High-intensity focused ultrasound (HIFU) ablation versus surgical interventions for the treatment of symptomatic uterine fibroids: a systematic review and meta-analysis

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HIFU vs surgery for treatment of symptomatic uterine fibroids

ABSTRACT

Background Non-invasive treatments such as high-intensity focused ultrasound (HIFU) have been developed as an effective and safe option in managing uterine fibroids.

Objective The purpose of this meta-analysis was to compare the effectiveness and safety of HIFU with surgical interventions for the treatment of symptomatic uterine fibroids in women according to the studies available in current literature.

Search strategy We conducted a literature search for studies in PubMed, EMBASE, Web of Science, Cochrane Library, Google Scholar and ClinicalTrials.gov from January 2000 to July 2020.

Selection criteria We considered all studies, of any study design, that compared the effectiveness and safety of HIFU with surgical interventions in patients with symptomatic uterine fibroids.

Data collection and analysis We assessed study quality using the Cochrane Handbook for Systematic Reviews of Interventions for evaluating risk of bias. Two independent researchers performed article selection according to the inclusion and exclusion criteria and rated the quality of evidence for each article. We calculated pooled mean difference (MD) with 95% confidence interval (CI) for continuous data and relative risk (RR) with 95% CI for dichotomous data.

Main results A total of 10 studies involving 4450 women were included in our meta-analysis. Compared with surgery group, the reduction of uterine fibroid symptom (UFS) scores at 6- and 12-month follow-up were higher in HIFU group, with the overall MD -4.16 (95% CI, -7.39 to -0.94, P=0.01) and -2.44 (95% CI, -3.67 to -1.20, P=0.0001), respectively. The increase of quality-of-life (QoL) scores at 6- and 12-month follow-up were also higher in HIFU group, with the overall MD 2.13 (95% CI, 0.86 to 3.14, P=0.001) and 2.34 (95% CI, 0.82 to 3.85, P=0.003), respectively. Both of the duration of hospital stay and the time to return to work was significantly shorter in HIFU group, with the overall MD -3.41 (95% CI, -5.11 to -1.70, P<0.0001) and -11.61 (95% CI, -19.73 to -3.50, P=0.005), respectively. The incidence of significant complications was significantly lower in HIFU group, with the overall RR 0.33 (95% CI, 0.13 to 0.81, P=0.02). The difference of incidence of adverse events, effective rate, symptom recurrence rate, re-intervention rate and pregnancy rate between HIFU and surgery were not statistically significant.

Conclusion Compared with surgical interventions, HIFU ablation therapy leads to more significant alleviation of symptoms and improvement of QoL, quicker postoperative recovery and fewer significant complications. However, HIFU showed comparable effects to surgery in terms of the incidence of adverse events, effective rate, symptom recurrence rate, re-intervention rate and pregnancy outcome.

Keywords uterine fibroids, high-intensity focused ultrasound, surgery, hysterectomy, myomectomy, UFS-QOL, complications, re-intervention, meta-analysis

Introduction

Uterine fibroids are the most common benign uterine tumors in women, with a considerable incidence of nearly 70% by the age of 50 years old[1]. Approximately 30-40% of women with uterine fibroids need treatment due to a variety of symptoms, including menorrhagia, abnormal uterine bleeding, pelvic pressure (pelvic masses, pelvic pain, urinary tract, bowel pressure symptoms), infertility and obstetric complications[2]. The management strategies for symptomatic uterine fibroids involve conservative medical treatment, surgical interventions, and non-surgical approaches such as uterine artery embolization (UAE) and ablation therapies performed under radiologic or ultrasound guidance, depending on the patients' age, their wishes to control symptoms or to avoid surgery, desire to preserve fertility, and the location and size of the fibroids[3]. However, there is discussion and uncertainty regarding the optimal management for uterine fibroids, because only a few randomized trials have compared these different therapies and data on their comparative effectiveness and long-term outcomes are lacking[4].

The available surgical interventions include hysterectomy and fertility-sparing myomectomy that can be carried out by laparotomy, laparoscopy, hysteroscopy or robotic-assisted, each of them having their pros and cons[5]. Hysterectomy is the definitive method of relieving symptoms associated with fibroids, but it is considered to be more invasive than other methods and fertility-sparing options are more popular with women seeking to preserve their fertility[6]. At present, myomectomy is the gold-standard fertility-sparing treatment for fibroids. Nevertheless, such surgeries may be costly due to the increased bleeding risk, longer duration of hospital stay, and possible intraoperative or postoperative complications[7]. Therefore, there is currently a trend toward the non-invasive alternatives to surgical interventions.

One of the alternatives is high-intensity focused ultrasound (HIFU) ablation that can cause instant coagulative necrosis of tissue deep under the skin in a well circumscribed area based on the ability to concentrate ultrasound waves to produce heat precisely[8]. Since HIFU was approved by the United States Food and Drug Administration (FDA) as a non-invasive treatment for uterine fibroids in 2004[9], growing studies have been conducted and showed that HIFU is effective and safe, providing obvious decrease of fibroid volume, rapid alleviation of symptoms, shorter hospital stay, quicker recovery and lower risks of complications[10-14]. However, data concerning the symptom recurrence, re-intervention rate and pregnancy outcomes after HIFU treatment are not enough, and the results of some studies were even inconsistent significantly[7, 15-17]. The effects of HIFU in these topics are inconclusive and more long-term randomized comparative researches are needed.

