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Original Articles

Percutaneous radiofrequency ablation for symptomatic uterine leiomyomas: a systematic review and meta-analysis

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Summary

Purpose: To evaluate the efficacy and safety of percutaneous radiofrequency ablation (RFA) in the treatment of uterine leiomyomas. *Materials and Methods:* Medline, Embase, and Cochrane databases were searched through August 2014 for all relevant studies on RFA for uterine leiomyomas. The efficacy and safety of RFA were assessed using the outcome measures of tumor volume, symptom severity score, health-related quality of life (HRQL) score, procedure-related complications, and reintervention. The authors calculated pooled event rates with 95% confidence intervals using random-effects model to assess the effects of RFA. *Results:* Eight observational studies were identified as eligible for inclusion in this meta-analysis and included 370 patients. All analyzed outcomes showed statistically significant improvements from baseline to final follow-up. Twenty-seven complications were identified and five of them qualified as major complications. Five patients required reintervention after RFA. *Conclusions:* Percutaneous RFA is an effective and safe treatment for patients with uterine leiomyomas.

Key words: Uterus; Leiomyomas; Radiofrequency ablation; Meta-analysis.

Introduction

Uterine leiomyomas (also called uterine myomas or uterine fibroids) are the most common solid benign pelvic tumors in the female reproductive system, causing significant morbidity including pain, pelvic pressure, menstrual disorder, and reproductive dysfunction [1, 2]. Although hysterectomy and myomectomy are the two conventional treatments, minimally invasive techniques have become increasingly accepted as alternative therapeutic modalities for symptomatic uterine leiomyomas. Since the first report from Lee [3] in 2002, radiofrequency ablation (RFA) has emerged as an effective treatment option for patients with symptomatic leiomyomas [4]. Image-guided percutaneous RFA also has advantages over surgery by potentially causing less morbidity and mortality, with reduced cost, and hospital stay.

The authors carried out a systematic review and meta-analysis to assess the efficacy and safety of RFA for symptomatic uterine leiomyomas based on all relevant studies.

Materials and Methods

This meta-analysis was performed according to guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [5]. Two authors (K.J.L. and J.H.K.) independently performed the literature search, eligibility assessment, data extraction, and quality assessment. A third author (D.Y.Y.) was consulted for discrepancies.

Literature search

The authors conducted a systematic review and meta-analysis of studies reporting the use, efficacy, and safety of RFA for the treatment of symptomatic uterine leiomyomas. Scientific articles were retrieved from the databases of Medline, Embase, and Cochrane Library from the time of inception to August 2014, and a search of relevant citations in appropriate articles was performed. Keyword search was conducted using combinations with Boolean operators "OR" and "AND" with the following medical subject heading (MeSH) terms and free-words: ("radiofrequency ablation" or "RFA") and ("uterus" or "uterine") and ("myoma" or leiomyoma" or fibroid"). The authors limited searches to publications of human studies reported in English.

Criteria for inclusion and exclusion

Articles were manually selected from the results as they pertained to the treatment of symptomatic uterine leiomyomas with RFA, with a set of predetermined inclusion and exclusion criteria. The study inclusion criteria for this systematic review and meta-analysis were as follows: 1) original articles, 2) cohort of patients aged over 18 years with a diagnosis of uterine leiomyomas treated with RFA, 3) minimum of ten patients treated, 4) study that assessed at least one clinical outcome measure, such as tumor vol-

