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Original Article

Comparative Meta-analysis of Radiofrequency Ablation and Microwave Ablation for the Treatment of Benign Thyroid Nodules

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Abstract:
Background: The efficacy and safety of radiofrequency ablation (RFA) and microwave ablation (MWA) in treating benign thyroid nodules (BTNs) remains unclear. This study was aimed to compare the efficacy and safety of RFA and MWA in treating BTNs.
Methods: A systematic search of PubMed, Embase, and Cochrane databases was conducted up to September 11, 2023, to identify relevant studies. The primary outcomes included volume reduction rate (VRR), symptomatic and cosmetic scores analyzed using standardized mean difference (SMD), and complications assessed by risk difference (RD).
Results: A meta-analysis of five eligible studies demonstrated that RFA and MWA had comparable pooled 3-month and 6-month VRRs (56.0% vs. 53.9%, p = .668; 80.8% vs. 74.9%, p = .080). However, RFA exhibited a significantly higher VRR than MWA after 12 months (86.2% vs. 80.0%, p = .036). Furthermore, both RFA and MWA showed significant reductions in pooled symptomatic and cosmetic scores over time, with no statistically significant differences between the two groups at 6 and 12 months. Additionally, there were no significant differences in the incidence of major or minor complications between RFA and MWA.
Conclusion: The meta-analysis indicates that both RFA and MWA are effective and relatively safe treatments for BTNs, with RFA potentially offering a slight advantage in long-term volume reduction. Nevertheless, further research is warranted to validate these findings and determine the optimal treatment strategy for BTNs.
Keywords: radiofrequency ablation, microwave ablation, meta-analysis, benign thyroid nodules

1. Introduction

Thyroid nodules are prevalent in clinical settings, affecting up to 68% of the general population. Among these, around 90% are benign, often asymptomatic, and typically require only periodic monitoring. However, certain cases necessitate intervention due to compressive symptoms, cosmetic concerns, or the potential for malignant transformation. While conventional surgery remains the standard for treating benign thyroid nodules (BTNs), it poses risks such as recurrent laryngeal nerve injury, damage to the parathyroid gland, hypothyroidism, and scarring [1].

Alternative therapies, including radioiodine therapy and thyroid-stimulating hormone suppression, have drawbacks. Consequently, ultrasound-guided thermal ablation, specifically radiofrequency ablation (RFA) or microwave ablation, emerges as a promising option for BTNs treatment [2].

RFA, a widely employed thermal ablation technique, has demonstrated effectiveness and safety in treating BTNs. Recent studies indicate a substantial reduction in mean nodule volume, ranging from 72.9% to 86.6% at the 12-month follow-up. microwave ablation, a more recent percutaneous thermal ablation technique, boasts advantages such as consistently higher intra-tumoral temperatures, faster ablation times, and an improved convection profile compared to RFA. The mean volume reduction rate (VRR) after microwave ablation at the 12-month follow-up ranges from 75% to 92.4%. Despite these advantages, limited research has directly compared the efficacy and safety of RFA and microwave ablation in treating BTNs. Therefore, a comprehensive analysis based on published data is essential [3].

This systematic review and meta-analysis aim to assess the efficacy and safety of RFA compared to microwave ablation in treating BTNs. We will evaluate parameters such as VRRs, symptomatic and cosmetic scores, and complications to provide a thorough understanding of their relative effectiveness and safety profiles [4].

1. Meterials and methods

2.1 Refining the Search Approach

To enhance the comprehensiveness of literature retrieval and reduce language and publication bias, this study conducted additional searches in the Web of Science, Scopus, China National Knowledge Infrastructure (CNKI), Wanfang, and KoreaMed databases, based on the PubMed, Embase, and Cochrane databases. The search time frame extended from the inception of each database to September 11, 2023. The search strategy combined both MeSH terms and free-text keywords, including "radiofrequency ablation," "RFA," "microwave ablation," "MWA," "benign thyroid nodule," and "volume reduction." Notably, this study did not impose language restrictions, and all Chinese and Korean literature were included in the initial screening to ensure that relevant data on microwave ablation in the Asian regions were identified. A search using the keywords "radiofrequency ablation, Meta-analysis, Benign thyroid nodules" in PubMed yielded 23 relevant articles. After a rigorous selection process (see Figure 1 flowchart), five studies were ultimately included [5].