There has been some studies that compared the clinical efficacies of HIFU with surgical interventions in the treatment of uterine fibroids[18-28]. In most of these studies, HIFU presented advantages over surgical interventions in terms of the postoperative recovery and incidence of complications. However, the results of some clinical outcomes were controversial in different studies. For example, the studies of Chen *et al.*[22] and Taran *et al.*[18] reported that the women undergoing HIFU had higher re-intervention rate than that undergoing surgery, whereas Wang *et al.*[27] reported the re-intervention rate in

surgery group was higher than in HIFU group. Therefore, it is necessary to perform a meta-analysis to assess the different results of these studies comprehensively. As far as we know, there was a meta-analysis comparing HIFU with other approaches including medical treatment, traditional surgery, and radiofrequency ablation[29]. However, no meta-analysis that concentrated on comparing HIFU to surgical interventions was performed in women with fibroids. To provide solid evidence for clinical decisions, we conducted a meta-analysis to examine the efficacy and safety of HIFU compared with surgical interventions for symptomatic uterine fibroids.

Objective

The purpose of this meta-analysis was to compare the effectiveness and safety of HIFU with surgical interventions (including hysterectomy and uterus-sparing surgery, such as trans-abdominal myomectomy, laparoscopic myomectomy and hysteroscopic myomectomy) for the treatment of symptomatic uterine fibroids in women, specifically in alleviation of symptoms, improvement of quality of life related to uterine fibroids, recovery time, the incidence of complications and adverse events, symptom recurrence, re-intervention rate and pregnancy outcome.

Methods

This systematic review and meta-analysis was reported according to the reporting guidelines outlined in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) statement. The protocol for this systematic review and meta-analysis was registered on INPLASY (202080012) and was available on inplasy.com (https://doi.org/10.37766/inplasy2020.8.0012).

Information sources

We performed a comprehensive search of PubMed, EMBASE, Web of Science, Cochrane Library, Google Scholar and ClinicalTrials.gov from January 2000 to July 2020 to retrieve studies comparing HIFU with surgical interventions in patients with symptomatic uterine fibroids. Reference lists of identified studies were also searched.

Search strategy

We adjusted the search strategy according to each database. For example, we searched using combination of MeSH terms and single-search strategies on PubMed (Figure 1): ((Leiomyoma[Mesh]) OR (*myomas [Title/Abstract]) OR (fibroid*[Title/Abstract])) AND ((High-Intensity Focused Ultrasound Ablation [Mesh]) OR (focused ultrasound[Title/Abstract]) OR (HIFU[Title/Abstract])) OR (MRgFUS [Title/Abstract])) AND ((Hysterectomy[Title/Abstract]) OR (uterectomy [Title/Abstract]) OR

(metrectomy [Title/Abstract]) OR (hysteromyomectomy [Title/Abstract]) OR (myomectomy [Title/Abstract])). We also hand-searched relevant articles and reviews for additional references. Articles were restricted to English only.

Study selection

The overview of study selection process was presented in Figure 2. Two independent researchers (L. L. and T. W.) performed article selection according to the inclusion and exclusion criteria. If they had different opinions, a third researcher (B. L.) resolved any discordance. First, the titles and abstracts of studies identified from database were screened, and then we collected all potentially relevant studies for full-text evaluation. We also scrutinized the references from the included studies and excluded reviews to search for studies that were not found during the primary literature search. When we found that the reporting data of multiple studies came from the same clinical trial, we selected the most relevant study.

Studies were included if they: (1) included patients with symptomatic uterine fibroids; (2) compared HIFU with surgical interventions such as hysterectomy and uterus-sparing surgery (open myomectomy, laparoscopic myomectomy, or hysteroscopic myomectomy); (3) included at least one of the outcome measures that we specified as follows; (4) were published in a peer-reviewed journal; and (5) were published in English.

Studies were excluded if they: (1) included only one treatment group without a comparison group; (2) were repeated or overlapped data; (3) were reviews, commentaries, case reports, abstracts, letters, secondary analyses, or summaries of meetings; (4) were non-English studies.

Outcome measures

The primary outcome measures of interest were:

(1) Alleviation of clinical symptoms and improvement of quality of life: the uterine fibroid symptom quality-of-life (UFS-QoL) questionnaire was used to evaluate the changes in the severity of fibroid-related symptoms and health-related quality of life before and after HIFU or surgery. The UFS-QoL questionnaire consists of 8 symptom severity scale items and 29 health-related QoL items comprising 6 domains: Concern, Activities, Control, Energy/Mood, Self-consciousness, and Sexual Function[30]. Both questionnaires provide a measure between 0 and 100 point scale, and higher scores indicate more serious symptoms on the UFS scale but better quality of life on the QoL questionnaire[31].