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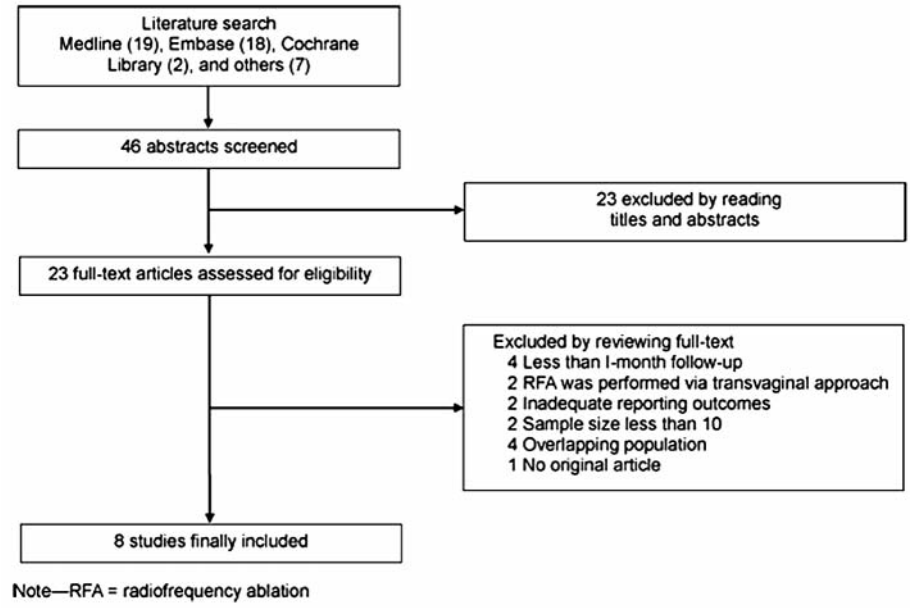

Figure 1. — Flowchart showing process of selection of articles reviewed in this study.

ume change, symptomatic improvement, procedure-related complication, and reintervention, and 5) clinical and imaging follow-up for at least one month. The rationale for the last of these inclusion criteria was that the majority of complications typically occur during or soon after the RFA procedure; thus, one-month follow-up duration captures a significant proportion of all complications.

Abstracts, letters to the editors, reviews without original data, expert opinions, editorials, supplements, case reports, systematic reviews, and studies in which the outcomes were not clearly reported were excluded from the analysis. Studies that mixed other effective interventions (i.e., uterine arterial embolization, other type thermal ablative therapy, and surgery) simultaneously in the same subject(s) were also excluded. Finally, studies on transvaginal RFA were excluded from this meta-analysis, because there is a basic difference between percutaneous and transvaginal approaches for RFA of leiomyomas. If multiple studies were reported by the same institution and/or authors, the one with the highest-quality data was included in the analysis.

Data extraction

Data were extracted from the entire content of each identified article using standardized forms. Descriptive data extracted from each study included the first author, country, year of publication, study design (prospective or retrospective; there were no randomized controlled trials [RFAs] or comparative studies), number of patients, age of patients, RFA system, and length of follow-up.

The outcome measures included change in tumor volume, change in symptom severity score, change in health-related quality of life (HRQL) score, major and minor complication rates, procedure-related mortality, and reintervention rates. Major complications were defined as those requiring hospitalization for therapy, prolongation of inpatient hospital stay (> 48 hours), or involving permanent adverse sequelae. The reintervention included repeated RFA procedure, uterine arterial embolization (UAE), myomectomy, and hysterectomy. When multiple follow-up data points were available, all post-treatment outcomes for each subject were abstracted from the longest follow-up data, with the exception of complications and reinterventions.

Data analysis

Statistical analyses of selected studies were performed with Cochrane Review Manager (RevMan) version 5.2 and the Comprehensive Meta-Analysis version 2.2. For the change in tumor volume, change in symptom severity score, and change in HRQL score, the standardized mean difference between pretreatment and post-treatment with a 95% confidence interval (95% CI) was calculated. For each meta-analysis, the I^2 tests were first calculated to assess the heterogeneity of the included studies. Studies without significant heterogeneity ($I^2 < 50$ %) were analyzed with a fixed-effects model, and studies with significant heterogeneity ($I^2 > 50$ %) were analyzed using a random-effects model to pool the results. In addition, the risk of bias of included studies was assessed by using Cochrane Collaboration's tool [6].

Results

Selection and characteristics of included studies

The PRISMA flowchart of the search and selection of studies is depicted in Figure 1. The extensive electronic search led to the identification of 46 articles. After screening the titles and abstracts of the search results, 23 studies were found to be eligible and their full-text publications were analyzed. Of these, 15 full-text articles were excluded, because they did not meet the predefined inclusion criteria. Finally, eight studies [7–14] published between 2005 and 2014 were included in this systematic review and meta-analysis.

