European Journal of Radiology 120 (2019) 108700

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Systematic review
Uterine fibroids
MR guided interventional procedures
High-intensity focused ultrasound ablation

ABSTRACT

Purpose: Reevaluation of the effectiveness of Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) therapy for uterine fibroids by excluding studies with restrictive treatment protocols that are no longer used.

Methods: The National Guideline Clearinghouse, Cochrane Library, TRIP, MEDLINE, EMBASE and WHO International Clinical Trials Registry Platform (ICTRP) databases were searched from inception until the 22nd of June 2018. Keywords included "MR-HIFU", "MRgFUS", and "Leiomyoma". Only studies about MR-HIFU treatment of uterine fibroids with at least three months of clinical follow-up were evaluated for inclusion. Treatments with ultrasound-guided HIFU devices or protocols not aiming for complete ablation were eliminated. The primary outcome was the improvement in fibroid-related symptoms. Technical outcomes included screening and treatment failures, treatment time, application of bowel-interference mitigation strategies and the Non-Perfused Volume (NPV) percentage. Other secondary outcomes were the quality of life, fibroid shrinkage, safety, re-interventions, reproductive outcomes, and costs. Meta-analysis was performed using a random-effects model (DerSimonian and Laird).

Results: A total of 18 articles (1323 treated patients) met the inclusion criteria. All selected studies were case series except for one cross-over trial. Overall, the quality of the evidence was poor to moderate. The mean NPV% directly post-treatment was 68.1%. The use of bowel-interference mitigation strategies may lead to increased NPV%. The mean symptom reduction at 12-months was 59.9% and fibroid shrinkage was 37.7%. The number of adverse events was low (8.7%), stratification showed a difference between HIFU systems. The re-intervention percentage at 3–33.6 months follow-up ranged from 0 to 21%. Longer follow-up was associated with a higher risk at re-interventions. Reproductive outcomes and costs couldn't be analyzed.

Conclusions: Treatment guidelines aiming for complete ablation enhanced the effectiveness of MR-HIFU therapy. However, controlled trials should define the role of MR-HIFU in the management of uterine fibroids.

Abbreviations: MR-HIFU, magnetic resonance imaging-guided high intensity focused ultrasound; MRgFUS, magnetic resonance guided focused ultrasound surgery; NPVN, on-perfused volume; UFS-QoL, uterine fibroid symptom and quality of life; tSSS, transformed symptom severity score; UAE, uterine artery embolization

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https://doi.org/10.1016/j.ejrad.2019.108700
Received 21 August 2019; Accepted 2 October 2019

1. Introduction

1.1. Background uterine fibroids

Uterine fibroids are common benign gynecological tumors which develop from uterine smooth muscle cells. The cumulative incidence during the reproductive period ranges from 70 to 80% depending on the patient's ethnicity [1]. Many women are asymptomatic, but in approximately 25% uterine fibroids cause clinically relevant symptoms [2]. Main symptoms include pelvic pain, dysmenorrhea, menorrhagia, urinary frequency, dyspareunia and subfertility. Pharmacological agents are effective in alleviating symptoms, but adequate control may not be achieved, or significant side-effects occur. Overall, a high percentage of patients will eventually require intervention. Uterine fibroids are still the leading indication for a hysterectomy worldwide [3,4]. Myomectomy is the therapy of choice for women who want to conceive. However, surgical approaches are associated with a high rate of short- and long-term morbidity, require a hospital stay and weeks to recover. Other minimally-invasive uterine-sparing treatment options are available including uterine artery embolization (UAE), hysteroscopic resection and Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU). MR-HIFU is the only entirely non-invasive intervention and has several proven advantages such as a lower morbidity, less complications, no general anesthesia and shorter recovery time [5].

1.2. MR-HIFU technique

MR-HIFU is a thermal ablation technique and enables non-invasive treatment of uterine fibroids by selective tissue heating [6]. The ultrasound transducer produces convergent high-intensity ultrasound waves. The targeted tissue absorbs the acoustic energy leading to a temperature rise which causes coagulative necrosis and apoptotic cell death [6]. Magnetic Resonance Imaging (MRI) facilitates treatment planning and real-time monitoring by temperature mapping [7]. Directly post MR-HIFU, a contrast enhanced MRI can visualize the ablated tissue, referred to as the non-perfused volume (NPV). Treatment result can be expressed as the NPV% which is the NPV divided by the fibroid volume. During MR-HIFU therapy, interference of bowel loops in the beam pathway could lead to treatment failure or untreated parts of the fibroid. Different mitigation strategies are developed to displace bowel loop. The BRB technique, which includes sequential applications of urinary bladder filling, rectal filling and urinary bladder emptying, is the most common technique. Three MR-HIFU devices are currently in clinical use. The ExAblate system (InSightec, Haifa, Israel) employs the conventional 'point-by-point' ablation technique. The Sonalleve system (Profound Medical Inc., Toronto, Canada) uses a volumetric ablation technology. The Chongqing system (Chongqing Haifu Technology, Chongqing, China) combines the 'point-by-point' treatment strategy with shot-sonication.

1.3. Background MR-HIFU

Since 2004, MR-HIFU treatment of uterine fibroids has been approved by the United States Food and Drug Administration (FDA). Initially, restricted protocols had to be used for safety reasons. However, over time it became clear that therapeutic outcomes are closely related to the NPV% [8,9]. Partially ablated fibroids tend to regrow, which may explain the relatively high re-intervention percentage reported in studies using a restricted protocol [10,11]. Moreover, MR-HIFU treatment proved to be safe even when complete ablation was pursued [12]. The FDA guidelines were modified in 2009, allowing operators to aim for complete ablation which has led improved outcomes in more recent studies [8,13]. Although this might also be partially explained by increased experience of the HIFU centers with the technique [13]. Furthermore, the safety guidelines were modified for women with symptomatic uterine fibroids and a desire for future fertility since uncomplicated pregnancies were reported after MR-HIFU therapy. Still, not all patients are eligible for MR-HIFU treatment. Exclusion criteria can be based on patient characteristics (BMI and MRI contraindications) or fibroid characteristics assessed by MR screening. Fibroids with a high T2 signal intensity are difficult to treat and therefore these fibroids, Funaki type 3, are generally excluded [14].

1.4. Rationale

To date, several reviews were published on the effectiveness of MR-HIFU treatment for uterine fibroids. Overall, they showed that MR-HIFU is effective in alleviating symptoms, but a relatively high re-intervention percentage is reported [15–17]. However, these reviews included studies using restrictive treatment protocols that are no longer in clinical use which affected the results.

1.5. Objectives

The purpose was to reassess the effectiveness of MR-HIFU on reducing fibroid-related symptoms using treatment protocols aiming for complete ablation only. We also investigated the technical success measured by the post-treatment NPV% and treatment failures. Additionally, we evaluated the disease specific quality of life, the re-intervention percentage, safety, fertility, costs and fibroid shrinkage.

2. Material and methods

In this review, we adhered to the standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. The review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42018100467.

2.1. Eligibility criteria

Studies about MR-HIFU treatment of women with clinically symptomatic uterine fibroids were evaluated for inclusion. Treatment protocols not aiming for complete ablation (except for a safety margin of five mm from the serosal surface) or ultrasound guided HIFU devices were excluded.

Randomized controlled trials (RCT), prospective or retrospective non-randomized studies and cross-over trials with at least three months of follow-up were evaluated for inclusion. Animal studies, case reports and ongoing trials were eliminated as well as studies not reporting on our primary outcome or NPV%. Gonadotropin-releasing hormone (GnRH) analogues prior to MR-HIFU were allowed.

2.2. Data search

We searched the following databases on the 22nd of June in 2018 (Appendix): National Guideline Clearinghouse, Cochrane Library, TRIPP, MEDLINE/PubMed, WHO International Clinical Trials Registry Platform (ICTRP) and Embase. Duplicate publications were detected by a reference manager (RefWorks) and removed. Two authors (IV and KA) independently completed the initial title and abstract screening for all six databases. Full texts were retrieved when studies possibly met our inclusion criteria. Reference lists of all retrieved full-text articles were manually searched to identify other relevant studies for full text screening.

2.3. Data extraction

The same two authors independently extracted data from all eligible studies. Data were collected in a summary of findings table containing (a) study characteristics: authors, year of publication, study design, MR-HIFU system, sample size, follow-up duration; (b) treatment

parameters: NPV%, patient's eligibility percentage, the number of technical failures, the use of bowel-interference mitigation techniques, sonication time; (c) primary outcome: reduction of fibroid-related symptoms preferably assessed by the validated disease-specific Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QoL) [19]; (d) secondary outcomes: Health-Related Quality of Life (HRQL) also assessed by the UFS-QoL questionnaire, fibroid shrinkage based on follow-up MR imaging, occurrence of any (serious) adverse events related to the MR-HIFU procedure, re-intervention percentage, evaluation of reproductive outcomes (fertility, pregnancy or obstetrical outcomes) and costs. The NPV% was calculated by the formula: (non-perfused volume/fibroid volume) 100% [20–22]. This UFS-QoL questionnaire includes eight questions about symptom severity and 29 HRQL questions. [19]. All items were scored on a 5-point Likert scale. Subscale scores were transformed to a scale of 0–100 by the following formula: transformed score = ((actual raw score – lowest possible raw score)/possible raw score range) x 100. Higher transformed Symptom Severity Score (tSSS) indicates greater symptom severity. Higher transformed HRQL (tHRQL) score is indicative of a better HRQL. Adverse events (AE) were categorized according to the Society of Interventional Radiology clinical practice guidelines [23]. Minor adverse events were defined as skin burns, vaginal bleeding or abnormal discharge, cystitis, urinary retention, constitutional symptoms, nerve damage or pain longer than seven days. The re-intervention percentage was defined as patients undergoing an additional intervention due to fibroid-related symptoms (second MR-HIFU, hysterectomy, myomectomy or UAE). Any disagreements were resolved by discussion or by consulting a third author. When multiple publications were available of one clinical trial, the most recent publication was used as the reference and additional details were derived from secondary papers. If outcomes were missing, we attempted to contact the corresponding authors by sending an email with request for additional data. If there was no response after seven days, a second email was sent.