(2) Recovery post-treatment: duration of hospital stay and time to return to work after treatment;

(3) Significant complications: significant clinical complications were defined as fever >38°Con any 2 post-treatment days, blood transfusion, skin burn during treatment, unintended major surgical procedure, discharge to a rehabilitation facility, anesthesia-related complications, outpatient interventional treatment, re-hospitalization, life-threatening event or death within 42 days of treatment[32];

(4) Adverse events: adverse events were defined as major or minor adverse events according to the Society of Interventional Radiology (SIR) grading system[33]. The events that were self-limited, might require no therapy or only symptomatic treatment, did not have long-term implications, and did not lead to hospitalization were classified as minor adverse events. The events that were serious or life-threatening, resulted in a great amount of morbidity which increased the level of care, had long-term implications, led to re-admission or substantially lengthened hospital stay were classified as major

adverse events[34];

(5) Effectiveness of the treatment: effectiveness was marked by shrinkage of fibroids or relief of clinical symptoms, while ineffectiveness was manifested by enlargement of fibroids or no significant relief of clinical symptoms;

(6) Symptom recurrence: the patients were asked to report whether they had recurrence of fibroid-associated symptoms, and whether they had undergone any additional intervention to alleviate the recurrent symptoms;

(7) Re-intervention rate: the performance of a new procedure in addition to the initial one owing to symptomatic recurrence of fibroids was considered to be a re-intervention;

(8) Pregnancy outcome: time of pregnancy, number and outcomes of pregnancy, pregnancy process, and delivery information after treatment was recorded.

Data extraction

Two investigators (L. L. and T. W.) independently extracted data by using a standardized data extraction sheets. We recorded study characteristics such as author, year of publication, country, study design, therapeutic methods, participant population, patient characteristics, location, duration of follow-up, and outcomes. We extracted the mean±standard deviation (SD) or median scores of UFS-QoL questionnaire before and after treatment, mean±SD or median days of duration of hospital stay and time to return to work, number of outcome events of significant complications, adverse events, effectiveness of the treatment, symptom recurrence, re-intervention and pregnancy. Discrepancies were resolved through consensus.

Assessment of study and evidence quality

Risk of bias of included randomized controlled trial (RCT), non-randomized studies and case series was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions for assessing risk of bias. The following characteristics will be evaluated: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias). (7) other bias. Studies were classified as “low risk of bias” “high risk of bias” or “unclear risk of bias” based on the assessment.

Statistical analysis

RevMan 5.4 provided by Cochrane collaboration was used for data analysis. The studies were aggregated according to the types of treatment being compared (HIFU vs surgery). We calculated mean difference (MD) with 95% confidence interval (CI) for continuous data (UFS-QoL questionnaire scores, days of duration of hospital stay and time to return to work) and relative risk (RR) with 95% CI for dichotomous data (number of outcome events of interest). If the means were not reported in studies, we estimated them using the sample size, median, and interquartile ranges[35].

Heterogeneity between studies reflects variance from individual studies and may be attributable to differences in study population, location, study design, analysis methods or other characteristics. We

tested the heterogeneity of intervention effects among studies using the I^2 statistic and its 95% CI (I^2 values >50% were indicative of significant heterogeneity). We used a fixed-effect model if there was no substantial or considerable heterogeneity, and used a random-effect model if there was a significant heterogeneity. If I^2 values demonstrated significant heterogeneity, the sensitivity analysis was considered to be performed, and subgroup analyses were performed according to the types of surgery (hysterectomy or uterus-sparing surgery).

Results

Study selection

Our database search resulted in 692 unique articles after removing duplicates, of which 314 met initial screening criteria and were further assessed for eligibility. Following title and abstract review, we assessed 17 full-text articles for eligibility according to inclusion criteria and exclusion criteria. Finally, 11 articles met all criteria for inclusion, among which we included 10 articles in our meta-analysis. We excluded 6 articles that did not include any outcome measure of interest and excluded 1 article[36] that was repeated data with an included article[20].

Demographic characteristics

A total of 10 clinical studies included in the meta-analysis represented 4450 women with symptomatic uterine fibroids, 2483 (56%) of whom underwent HIFU and 1967 (44%) of whom underwent surgery (555 hysterectomy and 1412 myomectomy). We included 1 randomized comparative trial (RCT) [19] and 9 nonrandomized studies[18, 21-28]. Details on the author, year of publication, study design, follow-up time, treatment methods, and outcome measures of included studies were summarized in Table 1. Characteristics of the patients before treatment were summarized in Table 2.

Among these articles, 8 studies[19, 21-23, 25-28] were conducted in China, and 2 studies[18, 24] were conducted in Israel, the United States and European countries. Three studies[18, 22, 28] were performed in multicenter and 7 studies[19, 21, 23-27] were performed in single center. One study[21] included women with intermural or subserosal fibroids, 2 studies[19, 23] included women with intermural fibroids only, 2 studies[26, 27] included women with submucosal fibroids only, and the rest studies[18, 22, 24, 25, 28] did not limit the types of fibroids. The HIFU ablation was performed under real-time ultrasound-guided (US-guided) monitoring of targeted lesions in 7 studies[21-23, 25-28] while under magnetic resonance-guided (MR-guided) monitoring in 3 studies[18, 19, 24]. Four studies[22, 25, 26, 28] reported UFS scores, and 2 studies[22, 26] reported QoL scores at baseline and after treatment. Five studies[19, 21-23, 26] calculated the duration of hospital stay and 4 studies[18, 21, 22, 26] calculated the time to return to work. Significant complications were recorded in 4 studies[18, 19, 21, 27] and adverse events were recorded in 5 studies[18, 19, 22, 23, 25]. The effective rate, symptom recurrence rate, re-intervention rate and pregnancy rate were reported in 3 studies[23, 25, 27], 2 studies[25, 27], 5 studies[18, 22, 24, 25, 27] and 2 studies[22, 28], respectively.