All eight studies were prospective observational studies; no RCTs or comparative studies were found. There were a total of 370 patients with uterine leiomyoma treated with percutaneous RFA. The design and baseline characteristics of included studies are described in Table 1. Final follow-

Table 1. — *Baseline characteristics of the studies included in the meta-analysis.*

First author (reference)	Country	Year of Publication	Study design	No. of patients	Age (years)* of patients	RFA System	Follow-up interval (months)*
Bergamini V. [7]	Italy	2005	Prospective	18	44.3 ± 2.5	RITA model	1, 3, 6, 9, 12
Ghezzi F. [8]	Italy	2007	Prospective	25	42.2 ± 2.5	RITA model	6, 12, 24, 36
Carrafiello G. [9]	Italy	2010	Prospective	11	40.4 ± 6.0	Le Veen coaxial	1, 3, 6, 9, 12
Garza Leal J.G. [10]	Mexico	2011	Prospective	31	40.2 ± 5.9	Halt 2000	3, 6, 12
Iversen H. [11]	Denmark	2012	Prospective	46	44.6 ± 7.5	RITA model	3, 6, 9
Chudnoff S.G. [12]	USA	2013	Prospective	135	42.4 ± 4.7	Accessa system	3, 6, 12
Robles R. [13]	Guatemala	2013	Prospective	35	43.6 ± 4.7	Halt Medical	3, 6, 12
Galen D.I. [14]	USA	2014	Prospective	69	42.1 ± 5.5	Accessa system	3, 6, 12

*mean ± standard deviation. Note—RFA = radiofrequency ablation.

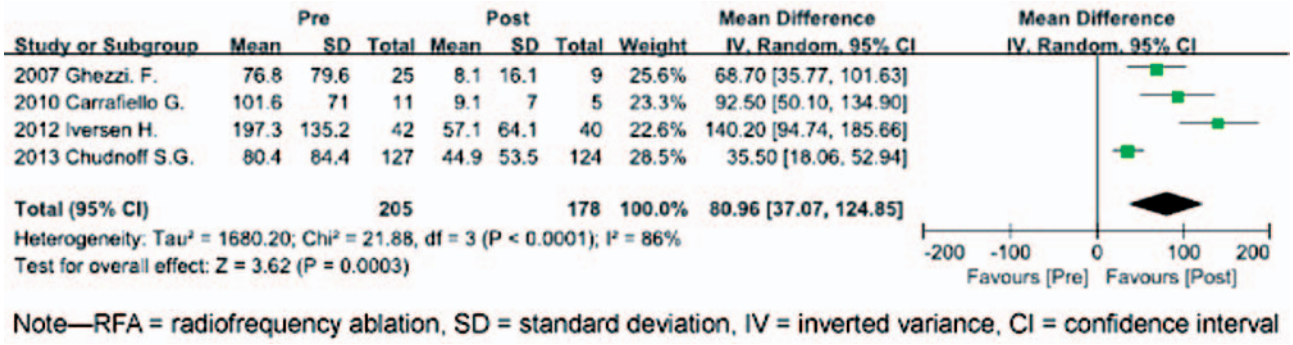

Figure 2. — Forest plot of change in tumor volume at 9-36 months after RFA.