2.2 Criteria for Inclusion and Exclusion

To ensure the relevance and reliability of the selected studies, we established specific criteria for inclusion and exclusion. Inclusion criteria encompassed: (1) studies involving human subjects; (2) direct comparisons of clinical outcomes between RFA and microwave ablation for BTNs; (3) reporting of volume reduction ratios (VRRs) at 3-, 6-, or 12-month follow-ups and complications. Exclusion criteria comprised: (1) duplicates, reviews, conference abstracts, case reports, letters, and animal studies; (2) studies lacking sufficient data for VRR calculation; (3) studies not published in English.

2.3 Data Extraction and Quality Assessment

Two independent investigators, DMG and ZC, undertook the meticulous extraction of data and assessment of study quality. Information gathered included: (1) study characteristics (author, publication year, country, study type, number of patients and nodules); (2) demographic and clinical characteristics of patients (sex, age, nodule volume, and follow-up); (3) VRRs, symptomatic scores, cosmetic scores; (4) major and minor complications. Follow-up evaluations at the third, sixth, and twelfth months postoperatively were chosen based on the common practice in previous articles. The VRR was calculated using the formula: [(initial nodular volume − final nodular volume) × 100]/initial nodular volume. Ablation-related major and minor complications were defined according to the Society of Interventional Radiology. Given that the studies included in this meta-analysis were all observational cohort studies rather than randomized controlled trials, the Cochrane Collaboration's tool was deemed less suitable. Therefore, we utilized the ROBINS-I (Risk Of Bias In Non-randomized Studies—of Interventions) tool to conduct a detailed assessment of each study in terms of selection bias, information bias, confounding bias, and other factors. Additionally, to complement the evaluation, we applied the Newcastle-Ottawa Scale (NOS) for further assessment. Two independent reviewers scored each study, and any discrepancies were resolved through discussion to reach a consensus [6].

2.4 Statistical Analysis and Synthesis

In assessing the heterogeneity among studies, we employed the Chi-square test and I2 statistic. A random-effects model was implemented for meta-analysis if the p-value of the Chi-square test <0.05; otherwise, a fixed-effects model was applied. Pooled VRRs were determined using an inverse-variance weighting model. Symptomatic and cosmetic scores were analyzed using standard mean differences (SMD) with 95% confidence intervals (95%CI), while complications were analyzed using risk difference (RD) with 95%CI. Statistical analyses were conducted using R version 3.6.1 with the 'meta' package, with a significance level set at $p < .05$. To address the issue of missing data in some of the studies (e.g., the missing age data marked as 'NA' in the study by Korkusuz et al., 2018), this study employed Multiple Imputation (MI) to handle the data gaps. The specific process was as follows: (1) Detection of Missing Data Distribution and Pattern: The distribution and pattern of missing data were assessed. (2) Imputation Model Construction: An imputation model was built using the Predictive Mean Matching (PMM) method, generating five complete datasets. (3) Independent Analysis of Each Dataset: Each of the five datasets was analyzed independently, and the results were combined using Rubin's rules. (4) Sensitivity Analysis: A sensitivity analysis was performed to compare the results before and after imputation, ensuring that the handling of missing data did not significantly affect the overall conclusions [6].

3. Results

3.1 Literature Search

The systematic approach to our study selection is schematically represented in Figure1. An initial identification yielded 39 records from databases including PubMed, Embase, and the Cochrane Library. After deduplication, 13 studies were excluded. The title and abstract screening phase led to the exclusion of 20 more publications based on criteria such as reviews, conference abstracts, irrelevant studies, or incomplete clinical trials. A subsequent meticulous full-text review of 6 articles resulted in the exclusion of one non-English publication. Ultimately, our meta-analysis incorporated 5 eligible studies.