2.4. Quality of evidence and risk of bias

Level of evidence of all articles was assessed independently by two authors (IV and KA) according to the Oxford Centre for Evidence-based Medicine (OCEBM) guidelines [24]. The quality of case series was assessed by an 18-criteria tool developed through a Delphi technique [25]. A score of 14-points or more indicated good quality. Discrepancies were identified and resolved through discussion. Where agreement couldn't be reached, a third author was consulted.

2.5. Data synthesis

The results of meta-analyses were presented in the form of tables and graphs. For continuous data using the same scale (*e.g.* difference in fibroid volume) the change from baseline (%) was reported. To combine data from eligible studies a random-effects model (DerSimonian and Laird) was used [26]. If the results showed statistical heterogeneity (I^2), we tried to explain the differences by stratification. We considered an I^2 value of greater than 50% indicative of substantial heterogeneity.

Outcomes were stratified by MR-HIFU device, the use of bowel-interference mitigation strategies and duration of follow-up: short-term (3-months), mid-term (4–6 months) and long-term (12-months or more). Explorative meta-regression was performed for all primary and secondary outcomes.

2.6. Missing data

Missing standard deviations were imputed by the arithmetic mean of all available standard deviations in the same category, unless reported otherwise. Sensitivity analyses were performed by comparison with point estimates when excluding studies with missing standard deviations [27].

Regarding change scores, the correlation coefficient was imputed by 0.5, unless reported otherwise [27]. The imputed correlation coefficients were used to calculate the SD of change scores using the following formula: $SD_c = \sqrt{SD_b^2 + SD_f^2 - 2 * 0.5 * SD_b * SD_f}$. When the SD of the change score was present (one study) correlation coefficient was calculated using the following formula: $r = \frac{SD_b^2 + SD_f^2 - SD_c^2}{2SD_b SD_f}$.

2.7. Software

Meta-analyses were performed using Comprehensive Meta-Analysis (calculations) and Open Meta-Analyst (figures and calculations) [28].

3. Results

3.1. Literature search

The search revealed 568 potentially relevant studies (appendix). After duplicates and textbooks were excluded 387 abstracts were screened and revealed 92 potentially relevant articles. By inspecting reference lists of these articles, no additional articles were identified. During full text screening, 55 studies appeared not to meet our inclusion criteria and 19 reviews were excluded. A total of 18 articles were finally selected [20–22,29–43] (Fig. 1). These 18 articles included 16 different clinical trials. One study reported results of an extended patient population and one study published their results at two different time points.

3.2. Study characteristics

We composed a summary of findings table of all included studies (Table 1). The studies mostly applied similar inclusion criteria: age above 18 years old, a pre-or perimenopausal state and exclusion criteria: contraindications to MRI with gadolinium or pregnant patients. Nine studies excluded fibroids larger than 10–12 cm or uterine size larger than 20–24 weeks of gestational age [20,30,33–35,41,42]. Another frequently reported exclusion criterion were Funaki type 3 fibroids (high T2W signal on MRI) [22,29,30,35,37,41]. Only four studies, including the two oldest studies, excluded patients with a desire for future fertility [21,29,34,38]. Three studies demanded a minimum tSSS at baseline of 41-points [33,34] or 21-points [38]. Smart et al. studied the effect of GnRH agonists prior to MR-HIFU [38]. Jeong et al evaluated the effectiveness of MR-HIFU in patients with concomitant adenomyosis [35].

3.3. Data extraction

From all studies included, we retrieved the tSSS except from Morita et al who reported subjective relief of symptoms instead of the tSSS [21]. Therefore, we excluded this study from this part of the meta-analysis. Furthermore, the tSSS scores of Funaki type 3 patients could not be evaluated as reported by Funaki et al, thus these patients were not included in our data extraction [20]. Jeong et al reported that patients were not followed longer than 3 months if they experienced sufficient symptom relief, so only outcomes until 3-months were analyzed [35]. Two authors were contacted for additional data. Unfortunately, we received no response.

3.4. Quality of the evidence

All included studies were case series, except for one cross-over trial [34] of which only the first phase was included in our analysis. The level of evidence for all included studies was IV according to OCEBM levels of evidence. The quality of the evidence ranged from 9 to 16 points using the 18-criteria tool [25], indicating substantial differences in quality between the included studies. Only 6 of the 18 studies

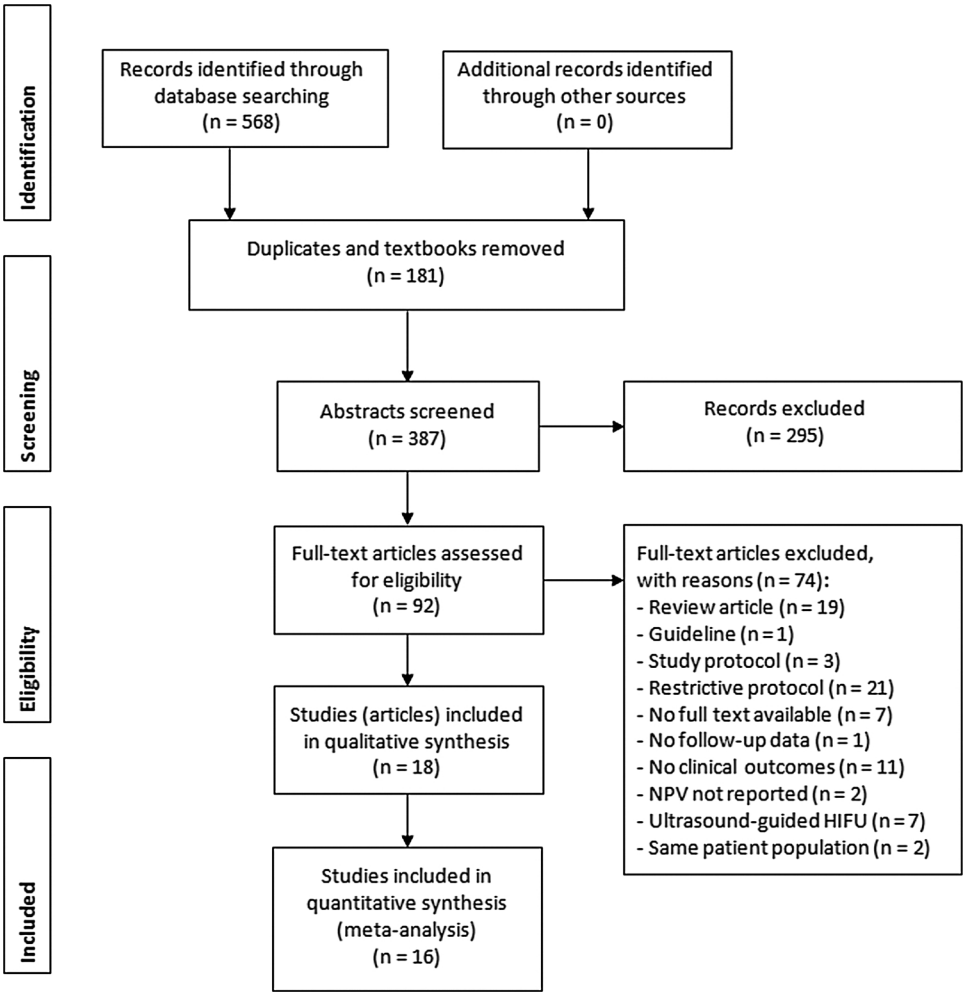

Fig. 1. Flow chart shows summary of the literature review process.

[29,34,36–38,40] were of acceptable quality. Furthermore, the included studies poorly reported the different statistical parameters and thus, standard deviations often had to be estimated. However, excluding studies with imputed standard deviations for all different outcome parameters indicated that estimates were reasonably robust for standard deviation imputation.

3.5. Technical parameters

3.5.1. Screening and treatment failures

The number of screening and treatment failures were not reported in all studies. Eligibility percentage was reported by five studies [29,37,39,41,43] with a mean percentage of 42.0% and a screening failure percentage of 58.0%. Mean technical failure percentage was 3.5% based on seven studies [29,31,32,36,37,40,43]. There was a slight decrease in the number of technical failures in the extended patient cohorts [31,32,36,40].

3.5.2. Bowel-interference mitigation strategies

Six trials stated that they used bowel-interference mitigation strategies if necessary [22,35–37,40,42,43]. Seven trials explicitly said not to use mitigation techniques [20,21,30–34,38]. In the other three studies it was unclear [29,39,41].

3.5.3. Treatment time

Sonication time was reported by 10 studies with a mean of 145,6 min [20,30,34–38,40,42,43]. The shortest sonication time was reported by the study using the Chongqing system [42]. More recent studies reported shorter treatment times and the average treatment time decreased in the extended patient cohorts [36,40].

3.5.4. NPV%

The point estimate (95% CI) of NPV% was 68.1% (59.9%–76.0%) with I^2 of 99.5%. The I^2 of 99.5% indicates substantial heterogeneity, which could not be explained by stratification or meta-regression. One borderline difference between no mitigation (adjusted mean 58.9) and mitigation (adjusted mean 78.7) was found by meta-regression ($p = 0.016$), suggesting that the use of bowel-interference mitigation strategies results in a higher NPV% (Fig. 2).

3.6. Symptom improvement

Baseline scores of tSSS were 46.1 (33.7–58.4) on 3-months, 56.1 (50.0–62.2) on 6-months and 53.6 (41.8–65.5) on 12-months follow-up, respectively. The combined estimates of the change percentages in the 3-month, 6-month and 12-month category showed symptom reduction following MR-HIFU treatment (decreased tSSS score; Fig. 3). The I^2's indicate substantial heterogeneity in the 3-months and 6-months category. In the 12-months category the I^2 was 75.35%. Explorative meta-regression analysis showed no association between NPV% and tSSS decrease. Similarly, there was no association between tSSS and fibroid shrinkage. Only Morita et al did not report the tSSS, but asked patients about symptom relief and reported a success percentage of 85.4% [21].

Table 1
Summary of the included articles.