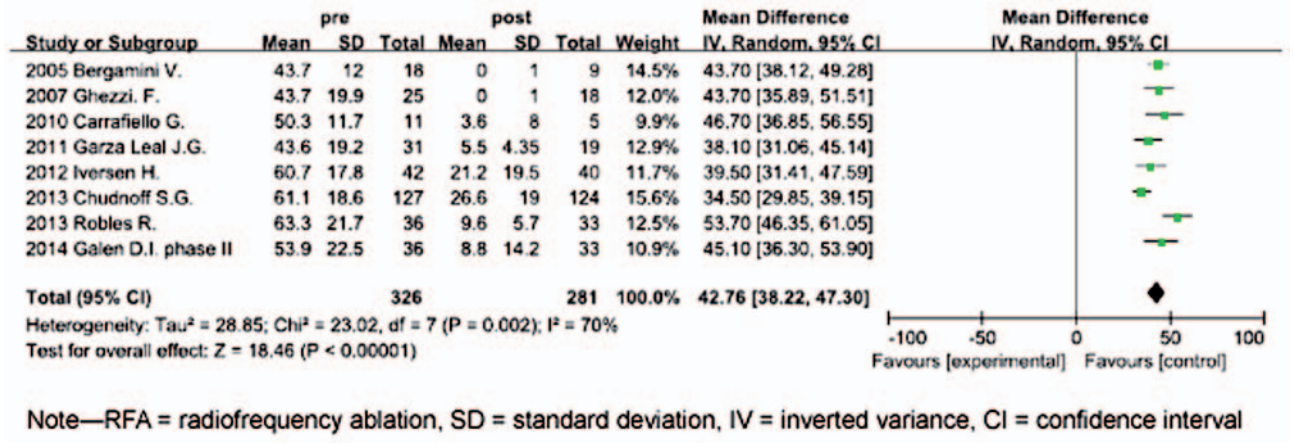

Figure 3. — Forest plot of change in symptom severity score at 9-24 months after RFA.

up time varied from nine to 36 months, with a duration of 12 months or shorter in six (75%) of studies.

Outcome assessment

In the analyses of the effects of RFA on tumor volume, symptom severity score, and HRQL score, there were significant heterogeneity among the studies (I^2 = 86%, 70%, and 76%, respectively), thus the random-effects model was used to pool the results. The pooled meta-analysis of these data demonstrated a statistically significant change in tumor volume of –80.96 ml (95% CI: –37.07 to –124.85), with follow-up ranging from nine to 36 months (Figure 2). The change in symptom severity score was statistically significant, with a mean of –42.76 (95% CI: –38.22 to –47.30), at 9–24 months' follow-up (Figure 3). The change in HRQL score was also statistically significant, with a mean of 38.34 (95% CI: 33.02 to 43.65) at 9–24 months' follow-up (Figure 4).

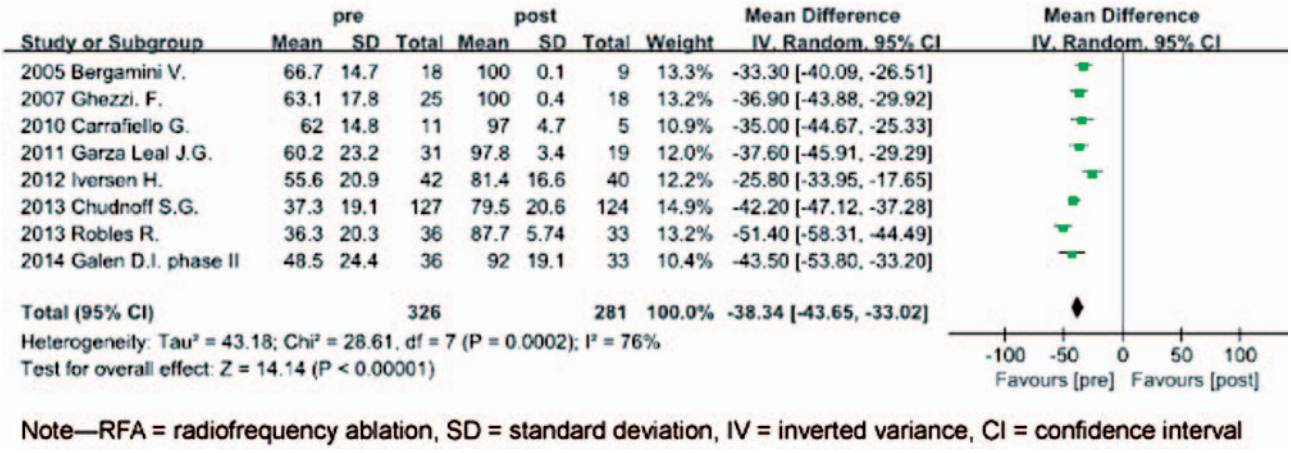

Figure 4. — Forest plot of change in health related quality of life score at 9-24 months after RFA.