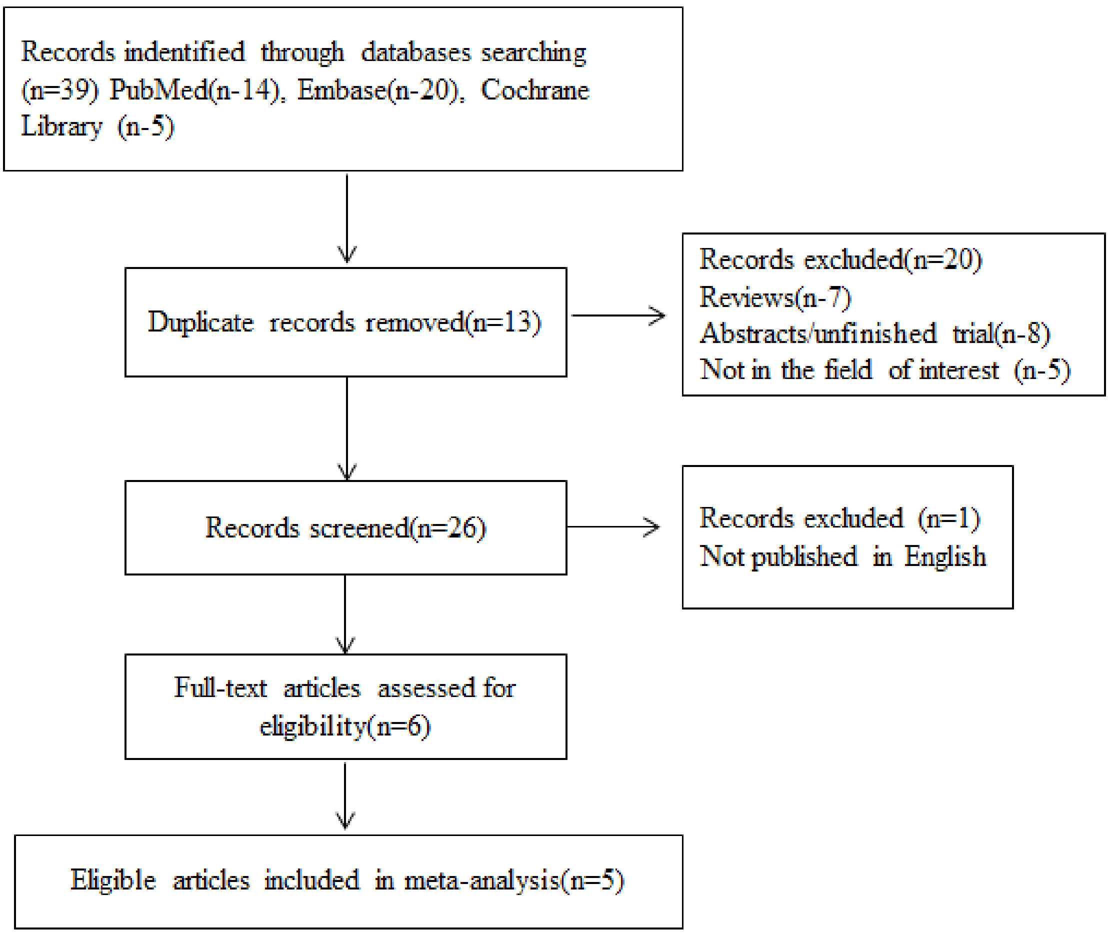

Figure 1. Searching and selection flow diagram of literatures.

3.2 Characteristics of Studies and Quality Assessment

We provide an exhaustive overview of the key characteristics of the eligible articles, as shown in Table 1. After an extended search and rigorous selection process, this study ultimately included five cohort studies. The RFA group comprised a total of 899 patients, while the MWA group included 869 patients. Notably, there were significant variations in sample sizes across the studies. For instance, in the study by Cheng et al., the RFA group had 649 patients, while in the study by Hu et al., the RFA group had only 72 patients [7-9]. Such extreme differences may have increased the overall heterogeneity ($I^2 > 90\%$) and could potentially introduce bias in the combined effect estimate. To address this, we conducted subgroup analyses and meta-regression in subsequent analyses to explore the sources of heterogeneity. Additionally, sensitivity analyses were performed to evaluate the impact of large versus small sample sizes on the overall conclusions [10-12]. Three studies originated from China, with the remaining two conducted in Germany. Notably, the preoperative mean nodule volume was not significantly different between the RFA (9.0 ml, 95%CI: 2.1-15.9 ml) and MWA groups (8.5 ml, 95%CI: 2.2–14.9 ml; p = .923). As depicted in Figure 2, quality assessments of the included studies were performed using the Cochrane Collaboration's tool, which revealed concerns regarding blinding of participants and personnel (performance bias) and blinding of outcome assessment (detection bias) in most studies [13-15].