Risk of bias of included studies

All studies had a high risk of bias in at least 2 domains, indicating a high risk of bias within the studies. Only 1 of the 10 studies was RCT while the rest studies were non-RCT, so a high risk in selection bias was observed in most of studies. None of the trials blinded the participants and personnel because all the participants were fully informed about the treatment methods they received. For ‘‘incomplete outcome data’’, loss to follow-up of <10% participants was considered to indicate low risk of bias and loss to follow-up of >10% participants was high risk of bias. The complete results of the risk of bias for the individual studies were shown in Figure 3 and 4.

Synthesis of results

Table 3 and 4 presented details of the results to compare the effectiveness and safety of HIFU with surgery for the treatment of symptomatic uterine fibroids. Figures 5 to 14 were the forest plots of each outcome.

Improvement of clinical symptoms and quality of life

Among all of the articles that reported the UFS-QoL questionnaire scores, the mean UFS scores reduced and the mean QoL scores increased significantly at the 6- and 12-month follow-up compared with baseline in both groups. The reduction (absolute value) of UFS scores at 6- and 12-month follow-up were higher in HIFU group compared with surgery group, with the overall MD -4.16 (95% CI, -7.39 to -0.94, P=0.01, I^2=80%; 4 studies, 2779 women) and -2.44 (95% CI, -3.67 to -1.20, P=0.0001, I^2=0%; 2 studies, 1852 women), respectively. The increase of QoL scores at 6- and 12-month follow-up were also higher in HIFU group than in surgery group, with the overall MD 2.13 (95% CI, 0.86 to 3.14, P=0.001, I^2=0%; 2 studies, 1935 women) and 2.34 (95% CI, 0.82 to 3.85, P=0.003, I^2=0%; 2 studies, 1852 women), respectively. (Figure 5-6)

Recovery after treatment

Compared with surgery group, both of the duration of hospital stay and time to return to work was significantly shorter in HIFU group, with the overall MD -3.41 (95% CI, -5.11 to -1.70, P<0.0001, I^2=99%; 5 studies, 2908 women) and -11.61 (95% CI, -19.73 to -3.50, P=0.005, I^2=100%; 4 studies, 2814 women), respectively. The mean duration of hospital stay and mean time to return to work was from 1.25 days to 3.86 days and from 2.7 days to 4.5 days respectively in HIFU group, while from 3.3 days to 9.7 days and from 6.09 days to 26.5 days respectively in surgery group. (Figure 7-8)

Significant complications

The incidence of significant complications in HIFU group was significantly lower than that in surgery group, with the overall RR 0.33 (95% CI, 0.13 to 0.81, P=0.02, I^2=63%; 4 studies, 816 women). Among included studies, the incidence of significant complications was from 0% to 19.10% in HIFU group, while from 3.10% to 39.76% in surgery group. (Figure 9)

Adverse events

The incidence of adverse events and major adverse events was lower in HIFU group than in surgery group, with the overall RR 0.59 (95% CI, 0.34 to 1.04, P=0.07, I^2=99%; 5 studies, 3077 women) and 0.14 (95% CI, 0.01 to 1.35, P=0.09, I^2=95%; 4 studies, 2911 women), respectively, but the difference was not statistically significant. The incidence of adverse events and major adverse events was from 2.02% to 81.67% and from 0% to 21.67% respectively in HIFU group, while from 11.94% to 98.80% and from 9.64% to 38.33% respectively in surgery group. (Figure 10)

Effectiveness of the treatment

The HIFU treatment had slightly higher effective rate than surgery, but no statistical difference was observed between the two therapies, with the overall RR 1.02 (95% CI, 0.97 to1.08, P=0.43, I^2=61%; 3 studies, 728 women). The effective rate was from 11.43% to 21.05% in HIFU group, while from 24.81% to 26.19% in surgery group.

Symptom recurrence rate and re-intervention rate

Compared with surgery group, the women in HIFU group had lower symptom recurrence rate but higher re-intervention rate, however, the results did not reach statistical significance, with the overall RR 0.60 (95% CI, 0.35 to 1.03, P=0.06, I^2=59%; 2 studies, 553 women) and 1.15 (95% CI, 0.54 to 2.46, P=0.72, I^2=59%; 5 studies, 2651women), respectively. The symptom recurrence rate and re-intervention rate was from 11.43% to 21.05% and from 1.14% to 13.68% respectively in HIFU group, while from 24.81% to 26.19% and from 0% to 17.86% respectively in surgery group. (Figure 11)

Pregnancy rate

The women undergoing HIFU had higher pregnancy rate than surgery, but the result was not statistically significant, with the overall RR 1.54 (95% CI, 0.51 to 4.59, P=0.44, I^2=72%; 2 studies, 2430 women). The pregnancy rate was from 1.71% to 68.44% in HIFU group, while from 0.55% to 66.67% in surgery group.

