, early treatment (mainly refer to the use of gonadotropin-releasing hormone agonist (GnRH)-a), and underlying diseases (including hypertension and diabetes) (all  $p > 0.05$ ). In addition, in the more detailed FIGO typing (Suppl. Tab. 1), there were no significant differences in the characteristics of uterine fibroids between the two groups ( $p = 0.168$ ).

### **Comparison of intraoperative outcomes**

Compared to the control group (Tab. 2), the operative time of observation group was remarkably shortened, and the intraoperative blood loss and intraoperative fluid replacement volume were significantly reduced (all  $p < 0.05$ ). However, there was no significant difference in the hemoglobin level between the two groups one month after surgery ( $p = 0.513$ ).

### **Efficacy comparison**

In terms of curative efficacy (Tab. 3), the total effective rate was 98.6% (283/287) in the observation group, significantly higher than the 95.3% (286/300) in the control group ( $p < 0.05$ ).

### **Comparison of complications**

The main complications in two groups were bleeding, intestinal obstruction, infection, fever, pain, nerve dysfunction, and skin lesions (Tab. 4). The observation group had a significantly lower incidence of bleeding and infection than the control group (both  $p < 0.05$ ). There were no serious complications in both groups, and the complications generally resolved spontaneously within hours without treatment.

### **Fibroid volume of observation group before treatment and after treatment**

Comparison of fibroid volumes (Tab. 5) before treatment and 3, 6 and 12 months after treatment in observation group showed that fibroid volume decreased significantly after treatment, with statistical significances (all  $p < 0.05$ ).

### **PFS comparison**

For all patients in the two groups, the median follow-up time was 30.6 months (range: 1–36). The mean PFS was 29.71 months (95%CI 28.24–29.75) in the observation group and 26.74 months in the control group (95%CI 26.49–28.33) (HR 0.47; 95%CI 0.29–0.76; log-rank  $p = 0.002$ ; Fig. 1).

## **DISCUSSION**

Uterine fibroids are the most seen tumors in the reproductive tract of women. To date, surgical removal remains the gold standard in the treatment of fibroid-related symptoms in women who wish to preserve their fertility [20]. Complications of MY include massive bleeding and intrauterine and intraperitoneal adhesions [21]. For patients receive laparoscopic or open MY, a recovery period of 4–8 weeks is additionally required, and pregnancy is generally not recommended until at least six months after treatment, so as to promote proper healing of uterine wounds [22]. At present, a novel method for treating uterine fibroids is HIFU, which has the characteristics of good efficacy, quick recovery and few adverse reactions and may be the best alternative to surgical treatment. One recent study indicated that HIFU, as a non-invasive procedure, has gradually become an alternative to hysteromyoma surgery [23].

The primary hazards for uterine fibroids involve age and race [24]. We included patients in their 40 s, consistent with current epidemiology. In addition, preoperative administration of GnRH-a is considered to delay the malignant proliferation of uterine fibroids. Evidence has proved that preoperative GnRH-a decreases uterine and fibroid volume and enhances preoperative hemoglobin level, making operation easier [25]. It should be noted that only a few patients had early treatment for uterine fibroids in our study, and we were unable to conduct stratification analysis for this factor.

Most previous studies have focused on pregnancy outcomes in patients with fibroids. For example, study by Jiang et al. [26] showed that HIFU group and LM group have no significant differences in pregnancy rate, abortion rate, natural pregnancy rate, live birth rate, cesarean section rate and perinatal complication rate. Both groups have similar pregnancy outcomes and both methods are safe in treating uterine fibroids patients who want to conceive [26]. Another study found that ultrasound-guided high-intensity focused ultrasound (USgHIFU) significantly reduces the time to conception compared to LM, even though pregnancy rates are similar for both procedures [27]. Compared with secondary MY, for patients with recurrent symptomatic uterine fibroids, HIFU provides similar long-term alleviation of symptoms, longer time intervals to reinterventions and less adverse events [28]. Our study mainly analyzed the intraoperative outcomes, clinical efficacy, complications and PFS of patients with uterine fibroids. It was found that in the HIFU group, the operative time was remarkably shorter, and the amount of intraoperative blood loss and intraoperative fluid replacement was significantly less compared to the control group. However, although patients treated with LM had lower hemoglobin level one month after surgery than those treated with HIFU, there was no significant difference in the hemoglobin level between the two groups. This may be due to the use of GnRH-a drug, which increases hemoglobin content [25, 29]. This is also consistent with a previous report showing a slight decrease in hemoglobin at 12 h after LM [30]. In terms of efficacy, the total effective rate of HIFU group was evidently better than that of LM group, and the incidence of bleeding and infection was lower. In addition,

compared with the control group, the PFS in the observation group was obviously longer. All the results showed that HIFU was superior to surgical treatment.

One of the earliest studies compared the efficacy, ultrasound energy efficiency, operative time and safety of USgHIFU and magnetic resonance guided HIFU (MRgHIFU) ablation. The results showed that both USgHIFU and MRgHIFU were safe and effective, with the same energy efficiency, and could completely ablate myomas, but the operative time of USgHIFU was shorter than that of MRgHIFU [31]. In this study, we adopted USgHIFU. Nevertheless, a relative study showed that operative time does not appear to lead to differences in safety or efficacy between the two HIFU regimens [32]. A network meta-analysis showed that HIFU and UAE treatment for uterine fibroids have advantages over surgery treatment, such as higher quality of life, lower incidence of major complications, shorter hospitalization time, and shorter recovery time, but have higher reintervention rate after operation [33]. A recent meta-analysis also confirmed the effectiveness of HIFU, which may help retain femininity and shorten hospital stays [34]. This is consistent with our results that HIFU has favorable efficacy and safety. Compared with previous studies, our study collected sufficient samples and studied the effect of HIFU on patients' PFS.

In conclusion, our study shows that HIFU is a treatment with great promise for patients with uterine fibroids due to its significant efficacy and good safety. Of course, in future clinical trials, it is still necessary to conduct prospective studies with larger sample size and better design to study the pregnancy outcomes and long-term outcomes, to provide support for clinical decision-making of uterine fibroids.

#### ***Ethics approval and consent to participate***

This study was conducted in accordance with the Helsinki Declaration II and was approved by the Institutional Review Boards of The People's Hospital of Nanchuan, Chongqing. Written informed consent was obtained from individual or guardian participants (QT-2021-008).

### ***Authors' contributions***

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

### ***Consent for publication***

All authors consent to submit the manuscript for publication.

### ***Availability of data and materials***

The data used to support the findings of this study are included within the article. The data and materials in the current study are available from the corresponding author on reasonable request.

### ***Conflict of interest***

The authors declare that they have no potential conflicts of interest.

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**Figure 1.** PFS comparison