Table 1. Characteristics of the included studies [10-21]

Author, Year	**Study type**	**patients/nodules (n/n)**	**Male/Female**	**age (year)**	**nodule volume (ml)**	**Follow-up (months)**
Vorländer, 2018	Cohort	36/40 24/25	12/24 9/15	54 ± 12 57 ± 13	29.44 ± 30.09 23.90 ± 17.35	3 3
Yue, 2016	Cohort	102/102 102/102	27/75 28/74	46.4 ± 13.3 49.5 ± 10.2	6.6 ± 4.9 6.2 ± 4.6	10.7 ± 5.1 10.6 ± 2.8
Cheng, 2017	Cohort	649/687 603/664	140/509 135/468	47.9 ± 13.6 47.1 ± 12.9	7.22 ± 6.76 7.72 ± 9.16	13.5 ± 6.3 13.9 ± 6.0
Hu, 2019	Cohort	72/72 100/100	25/47 34/66	46.3 ± 16.3 52.0 ± 15.9	10.7 ± 5.9 13.0 ± 7.9	12 12
Korkusuz, 2018	Cohort	40/55 40/47	18/22 19/21	NA NA	26.23 ± 26.59 30.57 ± 24.99	3 3

	Yue 2016	Vorländer 2018	Korkusuz 2018	Hu 2019	Cheng 2017
Random sequence generation (selection bias)	+	+	?	+	+
Allocation concealment (selection bias)	+	?	?	?	+
Blinding of outcome assessment (detection bias)	?	?	?	?	+
Blinding of participants and personnel (performance bias)	?	?	?	?	+
Incomplete outcome data (attrition bias)	+	-	-	+	+
Selective reporting (reporting bias)	+	+	+	+	+
Other bias	+	?	?	?	+

Figure 2. Bias risks in the included studies for the meta-analysis.

3.3 Comparison of VRRs between RFA and Microwave Ablation

All studies reported Volume Reduction Ratios (VRRs) at 3 months for both RFA and MWA, with three studies providing additional data at 6 and 12 months. As illustrated in Figure 3, the aggregated VRRs post-RFA at the 3-, 6-, and 12-month follow-ups were 56.0% (95%CI: 48.6%–63.6%, I2 = 97.9%), 80.8% (95%CI: 76.8%–84.8%, I2 = 92.3%), and 86.2% (95%CI: 81.6%–90.9%, I2 = 95.3%), respectively. In contrast, the aggregated VRRs post-MWA at the same intervals were 53.9% (95%CI: 47.6%–60.1%, I2 = 92.8%), 74.9% (95%CI: 69.5%–80.2%, I2 = 88.5%), and 80.0% (95%CI: 76.6%–83.5%, I2 = 74.1%), respectively. No significant differences were observed between RFA and MWA in the aggregated VRRs at 3 months (56.0% vs. 53.9%, p = .668) or 6 months (80.8% vs. 74.9%, p = .080). However, a significantly greater reduction in nodule volume was noted with RFA compared to MWA at the 12-month follow-up (86.2% vs. 80.0%, p = .036). Pronounced heterogeneities were present in both the RFA and MWA groups, and publication bias was not assessed due to the limited number of studies included [16].