Subgroup analysis

Subgroup analyses of the incidence of significant complications, adverse events and major adverse events were performed according to the different types of surgery (hysterectomy or uterus-sparing surgery), due to the I^2 values >50% that demonstrated significant heterogeneity. All of the subgroup analyses showed that the I^2 values were still >50%. The results were: (1) incidence of significant complications of HIFU vs hysterectomy with the RR 0.32 (95% CI, 0.19 to 0.56, P<0.001; 1 studies, 624 women),HIFU vs uterus-sparing surgery with the RR 0.17 (95% CI, 0.02 to 1.78, P=0.14, I^2=73%; 3 studies, 624 women); (2) incidence of adverse events of HIFU vs hysterectomy with the RR 0.54 (95% CI, 0.21 to 1.45, P=0.22, I^2=99%; 2 studies, 2017 women), HIFU vs uterus-sparing surgery with the RR 0.54 (95% CI, 0.29 to 1.02, P=0.06, I^2=98%; 4 studies, 2413 women), the overall RR 0.55 (95% CI, 0.34 to 0.87, P=0.01, I^2=98%; 5 studies, 3077 women); (3) incidence of major adverse events of HIFU vs hysterectomy with the RR 0.11 (95% CI, 0.00 to 8.48, P=0.32, I^2=97%; 2 studies, 2017 women), HIFU vs uterus-sparing surgery with the RR 0.07 (95% CI, 0.00 to 1.53, P=0.09, I^2=95%; 3 studies, 2247 women), the overall RR 0.09 (95% CI, 0.01 to 0.67, P=0.02, I^2=95%; 4 studies, 2911 women). (Table 3 and Figure 12-14)

Discussion

Main findings

There are several questionnaires developed to evaluate the fibroid-associated symptoms and QoL before and after treatment, one of which is UFS-QOL questionnaire. The UFS-QOL has been used in a number of studies regarding uterine fibroids treatment, and demonstrated to be reliable and valid to assess the effectiveness of various therapies[31]. Most of studies included in our meta-analysis were non-RCT and the patients' UFS-QOL scores at baseline were different. Therefore, we compared the change of UFS-QOL scores from baseline to follow-up time between HIFU and surgery group. The results showed that both the reduction of UFS scores and the increase of QoL scores at 6- and 12-month follow-up were significantly higher in HIFU group than that in surgery group, indicating the effect of HIFU was superior to surgical interventions in alleviation of symptom and improvement of QoL for treatment of uterine fibroids. This result was consistent with the study of Chen *et al.*[22], however, several studies reported that the UFS-QOL questionnaire revealed comparable results and no statistical difference between HIFU and surgery was observed[18, 21, 24-26]. The possible reasons for the inconsistent results were: (1) there were differences in demographic characteristics and UFS-QOL scores at baseline between two groups, as these studies were non-RCT; (2) studies of Sasson *et al.*[24] and Hu *et al.*[26] only compared the UFS-QOL scores at follow-up time rather than the change of scores from baseline to follow-up time; (3) some studies used other questionnaires such as Study 36-Item Short-Form General Health Survey (SF-36)[18, 21] or transformed symptom severity scale (tSSS)[25, 27]; (4) the types of surgical approaches were different.

In this meta-analysis, all the included studies reporting the recovery time showed that HIFU provided significantly shorter duration of hospital stay and faster recovery to return to work than surgery. The mean duration of hospital stay was from 1.25 days to 3.86 days and the mean time to return to work was from 2.7 days to 4.5 days in HIFU group, which was similar with previous studies. For example, Verpalen *et al.*[37] reported the median recovery time before patients returned to work was 2.0 (1.0–7.0) days. The reason why women undergoing HIFU had faster recovery may be that, as a non-invasive treatment, HIFU can exempt the patient from surgery, avoid surgical complications, significantly reduce the volume of fibroids without incision and lead to a better prognosis and quicker recovery to usual activities.

Our meta-analysis revealed that the incidence of significant complications in HIFU group (0% - 19.10%) was significantly lower than that in surgery group (3.10% - 39.76%). Skin burn and pain were the primary HIFU-related complications because HIFU is thermal ablation, whereas fever and anesthesia-related complications were the main complications associated with surgery. Wang *et al.*[19] reported 13.46% patients suffered from postoperative complications (fever) and 11.54% patients experienced anesthesia-related complications (slow heart rate and irregular spontaneous breathing) in myomectomy group, whereas no significant complications occured in HIFU group. Wang *et al.*[21] reported skin burn and pain occurred in 13.4% of patients undergoing HIFU, while fever and anesthesia-related complications occurred in 9.8% and 7.3% of patients undergoing surgery respectively. However, all skin burns were well tolerated and it can be prevented using measures such as temperature monitoring during treatment

and careful skin preparation[38]. This result was similar with many previous researches, such as the studies of Cheung *et al.*[39] and Lee *et al.*[40] which showed no significant symptoms or complications occurred after HIFU treatment, and Pron *et al.*[41] reported the incidence of significant complications after HIFU was only 1.6%. Overall, HIFU is a safer non-invasive treatment with fewer significant complications compared with surgery.