LoE	Quality	Author	Year	Study Design	Device	Follow-up	Patients	NPV% ± SD	FS%	tSSS↓	HRQL↑	RI%	(S)AE	Mitigation	Therapy time	TF	Eligiblity	Pregnancy
IV	14/18	Smart	2006	Prospective	ExAblate	12 months	49	51.0 ± 20.0	37.0	48.0%	NR	12.2	12.2%	No	183 minutes	NR	NR	0
IV	12/18	Morita	2008	Prospective	ExAblate	12 months	48	60.0 ± 18.0	33.0	NR	NR	4.0	8.3%	No	NR	NR	NR	1
IV	11/18	Funaki	2009	Prospective	ExAblate	24 months	80	54.3 ± 22.6	39.5	54.4%	NR	8.8	NR	No	170 minutes	NR	NR	4
IV	13/18	Gorny	2011	Retrospective	ExAblate	12 months	130	45.4 ± 22.5	NR	68.0%	NR	6.2	5.4%	Yes	NR	4.4%	NR	0
IV	12/18	Gorny	2014	Retrospective	ExAblate	33.6 months	138	45.5 ± 22.7	NR	NR	NR	21.0	5.1%	Yes	NR	4.2%	NR	0
IV	11/18	Desai	2012	Prospective	ExAblate	6 months	50	88.0 ± 6.0	30.0	49.7%	NR	0	8%	No	145 minutes	NR	NR	0
IV	12/18	Dobrotwir	2012	Prospective	ExAblate	12 months	51	67.0 ± 25.0	38.0	50.8%	NR	11.7	0%	Yes	NR	NR	NR	0
IV	12/18	Himabindu	2014	Prospective	ExAblate	6 months	32	70.0 ± 20.0	40.0	59.7%	NR	0	18.8%	No	NR	NR	NR	0
IV	14/18	Park	2014	Prospective	Sonalleve	3 months	74	62.7 ± 25.5	27.0	35.6%	NR	0	25.6%	Yes	165 minutes	6.3%	41%	0
IV	15/18	Jacoby	2015	Prospective	ExAblate	3 months	13	43.0 ± 20.0	18.0	55.4%	56.2%	0	0%	No	153 minutes	NR	NR	0
IV	10/18	Tan	2015	Prospective	ExAblate	12 months	100	65.0 ± 23.0	NR	61.8%	NR	9.0	4.3%	NR	NR	NR	47%	0
IV	16/18	Trumm	2012	Retrospective	ExAblate	6.5 months	115	88.0 ± 15.0	NR	40.0%	NR	NR	1.7%	Yes	198 minutes	6.5%	NR	0
IV	16/18	Mindjuk	2015	Retrospective	ExAblate	19.4 months	221	88.7 ± 15.0	NR	67.8%	NR	12.7	1.6%	Yes	180 minutes	3.2%	NR	15
IV	12/18	Xu CA	2015	Prospective	Chongquing	6 months	10	100	59.1	33.5%	NR	0	0%	Yes	25 minutes	NR	NR	0
IV	12/18	Xu PA	2015	Prospective	Chongquing	6 months	33	84.3 ± 15.7	40.1	45.5%	NR	0	2.3%	Yes	18 minutes	NR	NR	0
IV	14/18	Chen	2016	Prospective	Sonalleve	6 months	107	54.8 ± 21.2	50.2	30.2%	12.9%	0.9	6.5%	NR	NR	0%	43%	4
IV	9/18	Jeong	2016	Retrospective	Sonalleve	3 months	157	65.6 ± 22.7	35.3	55.0%	NR	5.7	12.7%	Yes	102 minutes	NR	NR	0
IV	9/18	Tung	2016	Retrospective	ExAblate	6 months	40	64.5 ± 11.4	31.7	43.7%	33.5%	0	0%	NR	NR	NR	31%	0
IV	13/18	Kerserci > 90	2018	Retrospective	Sonalleve	6 months	72	97.7 ± 3.2	54.0	86.0%	NR	0	26.4%	Yes	148 minutes	0%	46%	3
IV	13/18	Kerserci < 90	2018	Retrospective	Sonalleve	6 months	48	60.4 ± 27.3	14.0	26.0%	NR	0	22.9%	Yes	130 minutes	0%	46%	3

Abbreviations: LoE = Level of Evidence, NPV% = Non-Perfused Volume percentage, SD = Standard Deviation, FS% = Fibroid Shrinkage percentage, tSSS = transformed Symptom Severity Score, HRQL = Health Related Quality of Life, RI% = Re-intervention percentage, (S)AE = (Serious) Adverse Events, TF = Treatment failures, NR = Not Reported, Xu CA or PA = Complete Ablation or Partial Ablation of the uterine fibroid, Kerserci > 90 = Treatments NPV% > 90%, Kerserci < 90 = Treatments NPV% < 90%.

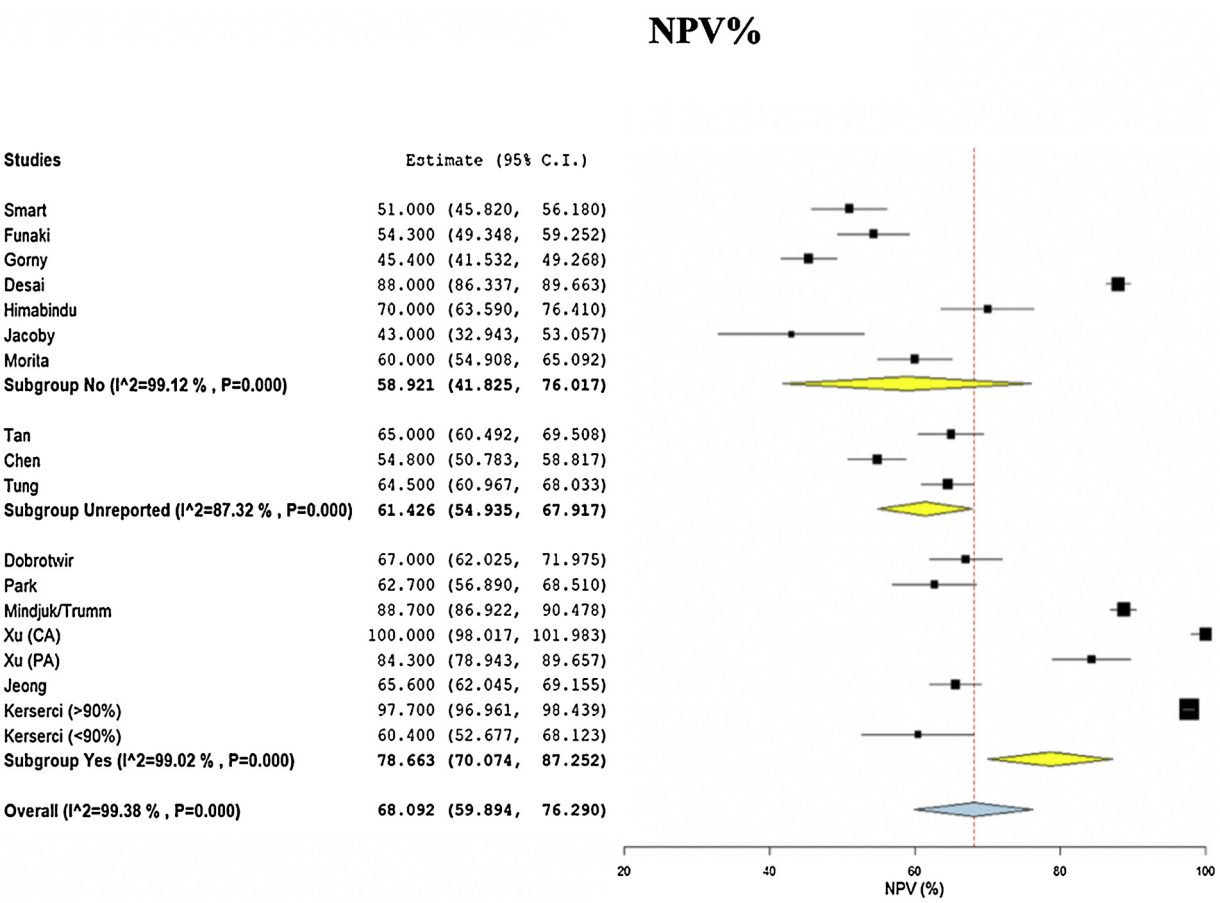

Fig. 2. Forest plot of NPV% directly post MR-HIFU, stratified by the use of mitigation.

3.7. HRQL

Only three of the included studies reported HRQL scores [29,34,41]. The baseline scores of QoL were 61.0 (36.5–84.5) on 3-months and 55.5 (21.1–89.9) on 6-months follow-up, respectively. The combined estimates of the change percentages in the 3-month and 6-month category showed improved HRQL scores (Fig. 4). The I^2's indicates substantial heterogeneity in the 3-month and 6-month category.

3.8. Fibroid shrinkage

All studies showed overall fibroid shrinkage after MR-HIFU treatment (Fig. 5). Stratification by follow-up category showed only small differences. However, three studies reported a substantial effect of time on fibroid shrinkage percentage [29,22,38]. The I^2's indicate substantial heterogeneity in the 3-months and 6-months category. This could be partly, although not significantly, explained by NPV%. In the 12-months category the I^2 was 0%. Explorative meta-regression analysis showed that NPV% was not significantly associated with fibroid shrinkage ($p = 0.012$; Fig. 6). A borderline difference/trend was seen at 6-months follow-up, suggesting a positive relationship.

3.9. Adverse events

Only one of the included studies did not report AE as outcome parameter [20]. Of the 1330 treatments analyzed, 112 of 1330 (8.7%) patients experienced an AE (Fig. 7). Importantly, 110 AE's were minor and self-limiting during follow-up. Only 2 patients (0.2%) experienced a serious adverse event (SAE), one deep venous thrombosis (DVT) and one third degree skin burn. These SAE's were reported in two of the most dated studies (patient enrollment between 2005 and 2009) [31,38]. Stratification of (S)AE resulted in a substantial difference between Sonalleve and ExAblate, 17.6% versus 5.7%, respectively (Fig. 6). The difference between Sonalleve and ExAblate was statistically significant as confirmed by meta-regression ($p < 0.001$). None of the other investigated covariates (NPV%, sonication time) were associated with adverse events.