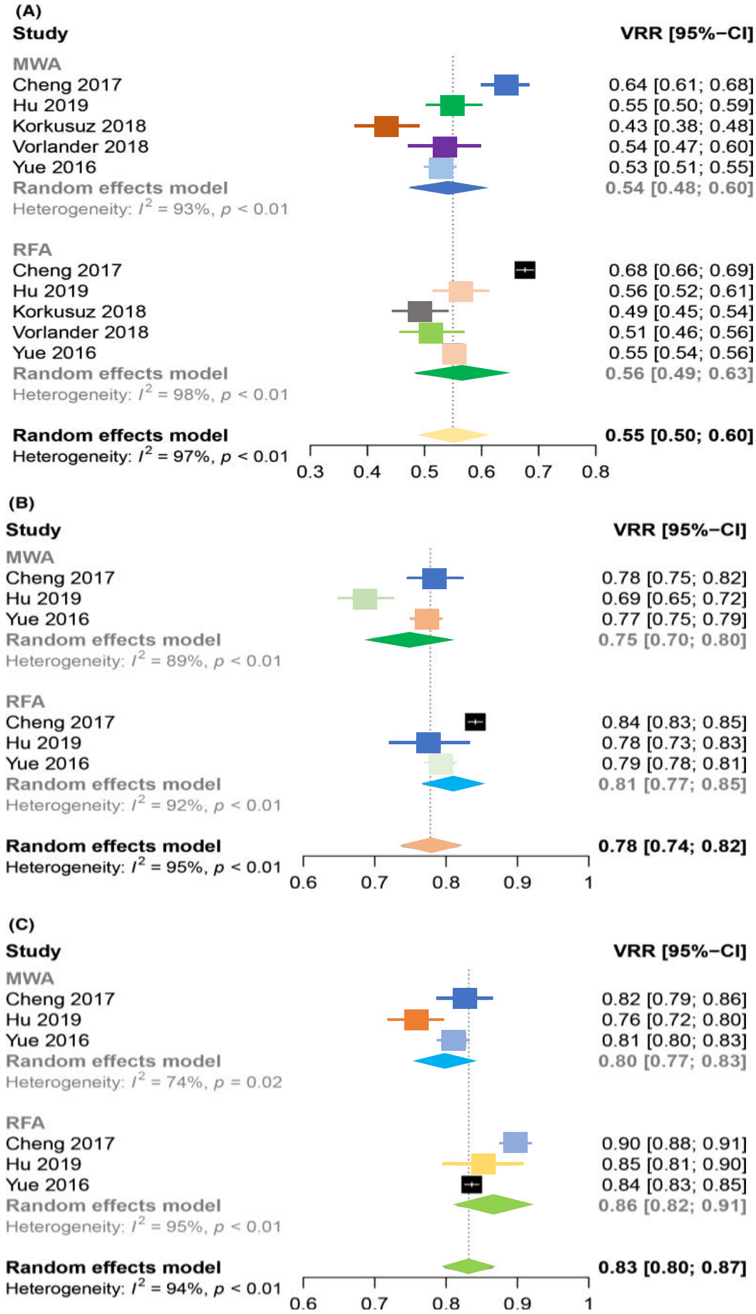

Figure 3. Rates of pooled volume reduction (VRRs) for benign thyroid nodules after microwave ablation and RFA treatment at different time points: (A) 3-month, (B) 6-month, (C) 12-month.

3.4 Symptomatic and Cosmetic Scores

Symptomatic and cosmetic scores post-treatment with both RFA and MWA were reported in three studies. In the RFA cohort (Figure 4), pooled symptomatic scores showed a significant decrease at both 6 and 12 months (SMD = 1.17, 95%CI: 0.36-1.98, p = .005; SMD = 1.46, 95%CI: 0.29–2.62, p = .014), and pooled cosmetic scores also demonstrated a marked reduction at these intervals (SMD = 0.87, 95%CI: 0.77–0.97, p < .001; SMD = 1.21, 95%CI: 0.66–1.76, p < .001).