We found that the difference of the incidence of adverse events and major adverse events between HIFU and surgery group was not statistically significant. Most of adverse events were minor and self-limiting during follow-up. The categories where HIFU treatment had a higher percentage of adverse events were sacrum pain, pain and distension of anus, blurred vision and transient pain, neurological symptoms, and weakness or numbness in the back, shoulder, or lower limb. Adverse events which were reported more frequently in women undergoing surgery included haemorrhage, infection, thromboembolic events, vaginal bleeding/abnormal vaginal discharge, irritation sign of bladder or injury to the bladder, urinary retention, and vomiting/abdominal distension[18, 19, 22, 23, 25]. Different treatments lead to different types of adverse events due to their various therapeutic principle and process. A previous meta-analysis of Verpalen *et al.*[42] showed that 112 of 1330 (8.7%) patients with fibroids after HIFU treatment experienced an adverse event, and only 2 patients experienced a serious adverse event (1 deep venous thrombosis and 1 third degree skin burn). The incidence of adverse events in different studies varied, and one of the reasons may be there is no consensus on the definition of adverse events related to HIFU. For example, whether abnormal vaginal discharge was defined as an adverse event was still controversial[43].

There was no significant difference in both the recurrence rate and re-intervention rate between HIFU and surgery groups according to our meta-analysis. The re-intervention rate was from 3.67% to 13.68% in HIFU group, and from 0% to 17.86% in surgery group (mean follow-up time, 41.2 months; range, 6–96 months). Some previous studies showed similar results, one of which reported the re-intervention rate was 12.7 % (mean follow-up time, 19.4 ± 8 months; range, 3–38 months) [44]. Another one was a meta-analysis from Verpalen *et al.*[42] that reported the range of re-intervention rate was from 0 to 21% at 3–33.6 months follow-up from 16 different trials. However, a meta-analysis from Sandberg *et al.*[45] showed completely conflicting results. They demonstrated that from 85 articles, re-intervention risk after 60 months was 12.2% for myomectomy, 7% for hysteroscopy, 53.9% for HIFU, and 14.4% for UAE. The re-intervention risk of HIFU procedure was the highest compared with other interventions and was also much higher than our result. The possible factors contributing to the discrepancy were: (1) the main reason was the different length of follow-up time. The follow-up time in our meta-analysis[18, 22, 24, 25] was shorter than that in meta-analysis of Sandberg *et al.*, except one study[27] which was followed for 8 years. However, it reported the re-intervention rate was 9.80% at the 8 years follow-up, which was also lower than the result of Sandberg *et al.* (2) only a few studies were available on the long term, and the authors of these studies[46-48] suggested that the high re-intervention risk after HIFU might be the result of inadequate patient selection. (3) all studies in our meta-analysis were comparative studies between HIFU and surgery, whereas most of the studies in meta-analysis of Sandberg *et al.* were single-arm trials. (4) types of fibroids in these studies were different, which might also affect the re-intervention rate. In conclusion, long-term outcomes on re-intervention risk is an important aspect to consider when choosing the best option for a patient with fibroids. Due to the limited evidence, long-term re-intervention risk of HIFU is inconclusive, and more long-term comparative studies are needed in future.

The difference of pregnancy rate between women undergoing HIFU and surgery was not statistically significant, but only two studies were available in our meta-analysis. According to the study

of Wu *et al.*[28] which focused on the pregnancy outcomes between HIFU and laparoscopic myomectomy (LM) for uterine fibroids with median follow-up duration 5 (1–8) years, HIFU ablation significantly shortened the time to pregnancy, although pregnancy rates of the two procedures were similar (68.4% after HIFU and 66.7% after LM). Incidences of placenta previa, placenta increta, and postpartum hemorrhage were lower in HIFU group, while incidences of preterm birth, fetal growth restriction, fetal distress, and puerperal infection were higher after HIFU than after LM. There was a risk of uterine rupture (0.6%) after both procedures. The studies of Łoziński *et al.*[49], Verpalen *et al.*[37], Mindjuk *et al.*[43] and Li *et al.*[50] reported the pregnancy rate after HIFU treatment was 7.25%, 36.4％, 15.0％and 69.3% respectively. A systematic review[51] showed a total of 420 pregnancies after fibroid ablation resulted in 70.5% live births, 11.9% miscarriages, 9.3% terminations and 8.3% ongoing pregnancies. A total of 1575 pregnancies after myomectomy resulted in 75.6% live births, 19.0% miscarriages, 2.7% ongoing pregnancies, 1.5% ectopic pregnancies and 2 stillbirths. So far, it is still unclear whether the pregnancy rate and adverse pregnancy outcomes after HIFU treatment differ from myomectomy due to lack of randomized comparative studies. Keserci and Duc[52] reported that the level of anti-Mullerian hormone after HIFU did not reduce and was not different from the level in control group, which indicated that ovarian vessels had not been destroyed during the ablation. Unlike with surgery that can change the physiological environment and induce pelvic adhesion to reduce the pregnancy rate, HIFU is non-invasive, so there is lower risk of uterine wall rupture and pelvic or intrauterine adhesion during gestation and delivery[53].