3.10. Re-intervention percentage

At the end of the follow-up from 16 different trials, data of 1323 treated patients were available. The re-intervention percentage at 3–33.6 months follow-up ranged from 0 to 21% (Table 2). A total of 97 re-interventions were reported of which 23 hysterectomies, 25 myomectomies, 7 surgical interventions (procedure not defined), 16 UAE, 15 repeat MR-HIFU, 1 thermal laser ablation, 1 transcervical resection and 9 unknown interventions. Results of three studies showed a substantial effect of time on re-intervention percentage (Fig. 8) [20,31,32,22]. Funaki et al calculated cumulative re-intervention percentages during follow-up [20]. The reintervention rates at 6-, 12- and 24-months follow-up were 1.4%, 2.9% and 14.0%, respectively. Additionally, Gorny et al reported the cumulative rates re-intervention percentages of 4% at 12-months, 13% at 24-months, 19% at 36-months and 23% at 48-months follow-up [31]. Explorative meta-regression analysis showed no association with NPV% or tSSS decrease.

3.11. Reproductive outcomes

A total of 27 pregnancies were reported by five of the included studies [20,21,29,36,44]. Interestingly, a desire for future pregnancy was an exclusion criterium in two of these studies [21,29] and four patients voluntarily terminated their pregnancies while enrolled in the

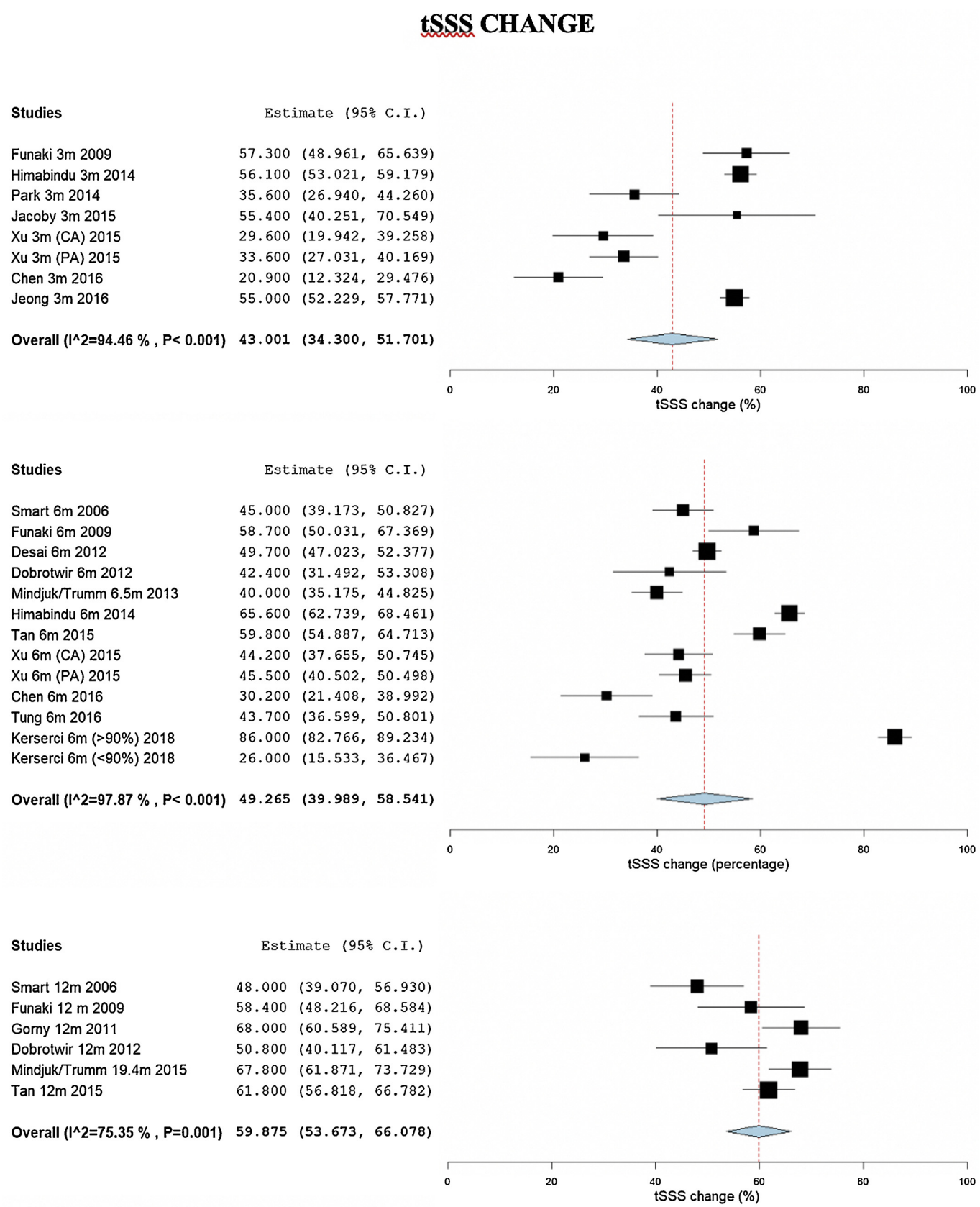

Fig. 3. Forest plots of tSSS decrease percentage, stratified by follow-up category. Only Kerserci and Gorny reported the SD of the change percentage of the tSSS and all other SD had to be imputed.

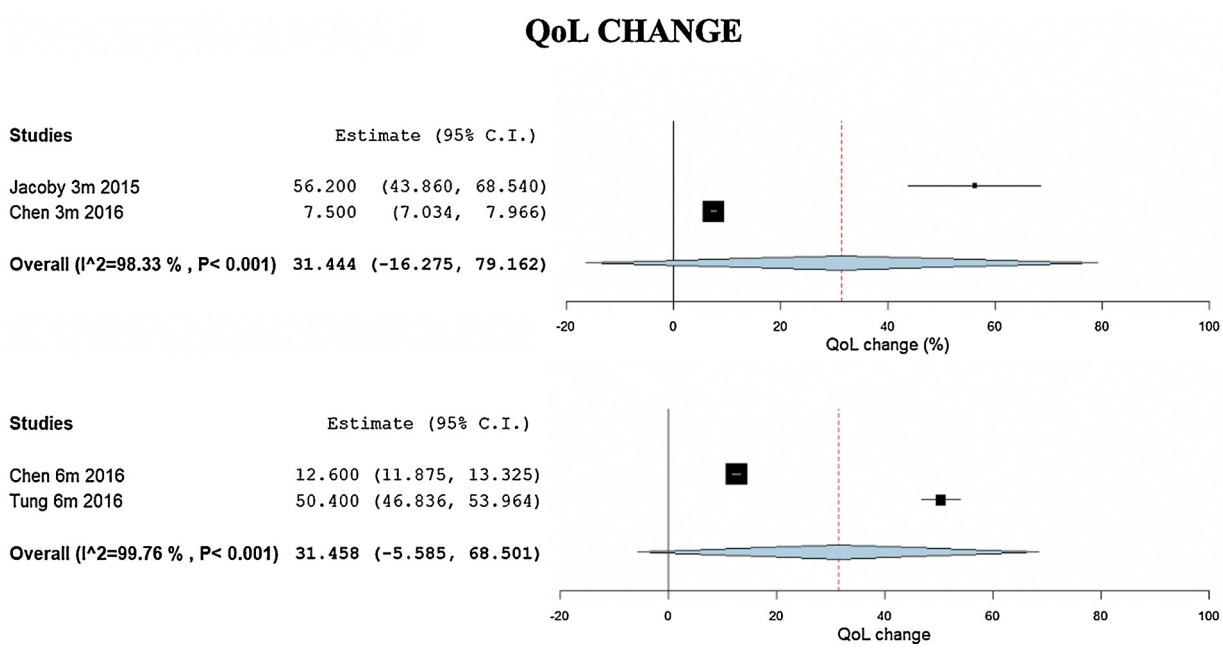

Fig. 4. Forest plots of HRQL increase in change percentage, stratified by follow-up category.

trial [29]. Morita et al described one uncomplicated pregnancy and birth [21]. Mindjuk et al reported 12 uncomplicated cases [36], one spontaneous abortion occurred and two patients still pregnant at the time of publication. Kerserci et al described three pregnant women loss to follow-up without further notice [44]. Funaki et al reported two live term births and two first-trimester miscarriages [20]. Kerserci et al considered the potential impact on the ovarian reserve because ovarian dysfunction is strongly associated with subfertility. The levels of the anti-Mullerian Hormone (AMH) were measured at baseline and 6-months follow-up, no significant changes were found, suggesting that the ovary and its vessels were not involved in the treatment area [43].

3.12. Costs

The authors did not report outcomes considering costs. Therefore, it is not possible to draw conclusions regarding cost-effectiveness on the included studies.

4. Discussion

This systematic review reevaluated the effectiveness of MR-HIFU therapy of uterine fibroids only including treatment protocols aiming for complete ablation, because restrictive protocols are no longer in clinical use. The results showed that symptom severity and fibroid volume continued to decrease during follow-up. The number of (S)AE was low and the re-intervention percentage at 3–33.6 months follow-up ranged from 0 to 21%. Reproductive outcomes were encouraging. Costs and HRQL were under-reported. Importantly, the symptom improvement in this review was greater compared to other MR-HIFU reviews and retreatment rates were lower [16,17]. So, implementing unrestrictive treatment protocols has led to better clinical outcome.

4.1. Quality of evidence

In general, all outcome parameters discussed in this review were influenced by the overall level of evidence which was poor to moderate. Only non-randomized, non-comparative trials were available for inclusion [24]. Sources leading to a high risk of bias were related to the specific study designs: inadequately reporting of loss to follow-up and potentially a selection bias. Weaknesses of the meta-analysis were caused by methodological limitations. Standard deviations often had to be estimated. Some studies were subject to loss of follow-up and some sub-studies were based on different sample sizes [27]. Therefore, the results should be interpreted with care. Moreover, results are based on reported means instead of individual patient data, thus ecological fallacy may have affected outcomes. Heterogeneity for each outcome parameter was often substantial, and mostly unexplained, questioning whether we should generalize our results. However, this method is valid because we used a random-effects model for meta-analysis [26].