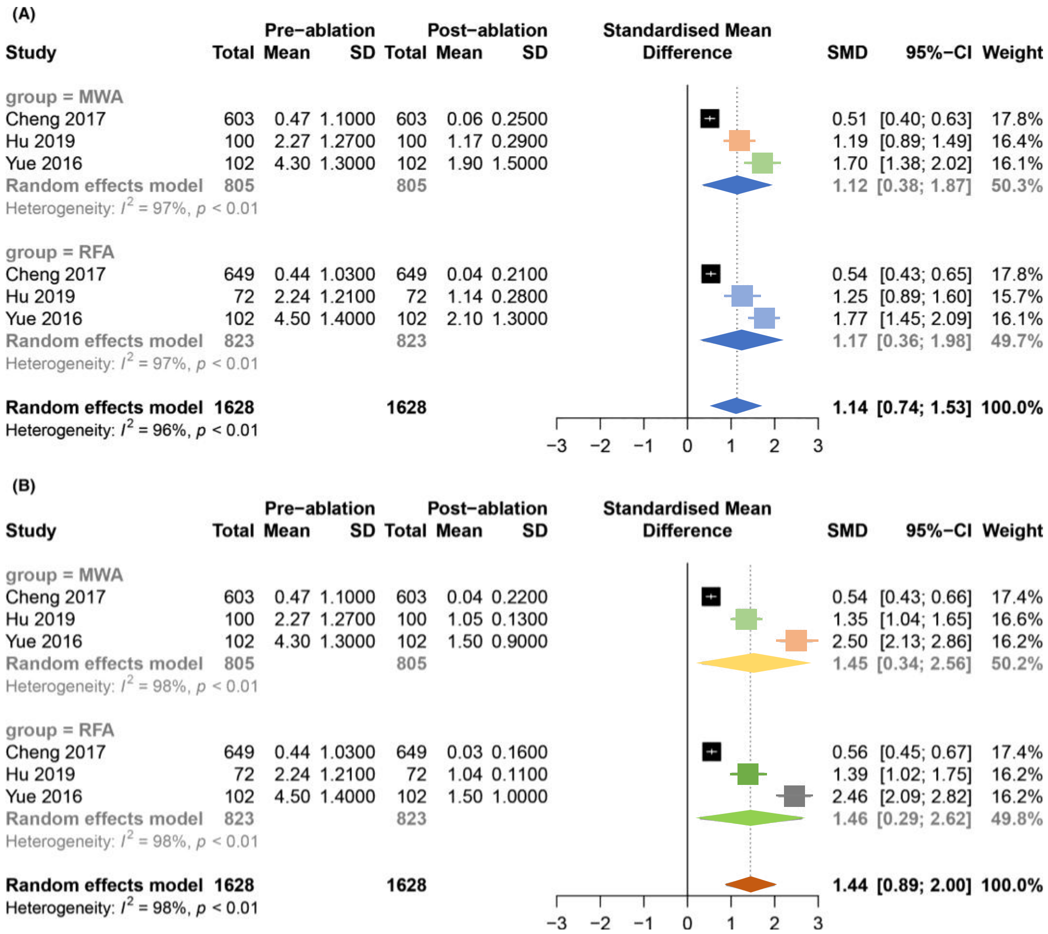

Figure 4. Forest plots of symptom improvement analyzed by standardized mean difference (SMD) after microwave ablation and RFA treatment at different time points: (A) 6-month, (B) 12-month.

In the MWA group (Figure 5), significant declines in symptomatic scores (SMD = 1.12, 95%CI: 0.38–1.87, p = .003; SMD = 1.45, 95%CI: 0.34–2.56, p = .011) and cosmetic scores (SMD = 0.94, 95%CI: 0.84-1.04, p < .001; SMD = 1.15, 95%CI: 0.83–1.47, p < .001) were also observed. No significant differences in symptom improvement were found between the two modalities at 6 (p = .930) and 12 (p = .993) months. Likewise, cosmetic outcomes did not significantly diverge between RFA and MWA at 6 (p = .334) and 12 (p = .872) months [17-19]. Thirty-seven major complications were reported following RFA, while fifty major complications followed MWA. For minor complications, forty instances were associated with RFA and thirty-six with MWA. A detailed breakdown of complications is presented in Table 2. As illustrated in Figure 6, the analysis of complications indicated that the overall risk difference between RFA and MWA (risk difference RD = -0.02, 95% CI: -0.05 to +0.01, p = 0.107) did not reach statistical significance. However, considering the very low incidence of rare adverse events (such as recurrent laryngeal nerve injury and skin burns), we further conducted a statistical power analysis using G*Power software [20-22]. The results revealed that the current overall sample size had a detection power of approximately 60% for these low-incidence adverse events, which is insufficient to adequately detect rare complications. Future studies should consider increasing the sample size or integrating individual patient data (IPD) to enhance statistical power [23].

