

Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) in uterine fibroids management: An updated meta-analysis.

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Abstract

Purpose: Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) has revolutionized the treatment of Uterine fibroids. Usually, they are associated with prolonged heavy bleeding during the menstrual period, sacral pain, and increased frequency of UTIs, secondary dysmenorrhea, constipation, and pregnancy-associated problems. It also impacts usual activities, which lead to diminished quality of life and rising healthcare costs. Generally, surgery is the only choice for uterine fibroids; however, MR-HIFU is an entirely non-invasive novel therapy, preferred in pregnancy desiring females. Excluding trials with stringent treatment protocols that are no longer used, the efficacy of Magnetic Resonance-High Intensity Focused Ultrasound (MRHIFU) therapy for uterine fibroids is being re-evaluated. **Methods:** RCTs, Prospective or Retrospective non-randomized, and cross-over studies that considered clinically symptomatic uterine fibroid treatment were included. The author has searched the data in Cochrane Library, PubMed/MEDLINE, SCOPUS, EMBASE databases. Meta-Analysis was performed using NCSS software, and data were analyzed at a 95% confidence level with a level of precision at 0.05. The NPV%, tSSS change%, and QoL were computed. Meta-Regression was done to evaluate the association between the different parameters. **Results:** The overall effect of NPV% was 70.24, where the 95% confidence interval ranged from 61.9% to 78.16%. The overall impact of tSSS% change is near 50% after the follow-up of 3 months, 6 months, and 12 months in the included studies. There was a significant improvement in the health-related quality of life (Hr-QoL). **Conclusion:** The efficacy of MR-HIFU therapy was improved as treatment protocols aimed for total ablation. On the other hand, regulated studies are required to determine the function of MR-HIFU in the treatment of uterine fibroids.

Introduction

Women, mostly in their reproductive age, suffer from uterine leiomyomas, also called uterine fibroids or uterine myomas. These are benign tumors of uterine muscle and are clinically detectable with prolonged heavy bleeding during the menstrual period, sacral pain, secondary dysmenorrhea, constipation, increased frequency of UTIs, and pregnancy-associated problems¹. About 25% of women are clinically symptomatic². Fibroids may affect fertility, thereby negatively influencing a woman who desires pregnancy. These uterine fibroids also impact the usual activities, leads to diminished quality of life and increasing healthcare costs³. Although surgeries like hysterectomy are the gold standard for most women⁴, this approach is not the prime choice for women who want to conceive. Enucleation via laparoscopy is a uterine-conserving treatment. Medical treatment options are also available and applied, but their aftermath is sizeable as it results in

the recurrence of leiomyomas. Non-invasive procedures are making ground in recent years because of fewer complications, patient compliance, short hospital stay, and cost-effectiveness. They include uterine artery embolization (UAE) and Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU)⁵⁻⁶.

In place of uterine conserving treatment and fertility, however, UAE leads to a potential reduction of the ovarian reserve. Even though it is an attractive efficacious treatment choice, its implication is confined only to pre-or post-menopausal women.

MR-HIFU is a non-invasive ablative novel therapy. The process of MR-HIFU involves coagulative necrosis of the fibroid by thermal effect and no disruption to the adjacent structures. There are no bleeding or drug side effects after this treatment modality⁷. Usually, tissue necrosis occurs when subjected to 43°C or more for at least an hour; however, the necrosis can occur within a second if subjected to 56°C or more^{8,9}. Two real times guided HIFU treatments are available; ultrasound-guided and MRI-guided. The ultrasonography-guided HIFU has a low resolution and limited precision for targeting and visualizing the adjacent structure's details. Simultaneously, MRI-guided HIFU has a high resolution allowing detection of even a tiny thermal increase outside the target points before any tissue damage¹⁰⁻¹¹. Various studies have also shown that MR-HIFU effectively eradicates multiple uterine fibroids and leads to a reduction in the non-perfused volume (NPV) of fibroids with no side effects¹².

Even after the effective therapy of MRI guided HIFU, all patients are not eligible for this treatment modality. Funaki type 3 fibroids are challenging to treat because of high T2 signal intensity and high BMI of women are the significant reasons for excluding this treatment option for uterine fibroid¹³.

Rationale: Several studies on the efficacy of MRHIFU therapy for uterine fibroids have been released to date. Overall, they found that MRHIFU successfully reduces symptoms, but there was a high rate of re-intervention¹⁴⁻¹⁷. However, trials that used restrictive treatment methods that are no longer in use in clinical practice influenced the findings of these analyses.