Substantial heterogeneity was observed in the analysis of recovery time, incidence of significant complications and adverse events, effective rate, symptom recurrence rate, re-intervention rate and pregnancy rate in our meta-analysis. Therefore, we performed subgroup analyses in the incidence of significant complications, adverse events and major adverse events according to the types of surgery (hysterectomy or uterus-sparing surgery). Subgroup analyses were not performed in the rest of outcome measures because of the small number of studies. All of the subgroup analyses showed that the I^2 values were still >50%, indicating that the difference of surgical types was not the resource of heterogeneity. Heterogeneity might derive from different types of study design, patients' characteristics at baseline (including age, menopause status, the size, number and location of fibroids) or the length of follow-up time. Sensitivity analysis did not reduce heterogeneity either.

Strengths and limitations

To the best of our knowledge, this was the first meta-analysis that focused on comparing the clinical outcome after HIFU and surgical interventions in women with symptomatic uterine fibroid. The findings can be directly applicable in daily practice for providing suitable treatment option to patients. However, there were several limitations in our study: (1) the main limitation was the small number of included studies, most of which were non-RCT due to lack of randomized comparative data. This limitation might affect the accuracy of the results and we cannot provide conclusive evidence on this topic. (2) all studies had a high risk of bias in at least 2 domains, indicating a high risk of bias within the studies. (3) substantial heterogeneity was observed in several outcome measures and we did not find out the source of heterogeneity. (4) owing to the limited evidence, we did not compare the mean non-perfused volume ratio of treated fibroids and the costs between HIFU and surgery. These findings would have also

been useful to determine relative effectiveness of the treatment and should be considered in future research. (5) we only included articles written in English.

Conclusion

This meta-analysis showed that HIFU treatment provided more significant alleviation of symptoms and improvement of quality of life, quicker recovery, and fewer significant complications than surgical interventions for the treatment of symptomatic uterine fibroids. Moreover, HIFU has shown comparable effects to surgery in terms of effective rate, symptom recurrence rate, re-intervention rate and pregnancy outcome in which HIFU was previously considered inferior to surgery in some studies. This result indicated that HIFU is a promising non-invasive method which seems not to raise the risk of recurrence and re-intervention or deteriorate fertility compared to surgical approaches in women with fibroids. However, there is still a lack of good-quality comparative data and further randomized studies are necessary to confirm the above results and get a more accurate conclusion, especially on re-intervention rate and pregnancy outcome.

Despite the limitations, this meta-analysis revealed valuable information on the relative clinical efficacy between HIFU and surgery for uterine fibroids. In our viewpoint, as one of the newest non-invasive alternatives to surgical interventions, HIFU may provide safe and effective treatment for patients with fibroids, especially for women who want to avoid surgery and preserve fertility.

Disclosure of interests:

The authors declare no competing interests.

Contribution to authorship:

Responsible for the initial concept, data acquisition and final review of the manuscript (Lu Liu). Data acquisition, analysis and interpretation, drafting the article (Lu Liu, Tianfu Wang). Final approval of the version to be published (Baiying Lei).

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Table 1. Characteristics of the studies included in this meta-analysis (N=10)

First author, year	Study design	Follow-up time	Interventions (No.)	Surgical procedures	Outcome measures	Center	Monitor
Taran, 2009[18]	Non-RCT	6 months	HIFU (109) Hysterectomy (83)	Laparotomy	④⑤⑥⑦⑩	Multi-center	MR-guided
Wang, 2013[19]	RCT	6 months	HIFU (60) Myomectomy (60)	Laparotomy	③⑤⑥⑦	Single center	MR-guided
Wang, 2014[21]	Non-RCT	12 months	HIFU (89) Myomectomy (41)	Laparoscopy	③④⑤	Single center	US-guided

Liu, 2017[23]	Non-RCT	12 months	HIFU (99) Myomectomy (67)	Laparoscopy	③⑥⑧	Single center	US-guided
Chen, 2017[22]	Non-RCT	12 months	HIFU (1353) Hysterectomy (472) Myomectomy (586)	Laparotomy Laparoscopy Hysteroscopy	①②③④⑥⑦⑩⑪	Multi-center	US-guided
Sasson, 2018[24]	Non-RCT	36 months	HIFU (68) Myomectomy (64)	Laparoscopy	⑩	Single center	MR-guided
Hu, 2020[26]	Non-RCT	12 months	HIFU (39) Myomectomy (42)	Hysteroscopy	①②③④	Single center	US-guided
Liu, 2020[25]	Non-RCT	60 months	HIFU (101) Myomectomy (87)	Laparotomy Laparoscopy Hysteroscopy	①⑥⑦⑧⑨⑩	Single center	US-guided
Wu, 2020[28]	Non-RCT	96 months	HIFU (320) Myomectomy (336)	Laparoscopy	①⑪	Multi-center	US-guided
Wang, 2020[27]	Non-RCT	140 months	HIFU (245) Myomectomy (129)	laparotomy Laparoscopy Hysteroscopy	⑤⑧⑨⑩	Single center	US-guided

RCT: randomized controlled trial; MR-guided: magnetic resonance-guided; US-guided: ultrasound-guided; Outcome measures: ①UFS scores ②QoL scores ③duration of hospital stay ④time to return to work after treatment ⑤significant complications ⑥adverse events ⑦major adverse events ⑧effectiveness of the treatment ⑨symptom recurrence rate ⑩re-intervention rate ⑪pregnancy rate.