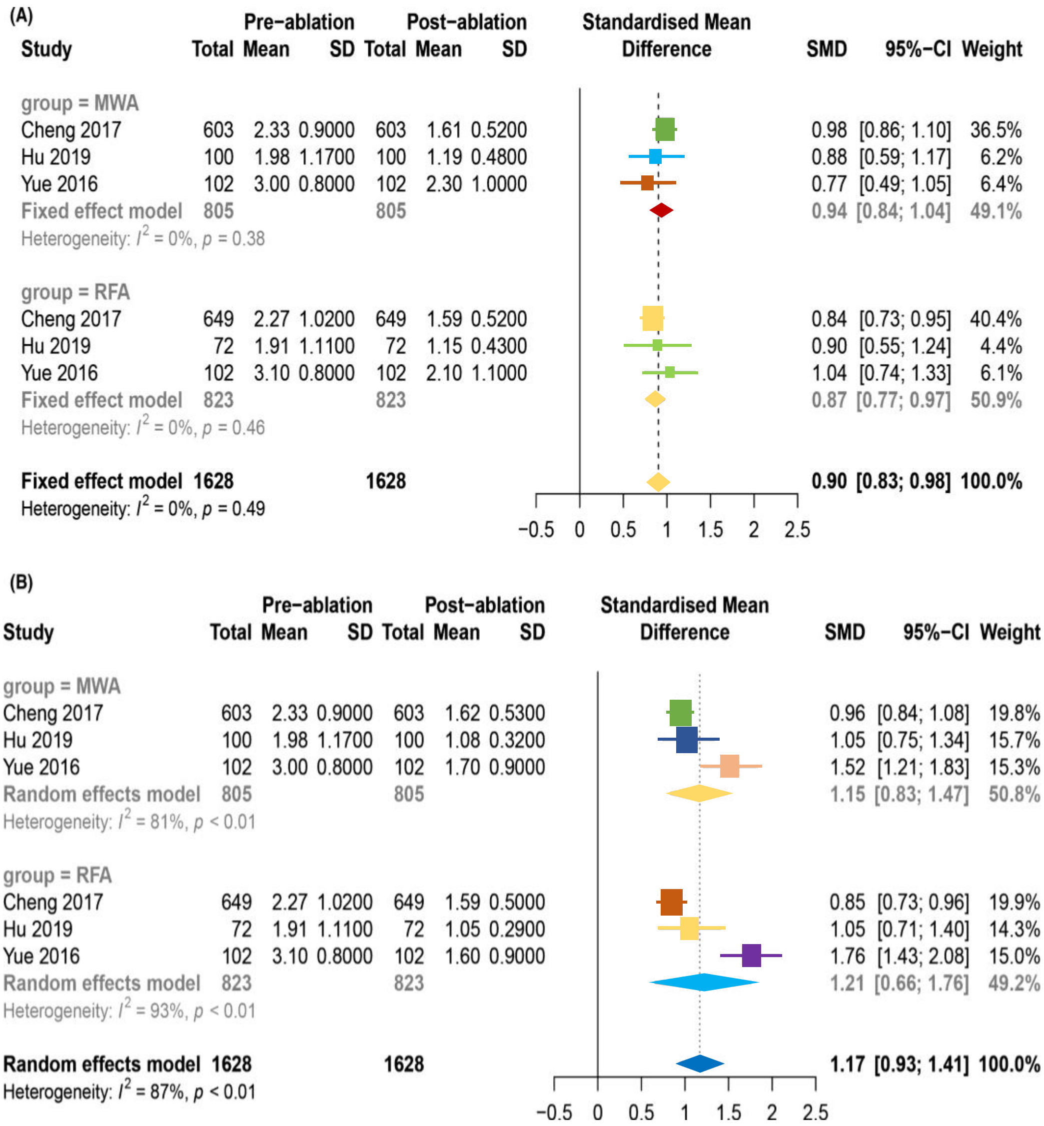

Figure 5. Forest plots of symptom improvement analyzed by standardized mean difference (SMD) after microwave ablation and RFA treatment at different time points: (A) 6-month, (B) 12-month.

Table 2. The complications of included studies

Major complications	**Minor complications**
Transient voice change, Nodule rupture	Haemorrhage/hematoma
Transient voice change	Haemorrhage
Hematoma	Hematoma
Transient voice change	Haemorrhage/hematoma, Skin burn, Vomiting, Hyperthyroidism
Transient voice change, Nodule rupture, Sympathetic nerve injury	Hematoma
Voice change	