Objectives: The aim was to re-evaluate the efficacy of MR-HIFU in reducing fibroid-related symptoms using treatment protocols that focused solely on total ablation. We also looked at care failures and technical performance as assessed by the post-treatment NPV percent. We also looked at the disease-specific quality of life, re-intervention rates, stability, fertility, costs, and fibroid shrinkage.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) normative recommendations in this study with the registration number WU # RC/IRB/2020/1040.

Eligibility Criteria:

For inclusion, studies on MR-HIFU treatment of women with clinically symptomatic uterine fibroids were reviewed. Treatment procedures that did not target complete ablation (except for a five-mm protection margin from the serosal surface) or ultrasound-guided HIFU systems were ruled out.

The RCTs, prospective or Retrospective non-randomized, and cross-over studies that considered the treatment of clinically symptomatic uterine fibroids were included. The studies that did not have treatment protocols regarded as complete removal of fibroid or used ultrasound-guided HIFU were excluded. Also, animal studies, case reports, and studies not reporting NPV were excluded.

Data Search:

The studies were searched in Cochrane Library, PubMed/MEDLINE, SCOPUS, EMBASE databases. Six hundred eighty-four articles were searched, out of which 230 were excluded because they were either duplicated or book chapters. The full article found in the database was 82, out of which the authors removed 73 articles. The reasons for eliminating these articles are mentioned in Table 1. The articles included in meta-synthesis were 11. Articles of the past five years were considered, that is, from 2014 to 2019.

Data Extraction:

Data were derived separately from all qualifying studies by the same two scientists. A description of findings table was developed, which included (a) research characteristics such as authors, year of publication, study style, MRHIFU method, sample size, and follow-up time; (b) Treatment parameters: NPV percent, patient eligibility percentage, number of technological errors, use of bowel-interference reduction methods, and sonication duration are all metrics to consider. (c) primary outcome: reduction of fibroid-related symptoms, preferably as measured by the validated disease-specific Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QoL); (d) secondary outcomes: Health-Related Quality of Life (HRQL), as measured by the UFS-QoL questionnaire, fibroid shrinkage as measured by follow-up MR imaging, and the occurrence of any (serious) adverse events.

The outcomes analyzed were NPV%, defined by the formula: $(\text{non-perfused volume}/\text{fibroid volume}) \times 100^{25-27}$. Fibroid shrinkage is defined as the reduction in the size of the uterine fibroids after MR-HIFU. A higher transformed Symptom Severity Score (ISS) indicates more significant symptom severity²⁸. Health-related quality of life concerning uterine fibroid comprises questions asked on a five-point Likert scale, and the score is transformed in numeric from 0 to 100²⁹. The patient who had to undergo a second intervention after MRI-HIFU treatment for uterine fibroid related problems was considered in reintervention percentage.

Skin burns, menstrual bleeding or unexplained discharge, cystitis, urinary obstruction, constitutional complications, nerve injury, or discomfort for more than seven days were all considered minor adverse events. Patients that needed a second injection due to fibroid-related symptoms were included in the re-intervention percentage (second MR-HIFU, hysterectomy, myomectomy, or UAE).

Disagreements are settled by dialogue or consultation with a third author. Several reports of a single clinical trial were available, the most recent publication was used as the guide, and additional information was gleaned from secondary journals. We tried to reach the relevant authors by submitting an e-mail with a submission for supplementary data if results were unavailable. A second e-mail was sent if there was no response after seven days.

Proof quality and the possibility of bias

Two reviewers separately measured the level of proof in all publications using the Oxford Centre for Evidence-based Medicine (OCEBM) recommendations. A Delphi methodology was used to build an 18-criterion method to determine the consistency of the case series. A score of 14 or higher showed high efficiency. Dissension was used to identify and address discrepancies. When the two authors could not agree, a third author was contacted.

The articles that were considered had applied similar inclusion criteria: patients of more than 18 years of age or at pre- or peri-menopausal state. These studies have excluded patients in whom MRI with gadolinium is contraindicated or pregnant women. Chen et al.¹⁵, Tung S L et al.¹⁶, Jeong J, H et al.¹⁷ and Tan N et al.²⁰ excluded uterine fibroids larger than 10 to 12 cm. Funaki Type 3 fibroid was also excluded in Chen et al.¹⁵, Tung S L et al.¹⁶, Jeong J H et al.¹⁷ and Park M J et al.²². Besides, Jeong J H et al.¹⁷ also included the effectiveness of MR-HIFU in patients with concomitant adenomyosis. The characteristics of these studies are tabulated in Table 2.