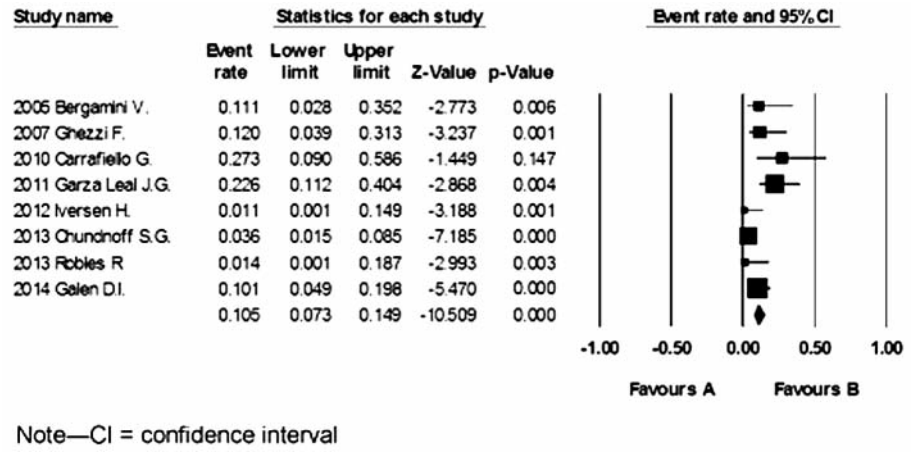

Figure 5. — Forest plot of complication rate.

Table 2. — *Complication rates in eight case studies (n = 370).*

Complications	No. of patients	Rate (%)	95% CI
Abdominal pain	16	4.32	2.67~6.94
Urinary tract infection	4	1.08	0.41~2.84
Abdominal wall hematoma	2	0.54	0.14~2.13
Abnormal fluid collection	1	0.27	0.04~1.89
Uterine serosal burn	1	0.27	0.04~1.89
Pelvic abscess	1	0.27	0.04~1.89
Sigmoid colon laceration	1	0.27	0.04~1.89
Vaginal bleeding	1	0.27	0.04~1.89

Note—CI = confidence interval.

Table 3. — *Reintervention rates in eight case studies (n = 370).*

Reinterventions	No. of Patients	Rate (%)	95% CI
Hysterectomy	4	1.08	0.41~2.84
Uterine artery embolization	1	0.27	0.04~1.89

Note—CI = confidence interval.

The pooled proportion of complication rate for RFA was 10.5% (95% CI: 7.3%–14.9%) (Figure 5). Table 2 summarizes the 27 complications found in the review. The most commonly reported complication was abdominal pain with 16 reported cases (59.3 % of total complications). There were five adverse events (including two abdominal wall hematomas, one pelvic abscess, one sigmoid colon laceration, and one vaginal bleeding) that could have been considered major complications. There were no reported deaths as a result of RFA or a related complication. A total of five reinterventions occurred, with the pooled rate of 2.7% (95% CI: 1.3–5.6%) (Figure 6). There were four hysterectomies and a UAE procedure performed across all the studies (Table 3).

Risk of bias

The risk of bias in this meta-analysis was assessed by Cochrane Collaboration's tool, and the outcome is shown in Figure 7. The percentages of high risk of bias in "Were incomplete outcome data adequately addressed?" and "Was

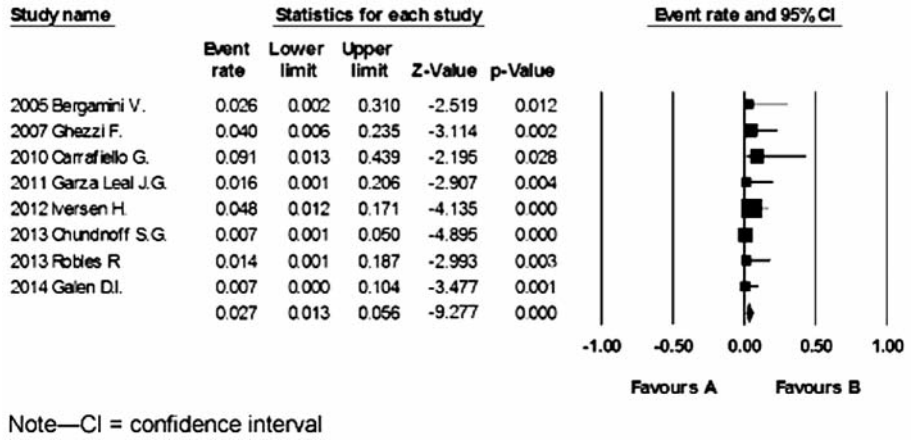

Figure 6. — Forest plot of reintervention rate.