4.2. Technical parameters

Decreases in the number of technical failures and treatment time in the extended patient cohorts suggests that increased experience enhances treatment efficacy. The shortest sonication time was reported by Xu et al, so the Chongqing system might improve treatment efficiency. The pooled NPV% directly post MR-HIFU was 68.1% which is higher than reported in other reviews [16,17], probably due to the exclusion of restrictive treatment protocols. Our results revealed a remarkable asymmetry in the distribution of scattered points into two groups. Unfortunately, we were unable to fully explain this. Only one borderline difference was found with the use of bowel-interference mitigation techniques suggesting that this may lead to higher NPV%. Interestingly, like Peregrino et al this review failed to show a statistically significant improvement in symptoms depending on different NPV% [16]. However, two of the included studies divided their patients into two groups based on NPV% and showed that higher NPV% result in better clinical outcomes [42,43]. One study showed that higher NPV% was associated with greater efficacy [36].

4.3. UFS-QoL

On average, the pooled tSSS was decreased and continued to improve during follow-up. There was no data available beyond 12 months. None of the included studies compared MR-HIFU to other treatment options. Jacoby et al did compare MRgFUS to placebo [34] and reported a larger tSSS decrease in the MRgFUS group, -31 *vs* -13 points, at 3-months follow-up. To compare the tSSS of MR-HIFU to other treatment options (UAE, hysterectomy and myomectomy), we searched other uterine fibroid trials that used the UFS-QoL questionnaire. Spies

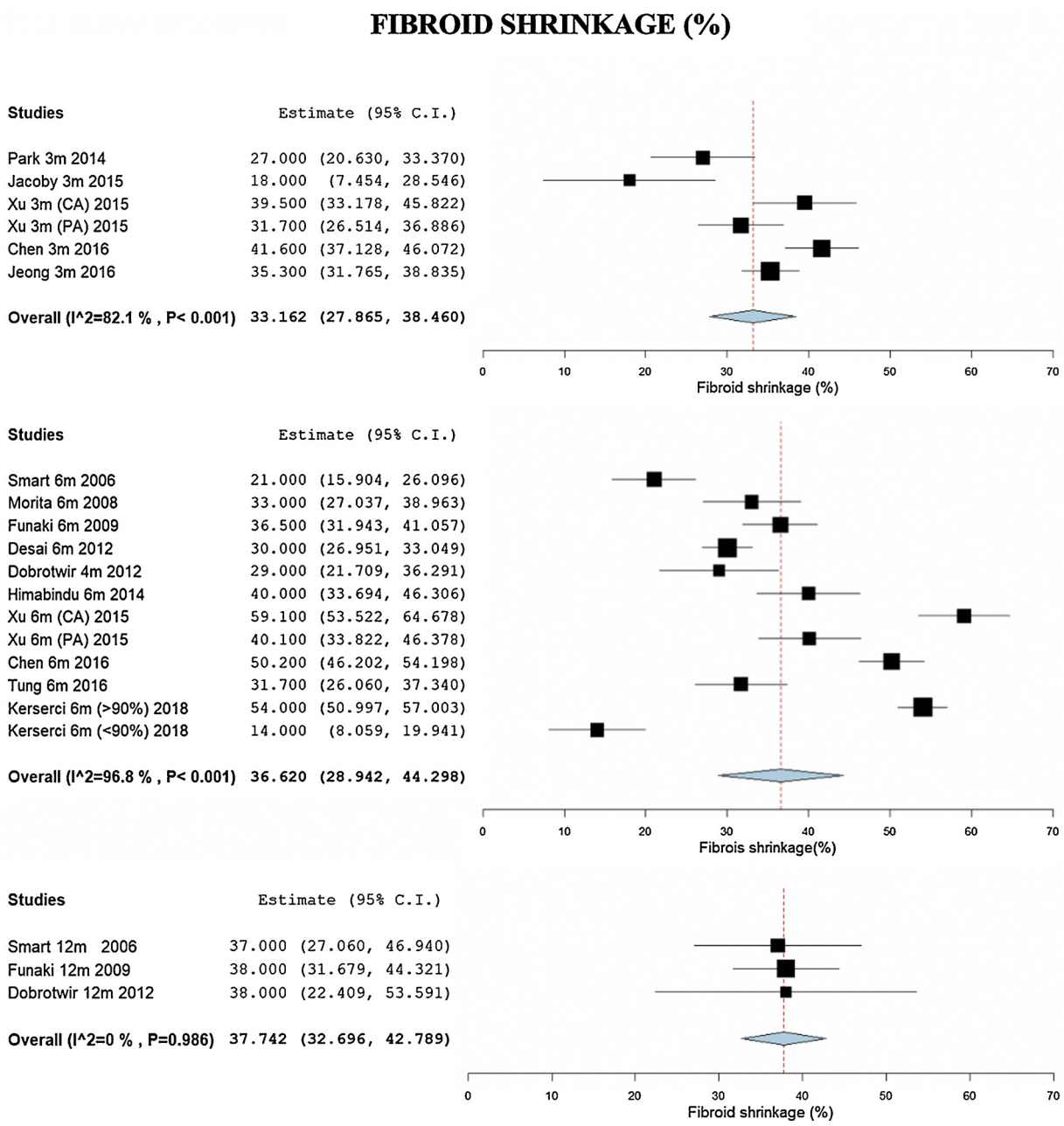

Fig. 5. Forest plots of fibroid shrinkage in percentage, stratified by follow-up category.

et al reported decreased tSSS: -40,2 for UAE, -40,5 for myomectomy and -57,3 for hysterectomy at 12-months follow-up [45]. The tSSS in the Fume trial [46] was -37.6 for myomectomy and -30,4 for UAE after 12-months. In this review, the tSSS at 12-months was -30.5, which is comparable to UAE, but less improvement compared to myomectomy and hysterectomy.

HRQL was clearly under-reported in this review which is remarkable because the HRQL is part of the UFS-QoL questionnaire. Three studies did show improved HRQL after MR-HIFU treatment. Jacoby et al showed greater HRQL improvement in the MRgFUS group compared to placebo, 27 *vs* 17-points.

4.4. Fibroid shrinkage

All studies showed fibroid shrinkage and the shrinkage percentage varied in time demonstrating that fibroids can continue to decrease in volume at least up to 1 year. A borderline significance was found between fibroid shrinkage and NPV% indicating that a higher NPV% could lead to more fibroid shrinkage. Please note that a follow-up MRI examination is expensive and often unnecessary.

4.5. Adverse events

The only two SAE's were reported in old studies [32,38] which could be explained by a small learning curve effect when MR-HIFU was implemented into clinical use [13]. Stratification of AE by system showed significantly more AE in trials using the Sonalleve system compared to the ExAblate device [29,35,37,43]. However, two ExAblate studies reported 'no unexpected or significant AE', suggesting under-reporting [22,41]. Moreover, there is no consensus on the definition of AE related to MR-HIFU. For example, abnormal vaginal discharge was often defined as AE, but one ExAblate study reported fibroid expulsion in 21% of their patients as normal finding [36]. Interestingly, a Sonalleve study reported constitutional symptoms as AE while none of

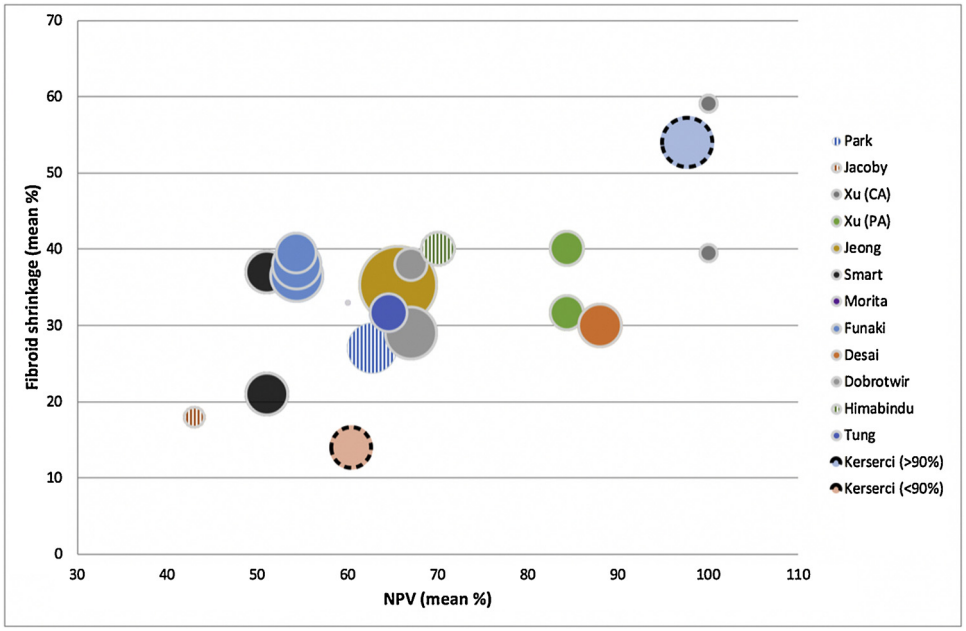

Fig. 6. Association between fibroid shrinkage percentage and NPV% directly post MR-HIFU, not stratified by follow-up category. Every study has a dot with a different color and all different time-points are shown. The size of the dot represents the number of patients.

the other studies reported this [37]. Although the difference between Sonalleve and ExAblate in AE might be explained by a reporting bias, it remains important to investigate this in the future.