Meta-analysis was performed using NCSS software. The data were analyzed at a 95% confidence level with a level of precision at 0.05. The NPV%, tSSS change%, and QoL were computed. Meta-Regression was done to evaluate the association between the different parameters.

Results

Literature search

Six hundred eighty-four articles were searched, out of which 230 were excluded because they were either duplicated or book chapters. The full article found in the database was 82, out of which the authors removed 73 articles. The reasons for eliminating these articles are mentioned in Table 1. The articles included in meta-synthesis were 11. Articles of the past five years were considered, that is, from 2014 to 2019.

Characteristics of the study and data extraction

The articles that were considered had applied similar inclusion criteria: patients of more than 18 years of age or at pre- or peri-menopausal state. These studies have excluded patients in whom MRI with gadolinium is contraindicated or pregnant women. Chen et al.¹⁵, Tung S L et al.¹⁶, Jeong J, H et al.¹⁷ and Tan N et al.²⁰ excluded uterine fibroids larger than 10 to 12 cm. Funaki Type 3 fibroid was also excluded in Chen et al.¹⁵, Tung S L et al.¹⁶, Jeong J H et al.¹⁷ and Park M J et al.²². Besides, Jeong J H et al.¹⁷ also included the effectiveness of MR-HIFU in patients with concomitant adenomyosis. The characteristics of these studies are tabulated in Table 2.

Evidence Quality

Except for one cross-over study, where only the first step was included in our review, all included trials were case series. According to the OCEBM standards of data, all of the included experiments had a degree of proof of IV. Using the 18-criteria tool, the consistency of the proof varied from 9 to 16 points, suggesting significant variations in quality between the included tests. The articles included in meta-synthesis were 11. Furthermore, the included studies did not adequately disclose the various statistical parameters, necessitating the estimation of standard deviations. However, where experiments with imputed standard deviations for all result parameters were excluded, predictions for standard deviation imputation were found to be sufficiently robust.

Technical Parameters

Bowel-interference mitigation strategies

The overall effect of NPV% was 70.24, where the 95% confidence interval ranged from 61.9% to 78.16%. The p-value after meta-regression was less than 0.05 (0.023), indicating that the use of bowel interference mitigation strategy results in higher NPV% “(Fig 1)”.

Time spent in treatment

11 studies recorded a mean sonication time of 146.2 minutes. The sonication time that took the least amount of time was the method used by Chongqing¹⁸. The latest findings have shown that extended patient cohorts have shorter waiting periods and that the total treatment period has declined¹⁹⁻²².

NPV percentage:

The included studies show that the overall effect of tSSS% change is nearly 50% after a follow-up of 3 months, 6 months, and 12 months in the included studies. The meta-regression showed no association between NPV%, fibroid shrinkage, and tSSS% change “(Fig 2)”.

Health-Related Quality of Life (HRQL)

There were only three studies that evaluated the health-related quality of life. The quality of life improved after the follow-up, and the combined effect revealed a better quality of life “(Fig 3)”.

Fibroid shrinkage

The fibroid shrinkage was also significant in the studies included for review^{15, 27,39}. After MR-HIFU therapy, all studies demonstrated average fibroid shrinkage. Only minor variations were seen when stratified by follow-up type. Three researches, however, found a significant impact of time on fibroid shrinkage percentage. NPV percent was not statistically correlated with fibroid shrinkage ($p=0.012$) in an exploratory meta-regression study. At the 6-month follow-up, there was a slight difference/trend, indicating a favorable relationship.

Costs

The writers did not mention any cost-related results. As a result, assumptions about cost-effectiveness cannot be drawn based on the studies used.

Adverse Events

Just one of the researches included in this review did not use AE as an endpoint parameter¹³. 124 of 1360 patients (9.1%) had an adverse reaction to one of the 1360 therapies studied. During the follow-up period, 120 AEs were minor and self-limiting. Just two patients (0.3%) had a severe adverse effect (SAE), one of which was a deep venous thrombosis (DVT), and the other was a third-degree skin burn. Two of the most recent studies listed these SAEs (patient enrollment between 2005 and 2009)^{24,39}. Sonalleve and ExAblate had a significant gap of (S) AE stratification, 18.4 percent, and 6.7 percent, respectively. Meta-regression verified that the difference between Sonalleve and ExAblate was statistically significant ($p < 0.05$). None of the other covariates studied (NPV percent, sonication time) was linked to adverse outcomes. However, not many serious adverse events were reported in the study.