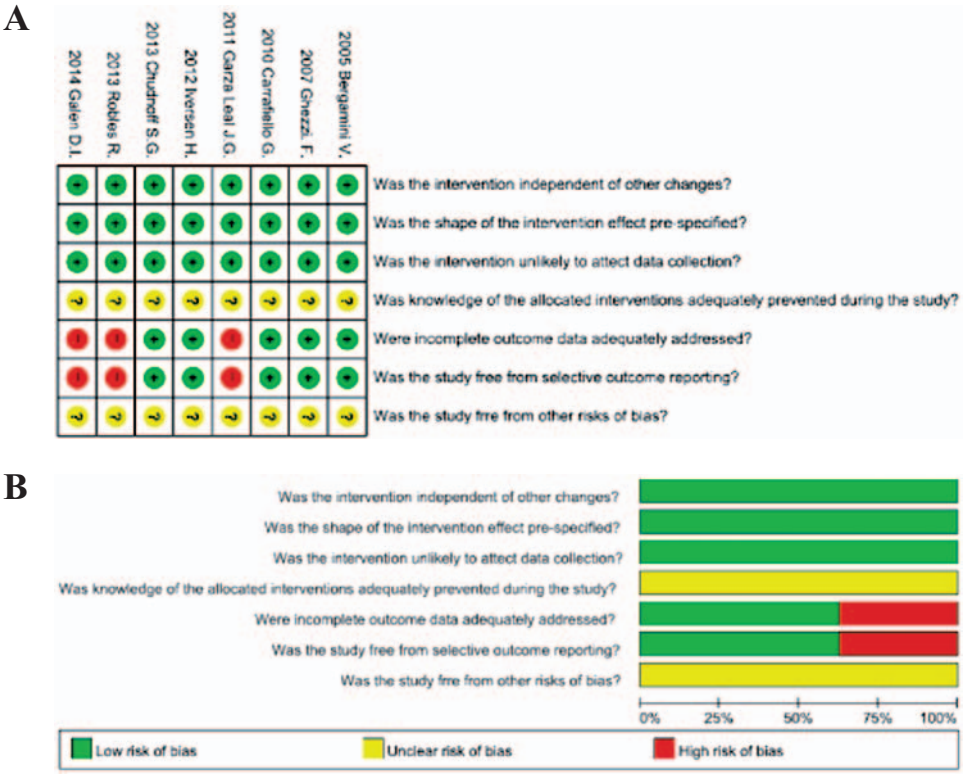

Figure 7. — Assessment of risk of bias in this meta-analysis. A) Summary of risk of bias for each trial assessed by Cochrane Collaboration' tool; plus sign was for a judgment of "yes or low risk of bias", minus sign was for a judgment of "no or high risk of bias", and question mark was for a judgment of "unclear, or uncertain risk of bias", which indicates there was insufficient information to permit a judgment of yes or no. B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

the study free from selective outcome reporting?" were both 50%, thus there were attrition bias and reporting bias in this meta-analysis.

Discussion

Although surgical resection remains the standard treatment for uterine leiomyomas, RFA has been accepted as one of the non-surgical treatment options for patients with symptomatic leiomyomas [7–14]. RFA causes tumor cell destruction through the application of a high frequency alternating current that generates high frictional heat leading to protein denaturation and coagulation necrosis [15, 16]. The major advantage of RFA therapy is to destroy tumor cells without damaging adjacent vital structures. In addition, RFA can be performed in a minimally invasive fashion under ultrasound guidance, which is used for accurate localization of the probe within the tumor [16].