Table 2. Characteristics of the patients before treatment included in this meta-analysis (N=10)

First author, year	Age (y)		Body mass index (kg/m^2)		Types of uterine fibroids	Max diameter of fibroid (cm)		Average numbers of fibroids	
	HIFU	Surgery	HIFU	Surgery		HIFU	Surgery	HIFU	Surgery
Taran, 2009[18]	44.8±4.9	44.4±5.6	25.8±5.2	29.9±6.0	All types	/	/	/	/
Wang, 2013[19]	39.92±5.07	38.60±4.36	22.07±2.86	22.07±2.82	Intermural fibroids	5.50 (3.90,11.00)	6.00 (2.70, 13.50)	1 (1, 4)	1 (1, 8)
Wang, 2014[21]	37.9±5.5	38.4±5.0	22.1±2.3	22.4±2.9	Intramural and subserosal fibroids	6.0±1.9	6.9±2.0	1.4±0.8	1.6±0.7
Liu, 2017[23]	/	/	/	/	Intermural fibroids	/	/	/	/
Chen, 2017[22]	41.31±5.08	43.43±5.21	22.68±2.99	23.41±3.02	All types	(Volume/ cm^3)104.84±81.73	(Volume/ cm^3)115.23±96.35	/	/
Sasson, 2018[24]	38 (34-43)	44 (38-47)	/	/	All types	7.0 (5.7-8.3)	7.0 (5.5-8.0)	/	/
Hu, 2020[26]	43.0±5.6	41.3±4.4	23.0±3.1	22.5±2.7	Type II Submucosal fibroid	22.5±2.7	3.6±0.8	Total 57	Total 42

Liu, 2020[25]	39.3±5.9	37.4±6.9	23.0±2.6	24.2±3.2	All types	6.1±2.0	6.5±2.3	/	/
Wu, 2020[28]	31.6 (22–42)	32.4 (25–41)	23.75 (18.1–27.8)	22.63 (18.0–27.3)	All types	5.6 (3–10)	5.8 (3–10)	4.3 (2–15)	3.9 (2–8)
Wang, 2020[27]	38.9±6.2	38.8±6.3	/	/	Type I or type II submucosal fibroids	6.0±2.1	6.0±1.9	/	/

609

610 **Table 3.** Meta-analysis results of the effectiveness and safety of HIFU vs surgery for symptomatic uterine
611 fibroids

Outcome measures	No. of studies	MD or RR (95% CI) HIFU vs surgery	*P* value	I^2,%	No. of patients
UFS scores at 6-month	4[22, 25, 26, 28]	-4.16 (-7.39, -0.94)	0.01	80	2779
UFS scores at 12-month	2[22, 26]	-2.44 (-3.67, -1.20)	0.0001	0	1852
QoL scores at 6-month	2[22, 26]	2.13 (0.86, 3.41)	0.001	0	1935
QoL scores at 12-month	2[22, 26]	2.34 (0.82, 3.85)	0.003	0	1852
Duration of hospital stay	5[19, 21-23, 26]	-3.41 (-5.11, -1.70)	<0.0001	99	2908
Time to return to work	4[18, 21, 22, 26]	-11.61 (-19.73, -3.50)	0.005	100	2814
Incidence of significant complications	4[18, 19, 21, 27]	0.33 (0.13, 0.81)	0.02	63	816
Incidence of adverse events	5[18, 19, 22, 23, 25]	0.59 (0.34, 1.04)	0.07	99	3077
Incidence of major adverse events	4[18, 19, 22, 25]	0.14 (0.01, 1.35)	0.09	95	2911
Effective rate	3[23, 25, 27]	1.02 (0.97, 1.08)	0.43	61	728
Symptom recurrence rate	2[25, 27]	0.60 (0.35, 1.03)	0.06	59	553
Re-intervention rate	5[18, 22, 24, 25, 27]	1.15 (0.54, 2.46)	0.72	59	2651
Pregnancy rate	2[22, 28]	1.54 (0.51, 4.59)	0.44	72	2430

612

613 **Table 4.** Subgroup analyses of the incidence of significant complications, adverse events and major
614 adverse events

Outcome measures	HIFU vs Hysterectomy			HIFU vs Uterus-sparing surgery			Overall		
	RR (95% CI)	*P*	I^2,%	RR (95% CI)	*P*	I^2,%	RR (95% CI)	*P*	I^2,%
significant complications	0.32(0.19,0.56)	<0.001	—	0.17(0.02,1.78)	0.14	73	0.33(0.13,0.81)	0.02	63
adverse events	0.54(0.21,1.45)	0.22	99	0.54(0.29,1.02)	0.06	98	0.55(0.34,0.87)	0.01	98
major adverse events	0.11(0.00,8.48)	0.32	97	0.07(0.00,1.53)	0.09	95	0.09(0.01,0.67)	0.02	95

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