4.6. Re-intervention percentage

The overall re-intervention percentage ranged from 0 to 21% at the end at follow-up (3–33.6 months). Longer follow-up was associated with a higher risk of further interventions. Unfortunately, due to the lack of longer follow-up data, it remains unclear whether MR-HIFU provides symptom relief until menopause without the need for additional therapy. No association was found with NPV%, tSSS or fibroid shrinkage, this may be explained by the exclusion of patients undergoing re-interventions from further follow-up. The re-intervention percentage in our review at 24-months ranged from 13 to 14% as reported by two studies (218 patients) [20,31]. This is comparable to the re-intervention percentage after UAE at 24-months. The EMMY trial [47] reported 23.5% re-interventions in the UAE group [48]. A review

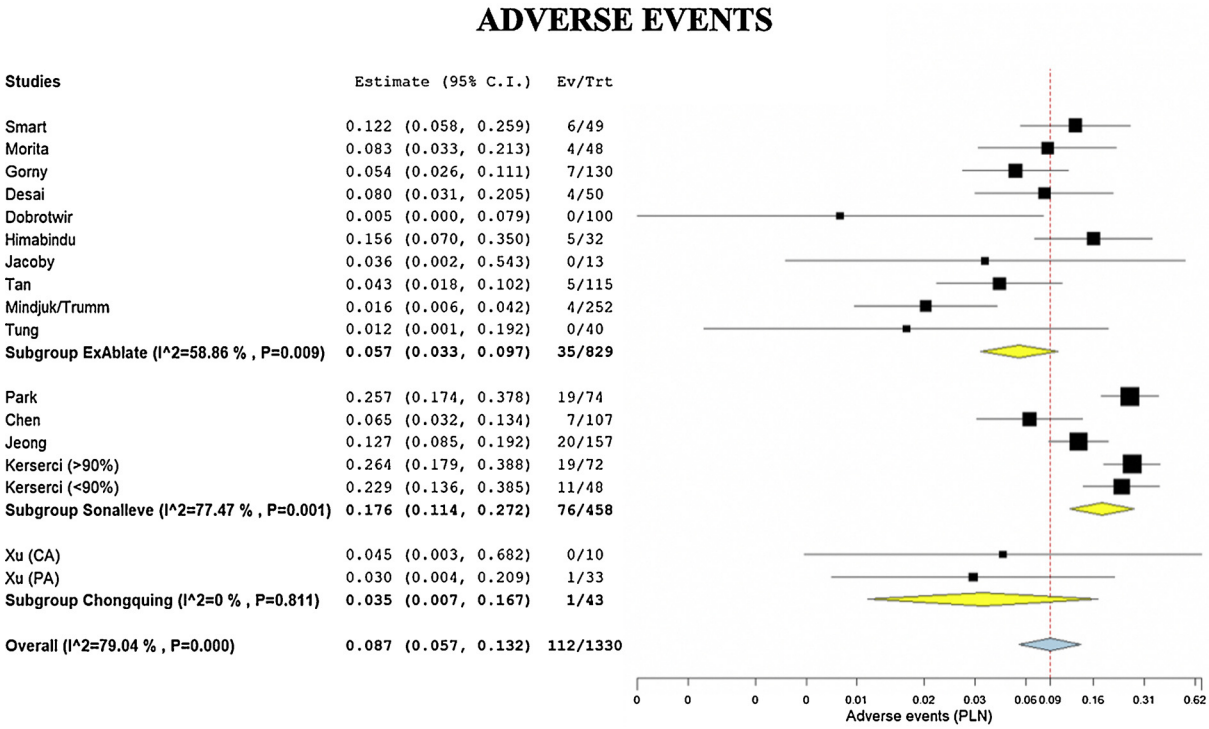

Fig. 7. Forest plots of AE during follow-up, stratified by system. Ev/trt: the reported number of AE and the number of patients treated. In the studies that reported no AE a percentage of 0.5% had to be imputed. Therefore, all percentages shown in the figures below are higher than in reality. PLN (Natural logarithm transformed proportion) was used.

Table 2
Number of re-interventions and re-intervention percentage at the end of the follow-up.

Study, year, length of follow-up in months (m)	Number of re-interventions/ number of patients	Re-intervention percentage (%)
Smart 2006, 12 m	*6/49*	*12.2%*
Morita 2008, 12 m	*2/48*	*4.0%*
Funaki 2009, 24 m	*7/57*	*12.3 %*
Gorny 2011, 33.6 m	*29/138*	*21.0%*
Desai 2012, 6 m	*0/50*	*0%*
Dobrotwir 2012, 12 m	*6/51*	*11.7%*
Himabindu 2014, 6 m	*0/32*	*0%*
Park 2014, 3 m	*0/74*	*0%*
Jacoby 2015, 3 m	*0/13*	*0%*
Tan 2015, 12 m	*9/100*	*9.0%*
Mindjuk 2015, 19.4 m	*28/221*	*12.7%*
Xu 2015, 6 m	*0/43*	*0%*
Chen 2016, 6 m	*1/107*	*0.9%*
Jeong 2016, 6 m	*9/157*	*5.7%*
Tung 2016, 6 m	*0/40*	*0%*
Kerserci 2018, 6 m	*0/120*	*0%*
Overall	97/1323	7.6%

comparing UAE with myomectomy and hysterectomy concluded that 15–32% will require further surgery within two years of UAE [49].

4.7. Reproductive outcomes

None of the included studies intended to investigate reproductive outcomes, but results were encouraging. Data is scarce since only one study investigated pregnancy outcomes after MR-HIFU treatment retrospectively [50]. However, the available evidence is reassuring [51], but our results must be interpreted with caution due to the very small number of post MR-HIFU pregnancies and the relative rarity of the pregnancy complications one might expect because of MR-HIFU (*i.e.* abnormal placentation, placental abruption and fetal growth restriction). Compared to myomectomy, the noninvasive character of MR-HIFU is advantageous for women trying to conceive because patients can attempt pregnancy much sooner. How MR-HIFU affects one's ability to conceive is unknown, although the finding that AMH levels did not change in three studies [43,52,53] suggests that ovarian function is not compromised by MR-HIFU.

4.8. Costs

Based on the included studies, it was impossible to analyze the cost-effectiveness of MR-HIFU therapy compared to other uterine fibroid treatments. Five cost-effectiveness analysis are published, but not included in this review [54–58]. They all suggested that MR-HIFU may be a cost-effective strategy at commonly accepted willingness-to-pay thresholds.

4.9. Future perspectives

Although MR-HIFU treatment of uterine fibroids has been performed for 14 years now, there is still no wide-spread implementation of MR-HIFU or reimbursement worldwide. A randomized controlled trial is the gold standard to obtain reimbursement and one is currently ongoing to compare UAE and MR-HIFU [59]. However, they experienced difficulties recruiting participants and some patients declined randomization. Thus, randomized trials are very hard to conduct and pose methodological challenges. To implement MR-HIFU treatment in regular clinical care, larger comparative controlled cohort studies with longer follow-up are warranted to define the role of MR-HIFU in the management of symptomatic uterine fibroids.

4.10. Core outcome set

Hitherto, there is no consensus on how to evaluate clinical outcome after MR-HIFU treatment. It is important to reach consensus, for example by developing a standardized Core Outcome Set [60], to improve the consistency of outcome reports in future MR-HIFU trials. Based on the outcomes identified via this systematic review we would recommend that clinical trials report the following outcomes: symptom improvement, QoL, NPV%, adverse events, fibroid shrinkage, re-intervention percentage, reproductive outcomes, recovery time and clinical efficacy. Symptom improvement and QoL should be assessed by a validated questionnaire such as the UFS-QoL [19]. Clinical efficacy should be a combination of symptom reduction and no re-intervention during follow-up [36]. Preferably, all patients are followed until menopause.

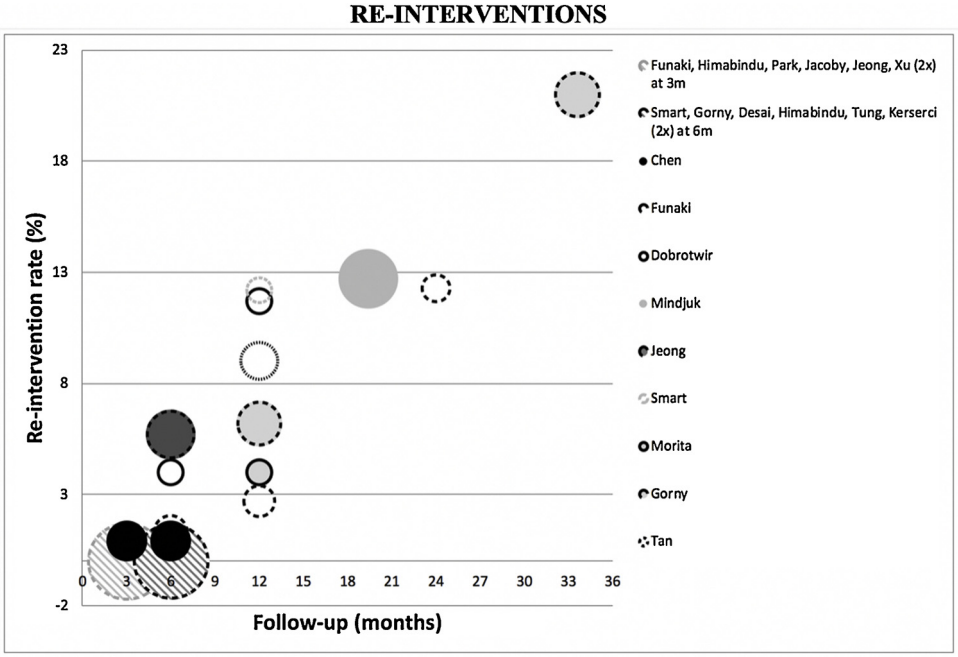

Fig. 8. Bubble chart of re-intervention percentage at follow-up. The size of the dot represents the number of patients.

Moreover, data of the patients undergoing an additional treatment should be published to identify risk factors for the need of re-interventions.

5. Conclusions

MR-HIFU therapy is a completely noninvasive safe therapy and is effective in alleviating fibroid-related symptoms for at least 12-months. Treatment protocols aiming for complete ablation led to better treatment outcomes. The re-intervention percentage is comparable to UAE at 24-months follow-up. Further trials should evaluate outcomes beyond 33.6 months and investigate reproductive outcomes. Moreover, controlled cohort trials are necessary to define the position of MR-HIFU compared to other treatment options for uterine fibroids.

Contribution to authorship

IV made a substantial contribution to the study design, acquisition of data, interpretation of data and writing of the manuscript. KJ made substantial contribution to the acquisition of data and interpretation of data. IN was involved in acquisition of data and had a contribution in analysing the data. JM and JR made a substantial contribution to the interpretation of the data. LB, CM and AF were involved in interpretation of data and drafting of the manuscript. ME had a major contribution in analysing the data. MB was responsible for the conception design of the study, interpretation of the data and drafting the article. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Disclosure

No grant or financial support was used for this research project. No author had any financial interest in the subject matter discussed in the submitted manuscript. No conflict of interest needs to be disclosed. All authors state that this study complies with the Declaration of Helsinki.