Although there are several articles in the literature supporting the application of RFA in the treatment of patients with symptomatic leiomyomas, the available evidence from those studies is weak due to the sparseness of data, disagreements among studies, the limited number of observa-

tions, or the lack of a systematic review. Meta-analysis is an important tool that combines the genotyping data from all eligible published studies and has the advantage of increasing statistical power and reducing random error, thus defining the effect of clinical interventions more precisely [17]. To the authors' knowledge, there has been no previous comprehensive systematic review or meta-analysis of RFA in the treatment of uterine leiomyomas. Thus, to provide the most comprehensive assessment of the efficacy and safety of RFA for leiomyomas, they performed this meta-analysis in which eight studies were finally included.

The outcomes from the present meta-analysis showed statistically significant improvements from baseline to final follow-up, including reduction in tumor volume, decrease of symptom severity score, and improvement of HRQL score. However, it should be noted that there was no consistency in follow-up durations between studies. Variable length of follow-up durations can affect the degree of tumor volume reduction and symptom improvement.

This systematic review and meta-analysis summarizes the available evidence on complication and reintervention rates of RFA in the treatment of leiomyomas. Although several complications were noted in the included studies, most of them were either easily managed or self-limiting, thus considered minor complications. Abdominal pain and urinary tract infection were the most commonly reported complications. Although the authors did not perform a subgroup analysis on this item owing to the limited data, the forest plot of complication rate of this meta-analysis showed lower rate of complications in more recent studies published in or after 2012 when compared with studies published before 2012 (Figure 5). Possible explanations for this difference are improved selection of patients for RFA, advanced techniques and devices, and greater operator experience in the procedure.

Only one study [9] included in the preset meta-analysis classified specific complications into major or minor categories. According to 'The Society of Interventional Radiology clinical practice guidelines' [18], major complications are events that may result in hospitalization for therapy, prolongation of inpatient hospital stay (> 48 hours) or permanent adverse sequelae. Based on this grading system for complications, the authors categorized minor and major complications in this review. Only five major complications of RFA were reported at a rate of approximately 1.4% in this study. However, none of these events resulted in death.

An additional outcome evaluated in this meta-analysis was the rate of reintervention to manage the residual uterine leiomyoma. The results of the present study showed that the pooled rate of reintervention after RFA was 2.7% within nine to 24 months after the procedure. The early reintervention after RFA might be related to the residual tumor tissue, which is mostly caused by insufficient tumor ablation. In cases of uterine leiomyoma in dangerous locations, it is often difficult to achieve curative tumor ablation by securing a specific safety margin in three dimensions. In contrast, late reintervention may be associated with tumor progression after RFA. Accordingly, the relatively short follow-up period in the present meta-analysis (9–24 months) may underestimate the precise reintervention rate.

Currently, there are no meta-analyses comparing the efficacy and safety of RFA and other less invasive therapy for uterine leiomyomas. Toor *et al.* [19] conducted a meta-analysis consisting of 54 studies for evaluation of the effects of UAE, including major complications and reintervention. In their study, the major complication rate defined by the same criteria to the present study was 2.9% (95% CI, 2.2–3.8%) and the rate of hysterectomy for resolution of a complication was 0.7% (95% CI, 0.5–0.9%). Although not directly comparable, the outcomes of the present meta-analysis indicated that RFA had lower rate of major complication and higher rate of reintervention than UAE.

Some possible limitations in this meta-analysis must be acknowledged. First, the present review mainly suffers from lack of RCTs comparing the use of RFA with other surgical or non-surgical treatment. The ten case series included in this meta-analysis were all observational studies. Second, the reported data in all reported series has been heterogeneous in terms of patient selections, utilization of RFA systems, and definitions of complications. All of these may have led to significant between-study heterogeneity for the outcome measurement. Third, the relatively short follow-up periods and the relatively small number of included patients make the interpretation of the efficacy of RFA difficult. Approximately half of patients (in seven of ten studies) included in the present meta-analysis had a follow-up duration that is equal to or less than 12 months. The relatively short follow-up period in included studies may result in the potential underestimation of the calculated complication and reintervention rates. Finally, the present authors did not include non-English language publications, which may create language bias. It has been well known that studies with statistically significant (positive) results are more likely to be published in English [20].

Conclusion

In conclusion, the results of this meta-analysis showed that RFA is a safe and effective treatment for symptomatic uterine leiomyomas. However, higher quality clinical trials are needed to identify this outcome and to provide sufficient evidence on the matter.

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