However, a follow-up MRI is expensive and not required. Similarly, re-interventions were found in two studies that showed reintervention needed in 18-24% of patients.

Discussion

This meta-analysis aimed to evaluate the effectiveness of MRI-HIFU on patients with uterine fibroids. The results showed that there was an overall decrease in NPV% and tSSS% change. The health-related quality of life among patients with uterine fibroids also improved with follow-up; however, this was seen only in three studies and needs to be assessed further. Studies involved in the meta-analysis have also proclaimed improved reproductive outcomes. It has come to light that reintervention was needed in 18-24% of patients. This meta-analysis has included studies that have focussed on complete ablation for looking at the overall effect of MR-HIFU.

The overall level of data, which was low to moderate, affected all of the outcome criteria examined in this study. For inclusion, only non-randomized, non-comparative trials were available. The sources of a high risk of prejudice are linked to the sample designs themselves: insufficient documentation of loss of follow-up and the possibility of selection bias.

Increased expertise improves care effectiveness by reducing technical errors and treatment time in extended patient cohorts. Xu et al. registered the shortest sonication duration, suggesting that the Chongqing method could increase treatment effectiveness. The pooled NPV percent immediately after MR-HIFU was 70.24 percent, which is higher than other reviews^{14,18}, owing to the lack of stringent treatment protocols. The distribution of dispersed points into two classes showed a remarkable asymmetry in our findings. Unfortunately, we were unable to provide a complete explanation. Through bowel-interference avoidance methods, only a minor disparity was discovered, meaning that this may lead to a higher NPV percent.

The pooled tSSS declined on average and continued to increase during follow-up. There was no data available for more than a year. MR-HIFU was not linked to other therapeutic choices in any of the trials included. At a 3-months follow-up, Jacoby et al. compared MRgFUS to placebo²¹ and found that the MRgFUS community had a more significant tSSS decline, -31 vs. -13 points. We looked for other uterine fibroid studies that used the UFS-QoL questionnaire to equate the tSSS of MR-HIFU to other treatment alternatives (UAE, hysterectomy, and myomectomy). Similarly, studies by Spies JB³⁰ and Manyonda IT³¹ have also reported a decrease in tSSS% change in myomectomy and hysterectomy, and the present meta-analysis has indicated an overall tSSS% change of 49.27, which is comparable to hysterectomy and myomectomy. Few studies reported health-related quality of life, but the enrolled studies have improved uterine fibroid-related quality of life.

Fibroid shrinkage was shown in all the studies, and the percentage of shrinkage ranged over time, indicating that fibroids will continue to shrink in volume for at least a year. The relationship between fibroid shrinkage and NPV percent was marginally significant, implying that a higher NPV percent could lead to more fibroid shrinkage. Please keep in mind that a follow-up MRI exam is costly and mostly needless.

The reintervention has seen in Tan et al.²⁰, Mindjuk et al.¹⁹, and Chen et al.¹⁶ was 9%, 12.7%, and 0.9%, respectively, while other studies did not report the need for reintervention on the follow-up period. This particular result pointed at the efficacy of the procedure. The procedure of MR-HIFU is non-invasive and does not indicate any effect on the reproductive outcome of the patients after the treatment. None of the

studies has included the reproductive outcome and hence raised concern. However, studies by Lee JS³² and Cheung VY³³ have shown no effect on the Anti-Mullerian Hormone, indicating that women can try for pregnancy after treating uterine fibroids.

Just two SAEs were identified in older studies^{24,39}, which may be clarified by a slight learning curve effect when MR-HIFU was first used in clinical practice [13]. As AE was stratified by method, trials using the Sonalleve system had slightly more AE than trials using the ExAblate device^{14,15,17,22}. Two Ex-Ablate reports, on the other hand, reported ‘no unforeseen or major AE,’ implying under-reporting^{16,27}. Furthermore, there is no agreement about how to define AE in the context of MR-HIFU. For example, although irregular vaginal discharge is often classified as AE, fibroid expulsion was identified as a common finding in 21% of ExAblate patients¹⁹. Surprisingly, a Sonalleve study classified constitutional symptoms as AE, although none of the other studies did²². Although a reporting bias may clarify the disparity in AE between Sonalleve and ExAblate, more research is needed in the future.