Appendix A

Literature search
National Guideline Clearinghouse
Keywords contains:

1 “Leiomyoma”: 5 hits
2 “Myoma”: 2 hits
3 “Fibroid”: 13 hits
4 “Uterine fibroid”: 12 hits
5 #1 OR #2 OR #3 OR #4: 13 hits
6 “HIFU”: 6 hits
7 “FUS”: 34 hits
8 “High Intensity Focused Ultrasound”: 33 hits
9 “Magnetic Resonance-Guided Focused Ultrasound”: 50 hits
10 “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 13 hits
11 #5 AND (#6 OR #7 OR #8 OR #9 OR #10): **12 hits**

Cochrane Library
Title, abstract, keywords contains:

1 “Leiomyoma”: 796 hits
2 “Myoma”: 643 hits
3 “Fibroid”: 311 hits
4 “Uterine Fibroid”: 120 hits
5 #1 OR #2 OR #3 OR #4:1298 hits
6 “HIFU”: 133 hits
7 “FUS”: 50 hits
8 “High Intensity Focused Ultrasound”: 195 hits
9 “Magnetic Resonance-Guided Focused Ultrasound”: 38 hits
10 “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 7 hits
11 #5 AND (#6 OR #7 OR #8 OR #9 OR #10): **43 hits**

TRIP
Keywords contains:

1 “Leiomyoma”: 3671 hits
2 “Myoma”: 913 hits
3 “Fibroid”: 4746 hits
4 “Uterine Fibroid”: 1206 hits
5 #1 OR #2 OR #3 OR #4: 5514 hits
6 “HIFU”: 691 hits
7 “FUS”: 12.753 hits
8 “High Intensity Focused Ultrasound”: 618 hits
9 “Magnetic Resonance-Guided Focused Ultrasound”: 101 hits
10 “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 34 hits
11 #5 AND (#6 OR #7 OR #8 OR #9 OR #10): 239 hits
12 #11 AND (“Magnetic resonance Imaging” OR “MRI”): **167 hits**

Medline/PubMed
Keywords contains:

1 “Leiomyoma” [Mesh]: 19,655 hits
2 “Leiomyoma” [tiab]: 9994 hits
3 "Leiomyoma"[tiab]) AND "Leiomyoma"[Mesh]: 7752 hits
4 "leiomyomas"[tiab]: 4488 hits
5 "Myoma"[tiab]: 3852 hits
6 "Myomas"[tiab]: 2140 hits
7 "Fibroid"[tiab]: 3124 hits
8 "Fibroids"[tiab]: 4122 hits 9. #3 OR #4 OR #5 OR #6 OR #7 OR #8: 19.247 hits
9 “High-Intensity Focused Ultrasound ablation” [Mesh]: 1679 hits
10 “High-Intensity Focused Ultrasound ablation”[tiab]: 242 hits
11 "High-Intensity Focused Ultrasound"[tiab]: 2542 hits
12 "focused ultrasound"[tiab]: 4552 hits
13 “Magnetic Resonance-Guided Focused Ultrasound” [tiab]:248 hits
14 “Magnetic Resonance-Guided High-Intensity Focused Ultrasound” [tiab]: 103 hits
15 #10 OR #11 OR #12 OR #13 OR #14 OR #15: 5020 hits
16 "Sonalleve"[tiab] OR "insightec"[tiab] OR "ExAblate 2000″[tiab]: 65 hits
17 “Magnetic Resonance Imaging"[Mesh]: 393,422 hits
18 “Magnetic Resonance Imaging"[tiab]: 198,173 hits
19 #18 OR #19: 464,194 hits
20 #9 AND #16: 408 hits
21 #20 AND #21 AND (("Treatment outcome"[MeSH Terms] OR "Follow-Up Studies"[MeSH Terms])): 87 hits.

13. #20 AND #21: **202 hits**
WHO International Clinical Trials Registry Platform (ICTRP)

1 “Leiomyoma”: 123 trials
2 “Myoma”: 103 trials
3 “Fibroid”: 112 trials
4 “Uterine Fibroid”: 60 trials
5 #1 OR #2 OR #3 OR #4: 298 trials
6 “HIFU”: 128 trials
7 “FUS”: 13 trials
8 “High Intensity Focused Ultrasound”: 143 trials
9 “Magnetic Resonance-Guided Focused Ultrasound”: **28 trials**
10 “Magnetic Resonance-Guided High-Intensity Focused Ultrasound”: 19 trials
11 #5 AND (#6 OR #7 OR #8 OR #9 OR #10): 440 trials

Embase

1 'leiomyoma'/exp OR 'leiomyoma': 23.539 hits
2 'myoma': 19.060 hits
3 'fibroid': 5598 hits
4 'uterine fibroid': 1658 hits
5 'uterine myoma': 14.251 hits
6 #1 OR #2 OR #3 OR #4 or #5: 38.641 hits
7 'HIFU': 3451 hits
8 'FUS': 3948 hits
9 'High Intensity Focused Ultrasound': 5341 hits
10 'Magnetic Resonance-Guided Focused Ultrasound': 417 hits
11 'Magnetic Resonance-Guided High-Intensity Focused Ultrasound': 146 hits
12 #6 AND (#7 OR #8 OR #9 OR #10 OR #11): 580 hits
13 #12 AND [English]/lim: 514 hits
14 'leiomyoma'/exp OR 'leiomyoma' AND ('high intensity focused ultrasound'/exp OR 'high intensity focused ultrasound') AND [English]/lim: 79 hits
15 ('leiomyoma'/exp OR 'leiomyoma') AND ('high intensity focused ultrasound'/exp OR 'high intensity focused ultrasound' OR 'magnetic resonance-guided high-intensity focused ultrasound'/exp OR 'magnetic resonance-guided high-intensity focused ultrasound' OR 'magnetic resonance-guided focused ultrasound'/exp OR 'magnetic resonance-guided focused ultrasound') AND [English]/lim: 116 hits

Total screened hits: 568 hits

References

[1] D.D. Baird, D.B. Dunson, M.C. Hill, D. Cousins, J.M. Schectman, High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence, Obstet. Gynecol. 188 (1) (2003) 100–107.
[2] E.A. Stewart, Uterine fibroids, Lancet (London, England) 357 (9252) (2001) 293–298.
[3] J.W. Aarts, T.E. Nieboer, N. Johnson, et al., Surgical approach to hysterectomy for benign gynaecological disease, Cochrane Database Syst. Rev. (8) (2015) CD003677.
[4] M.K. Whiteman, S.D. Hillis, D.J. Jamieson, et al., Inpatient hysterectomy surveillance in the United States, 2000–2004, Obstet. Gynecol. Surv. 63 (5) (2008) 304–305.
[5] E.P. Barnard, A.M. AbdElmagied, S.K. Laughlin-Tommaso, et al., Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis, Am. J. Obstet. Gynecol. 216 (5) (2017) 500.e1–500.e11.
[6] K. Hynynen, MRIgHIFU: A tool for image-guided therapeutics, J. Magn. Reson. Imaging 34 (3) (2011) 482–493.
[7] I. Rivens, A. Shaw, J. Civale, H. Morris, Treatment monitoring and thermometry for therapeutic focused ultrasound, Int. J. Hyperthermia 23 (2) (2007) 121–139.
[8] F.M. Fennessy, C.M. Tempany, N.J. McDannold, et al., Uterine leiomyomas: MR Imaging–guided focused ultrasound surgery—results of different treatment protocols, Radiology 243 (3) (2007) 885–893.
[9] S.D. LeBlang, K. Hoctor, F.L. Steinberg, Leiomyoma shrinkage after MRI-guided focused ultrasound treatment: report of 80 patients, AJR Am. JR 194 (1) (2010) 274–280.
[10] V. Froeling, K. Meckelburg, N.F. Schreiter, et al., Outcome of uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for uterine fibroids: long-term results, Eur. J. Radiol. 82 (12) (2013) 2265–2269.
[11] H.S.M. Kim, J.M. Baik, L.D.M. Pham, M.A.P. Jacobs, MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata : long-term outcomes, Acad. Radiol. 18 (8) (2011) 970–976.
[12] Y. Morita, S. Takeuchi, H. Hikida, H. Ohashi, N. Ito, Decreasing margins to the uterine serosa as a method for increasing the volume of fibroids ablated with magnetic resonance-guided focused ultrasound surgery, Eur. J. Obstet. Gynecol. Reprod. Biol. 146 (1) (2009) 92–95.
[13] A. Okada, Y. Morita, H. Fukunishi, K. Takeichi, T. Murakami, Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population: impact of the learning curve on patient outcome, Ultrasound Obstet. Gynecol. 34 (5) (2009) 579–583.
[14] K. Funaki, H. Fukunishi, T. Funaki, K. Sawada, Y. Kaji, Maruo, Takeshi Department of Electrical Engineering, Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images, Obstet. Gynecol. 196 (2) (2007) 184.e1–184.e6.
[15] S. Gizzo, C. Saccardi, T.S. Patrelli, et al., Magnetic resonance-guided focused ultrasound myomectomy: safety, efficacy, subsequent fertility and quality-of-life improvements, a systematic review, Reprod Sci (Thousand Oaks, Calif.) 21 (4) (2014) 465–476.
[16] P.F.M. Peregrino, M. de Lorenzo Messina, R. Dos Santos Simoes, J.M. Soares-Junior, E.C. Baracat, Review of magnetic resonance-guided focused ultrasound in the treatment of uterine fibroids, Clinics Sao Paulo (Sao Paulo) 72 (10) (2017) 637–641.
[17] G. Pron, Magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU) treatment of symptomatic uterine fibroids: an evidence-based analysis, Ont. Health Technol. Assess. Ser. 15 (4) (2015) 1–86.
[18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P.R.I.S.M.A. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269 W64.
[19] J.B. Spies, K. Coyne, N. Guaou Guaou, D. Boyle, K. Skyrnarz-Murphy, S.M. Gonzalves, The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata, Obstet. Gynecol. 99 (2) (2002) 290–300.
[20] K.K. Funaki, H. Fukunishi, K. Sawada, Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up, Ultrasound Obstet. Gynecol. 34 (5) (2009) 584–589.
[21] Y. Morita, N. Ito, H. Hikida, S. Takeuchi, K. Nakamura, H. Ohashi, Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids - early experience, Eur. J. Obstet. Gynecol. Reprod. Biol. 139 (2) (2008) 199–203.
[22] A. Dobrotwir, E. Pun, Clinical 24 month experience of the first MRgFUS unit for treatment of uterine fibroids in Australia, J. Med. Imaging Radiat. Oncol. 56 (4) (2012) 409–416.
[23] D. Sacks, T.E. McClenny, J.F. Cardella, C.A. Lewis, Society of interventional radiology clinical practice guidelines, J. Vasc. Interv. Radiol. 14 (9) (2003) S199–S202.
[24] B. Phillips, C. Ball, D. Sackett, et al., Oxford Centre for Evidence–based Medicine Levels of Evidence, (2009).
[25] C. Moga, B. Guo, D. Schopflocher, C. Harstall, Development of a quality appraisal tool for case series studies using a modified delphi technique, Edmonton AB: Inst. Health Econ. (2012).
[26] M. Borenstein, L.V. Hedges, J.P.T. Higgins, H.R. Rothstein, A basic introduction to fixed-effect and random-effects models for meta-analysis, Res. Synth. Methods 1 (2) (2010) 97–111.
[27] J.P.T. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions, Available from The Cochrane Collaboration, 2011, www.handbook.cochrane.org.:.
[28] B.C. Wallace, I.J. Dahabreh, T.A. Trikalinos, J. Lau, P. Trow, C.H. Schmid, Closing the gap between methodologists and end-users: r as a computational back-end, J. Stat. Softw. 49 (5) (2012).
[29] R. Chen, B. Kerserci, H. Bi, et al., The safety and effectiveness of volumetric magnetic resonance-guided high-intensity focused ultrasound treatment of symptomatic uterine fibroids: early clinical experience in China, J. Ther. Ultrasound 4 (2016).
[30] S.B. Desai, A.A. Patil, R. Nikam, A.S. Desai, V. Bachhav, Magnetic resonance-guided focused ultrasound treatment for uterine fibroids: first study in indian women, J. Clin. Imaging Sci. 2 (2012).
[31] K.R.P. Gorny, B.J.P. Borah, D.L.M. Brown, D.A.M. Woodrum, E.A.M. Stewart, G.K.M. Hesley, Incidence of additional treatments in women treated with MR-Guided focused US for symptomatic uterine fibroids: review of 138 patients with an average follow-up of 2.8 years, J. Vasc. Interv. Radiol. 25 (10) (2014) 1506–1512.
[32] K.R.P. Gorny, D.A.M. Woodrum, D.L.M. Brown, et al., Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients, J. Vasc. Interv. Radiol. 22 (6) (2011) 857–864.
[33] Y. Himabindu, M. Sriharibabu, V. Nyapathy, A. Mishra, Early evaluation of magnetic resonance imaging guided focused ultrasound sonication in the treatment of uterine fibroids, Indian J. Med. Res. 139 (2) (2014) 267–272.
[34] V.L. Jacoby, M.P. Kohi, L. Poder, A. Jacoby, J. Lager, M. Schembri, PROMISe trial: a pilot, randomized, placebo-controlled trial of magnetic resonance guided focused ultrasound for uterine fibroids, Fertil. Steril. 105 (3) (2016) 773–780.
[35] J.H. Jeong, G.P. Hong, Y.R. Kim, J.E. Ha, K.S. Lee, Clinical consideration of treatment to ablate uterine fibroids with magnetic resonance imaging-guided high intensity focused ultrasound (MRgFUS): sonalleve, J. Menopausal Med. 22 (2) (2016) 94–107.
[36] I. Mindjuk, C.G. Trumm, P. Herzog, R. Stahl, M. Matzko, MRI predictors of clinical success in MR-guided focused ultrasound (MRgFUS) treatments of uterine fibroids: results from a single centre, Eur. Radiol. 25 (5) (2015) 1317–1328.
[37] M.J. Park, Y.S. Kim, H. Rhim, H.K. Lim, Safety and therapeutic efficacy of complete or near-complete ablation of symptomatic uterine fibroid tumors by MR imaging-guided high-intensity focused US therapy, J. Vasc. Interv. Radiol. 25 (2) (2014) 231–239.
[38] O.C. Smart, J.T. Hindley, L. Regan, W.M.W. Gedroyc, Magnetic resonance guided focused ultrasound surgery of uterine fibroids–the tissue effects of GnRH agonist pre-treatment, Eur. J. Radiol. 59 (2) (2006) 163–167.
[39] N. Tan, D. Lu, S. Raman, S. Bahrami, MR guided focused US for treatment of uterine fibroids: symptom reduction in a multicenter trial using a novel treatment algorithm, J. Ther. Ultrasound 3 (Suppl. 1) (2015) O91.
[40] C.G. Trumm, R. Stahl, D.A. Clevert, et al., Magnetic resonance imaging-guided focused ultrasound treatment of symptomatic uterine fibroids: impact of technology advancement on ablation volumes in 115 patients, Invest. Radiol. 48 (6) (2013) 359–365.
[41] S.L. Tung, T.Y. Chou, H.S. Tseng, C.M. Lee, A retrospective study of magnetic resonance-guided focused ultrasound ablation for uterine myoma in Taiwan, Taiwanese J. Obstet. Gynecol. 55 (5) (2016) 646–649.
[42] Y. Xu, Z. Fu, L. Yang, Z. Huang, W.Z. Chen, Z. Wang, Feasibility, safety, and efficacy of accurate uterine fibroid ablation using magnetic resonance imaging-guided high-

intensity focused ultrasound with shot sonication, J. Ultrasound Med. 34 (12) (2015) 2293–2303.
[43] B. Keserci, N.M. Duc, Magnetic resonance imaging parameters in predicting the treatment outcome of high-intensity focused ultrasound ablation of uterine fibroids with an immediate nonperfused volume ratio of at least 90%, Acad. Radiol. 25 (2018) 1257–1269.
[44] B. Keserci, N.M. Duc, Volumetric magnetic resonance-guided high-intensity focused ultrasound ablation of uterine fibroids through abdominal scars: the impact of a scar patch on therapeutic efficacy and adverse effects, J. Ther. Ultrasound 5 (2017) 22.
[45] J.B. Spies, L.D. Bradley, R. Guido, G.L. Maxwell, B.A. Levine, K. Coyne, Outcomes from leiomyoma therapies: comparison with normal controls, Obstet. Gynecol. 117 (4) (2011) 987–988.
[46] I.T. Manyonda, M. Bratby, J.S. Horst, N. Banu, M. Gorti, A. Belli, Uterine artery embolization versus myomectomy: impact on quality of life—results of the FUME (Fibroids of the uterus: myomectomy versus embolization) trial, Cardiovasc. Intervent. Radiol. 35 (3) (2012) 530–536.
[47] N.A. Volkers, W.J.K. Hehenkamp, E. Birnie, W.M. Ankum, J.A. Reekers, Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial, Am. J. Obstet. Gynecol. 196 (6) (2007) 519e1.
[48] A.M. de Bruijn, W.M. Ankum, J.A. Reekers, et al., Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial, Obstet. Gynecol. 215 (6) (2016).
[49] J.K. Gupta, A. Sinha, M.A. Lumsden, M. Hickey, Uterine artery embolization for symptomatic uterine fibroids, Cochrane Database Syst. Rev. (12) (2014) CD005073.
[50] J. Rabinovici, M. David, H. Fukunishi, Y. Morita, B.S. Gostout, E.A. Stewart, Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery for conservative treatment of uterine fibroids, Obstet. Gynecol. Surv. 65 (5) (2010) 316–318.
[51] J. Keltz, M. Levie, S. Chudnoff, Pregnancy outcomes after direct uterine myoma thermal ablation: review of the literature, J. Minim. Invasive Gynecol. 24 (4) (2017) 538–545.
[52] J.S. Lee, G.Y. Hong, K.H. Lee, T.E. Kim, Changes in anti-müllerian hormone levels as a biomarker for ovarian reserve after ultrasound-guided high-intensity focused ultrasound treatment of adenomyosis and uterine fibroid, BJOG 124 (2017) 18–22.
[53] V.Y. Cheung, T.P. Lam, C.R. Jenkins, G.K. Cheung, S.S. Chan, W.K. Choi, Ovarian reserve after ultrasound-guided high-intensity focused ultrasound for uterine fibroids: preliminary experience, J. Obstet. Gynaecol. Can. 38 (4) (2016) 357–361.
[54] H. Zowall, J.A. Cairns, C. Brewer, D.L. Lamping, W.M.W. Gedroyc, L. Regan, Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids, Obstet. Gynecol. Surv. 63 (7) (2008) 427–428.
[55] A.K. O'Sullivan, D. Thompson, P. Chu, D.W. Lee, E.A. Stewart, M.C. Weinstein, Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids, Int. J. Technol. Assess. Health Care 25 (1) (2009) 14–25.
[56] C.Y. Kong, L. Meng, Z.B. Omer, et al., MRI-guided focused ultrasound surgery for uterine fibroid treatment: a cost-effectiveness analysis, Am. J. Roentgenol. 203 (2) (2014) 361–371.
[57] A.H. Cain-Nielsen, J.P. Moriarty, E.A. Stewart, B.J. Borah, Cost-effectiveness of uterine-preserving procedures for the treatment of uterine fibroid symptoms in the USA, J. Comp. Eff. Res. 3 (5) (2014) 503–514.
[58] V. Babashov, S. Palimaka, G. Blackhouse, D. O'Reilly, Magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU) for treatment of symptomatic uterine fibroids: an economic analysis, Ont. Health Technol. Assess. Ser. 15 (5) (2015) 1–61.
[59] S.K. Laughlin-Tommaso, A.L. Weaver, L.E. Vaughan, V. Jacoby, E.A. Stewart, Long term outcomes in a randomized controlled trial of uterine artery embolization and MR-guided focused ultrasound: the firstt study, Fertil. Steril. 108 (3) (2017) e26.
[60] P.R. Williamson, D.G. Altman, J.M. Blazeby, et al., Developing core outcome sets for clinical trials: issues to consider, Trials 13 (132) (2012).