These treatment modalities may have shown to be cost effective³⁴⁻³⁸ but not included in this analysis. MR-HIFU can be considered a cost-effective treatment for patients ready to pay.

Methodological flaws were to blame for the meta-analysis’s flaws. Standard deviations were often estimated. There was a lack of follow-up in some trials, and some sub-studies had different sample sizes⁴¹. As a consequence, the findings should be viewed with caution. Furthermore, since the findings are based on published means rather than actual patient records, the ecological fallacy may have influenced the results. We questioned if we should generalize our findings because of the significant and often mysterious heterogeneity in each outcome parameter. However, since we used a random-effects model for meta-analysis⁴⁰, this approach is accurate.

Even though MR-HIFU has been used to treat uterine fibroids for 14 years, it is still not widely used or reimbursed worldwide. The gold standard for obtaining reimbursement is a randomized clinical experiment, and one is currently underway to compare UAE and MR-HIFU⁴². However, they had difficulty selecting volunteers, and some patients refused to be randomly assigned. As a result, randomized experiments are challenging to perform and face statistical difficulties. More extensive retrospective randomized cohort trials with longer follow-up are needed to establish the role of MR-HIFU in the management of symptomatic uterine fibroids before it can be used in routine clinical care.

Conclusion

The present meta-analysis has shown that it is an entirely effective non-invasive treatment for uterine fibroids; this is evident by reducing the overall NPV, tSSS% change, and decrease in the fibroid size. The studies focussing on the impact of HrQoL are needed in this aspect. The trials focusing on the reproductive outcomes should focus on the recommendation of this therapy for uterine fibroids.

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Statement of Ethics: All procedures performed in the study were in accordance with the institutional and/or national research committee’s standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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“All authors read and approved the final version of the manuscript”.

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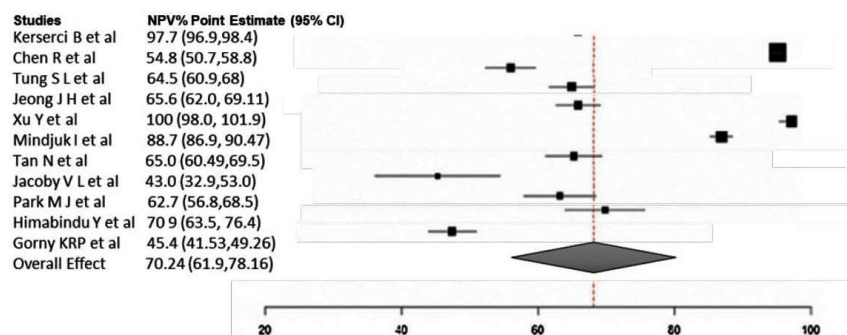
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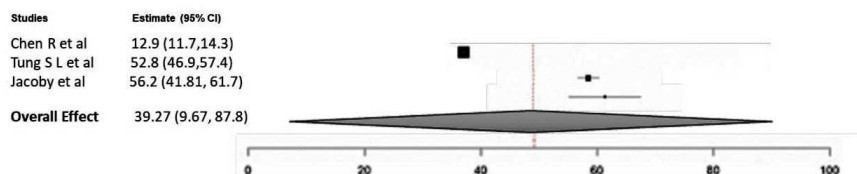
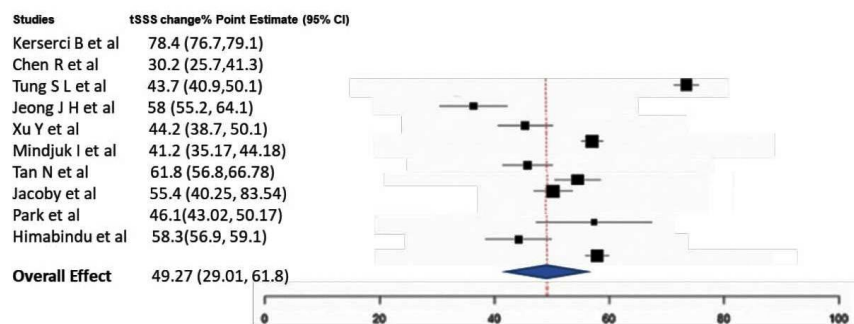
Figure Legends

Figure 1: Forest Plot of studies included for NPV%.

Figure 2: Forest Plot of studies included for tSSS change%.

Figure 3: Forest Plot of studies included for Disease-specific quality of life.





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