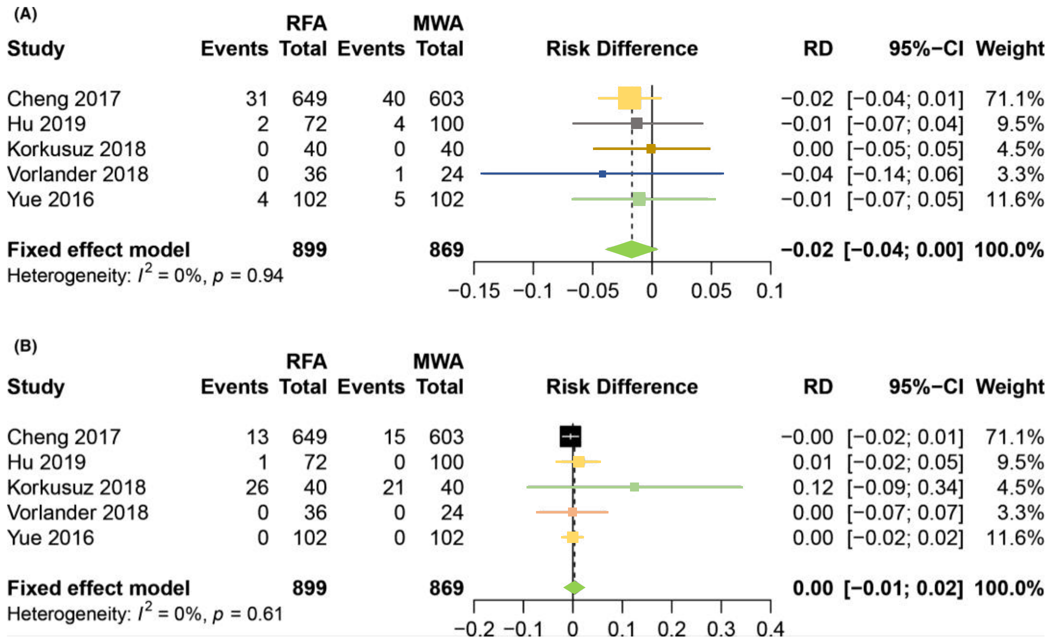

Figure 6. Forest plots of complications analyzed by risk difference (RD) after microwave ablation and RFA treatment: (A) major complications, (B) minor complications.

4. Discussion

In the vanguard of therapeutic innovation for benign thyroid nodules (BTNs), percutaneous thermal ablation techniques have advanced precipitously. Among these, Radiofrequency Ablation (RFA) has burgeoned as a minimally invasive yet efficacious surrogate to conventional surgical interventions, heralding propitious outcomes for BTN management. Concomitantly, Microwave Ablation (MWA) has emerged, showcasing auspicious clinical efficacies in BTN remediation. Despite the ostensible ascendancy of RFA over MWA, the discourse on their relative effectiveness and safety profiles remains nebulous. To our cognizance, this meta-analysis pioneers a systematic evaluation of the efficacious dichotomy and safety paradigms between RFA and MWA in BTN treatment [24-26].

Our exhaustive meta-analysis underscored a pronounced volumetric diminution in thyroid nodules post both RFA and MWA interventions. This meta-analysis showed no significant differences between RFA and MWA in terms of nodule volume reduction rate (VRR), symptom improvement, and aesthetic evaluation during the 3-month and 6-month follow-up periods, with VRRs of approximately 56.0% and 53.9%, and symptom improvement rates of 80.8% and 74.9%, respectively. However, at the 12-month follow-up, the VRR of the RFA group was significantly higher than that of the MWA group (86.2% vs. 80.0%, p = 0.036), suggesting that RFA has a more durable therapeutic effect. Although no overall significant differences in safety were observed between the two techniques, the limited statistical power due to small sample sizes and high heterogeneity should be considered. Future studies should aim to design large-scale, multi-center, prospective RCTs or IPD meta-analyses, while exploring the optimal application of these two techniques for different nodule characteristics and patient populations, all while reducing confounding factors to achieve truly individualized treatment. This study made rigorous methodological improvements in literature retrieval, missing data handling, and quality assessment, highlighted clinical innovations, and provided more reliable evidence for the promotion of minimally invasive treatments [27-29]. This is in alignment with recent empirical evidence positing RFA's heightened mean VRRs vis-à-vis MWA and Laser Ablation in addressing primary papillary thyroid microcarcinoma. A salient prospective clinical trial further corroborated RFA's dominance in volumetric reduction of benign non-functioning thyroid nodules at a semiannual milestone. Collectively, these findings bolster the proposition of RFA's enhanced long-term therapeutic impact across the spectrum of thermal ablation modalities, potentially nominating it as a more advantageous treatment modality for BTNs [30].

The heterogeneity observed in the outcomes of RFA and MWA could be attributed to variances in technical execution, study design, regional practices, subject demographics, operator proficiency, or institutional protocols. The paucity of studies included in our analysis curtails a granular exploration into these differentials. Ergo, a clarion call for further cohort studies with protracted follow-up durations, particularly extending beyond the 12-month threshold, is imperative to reinforce the veracity of our findings.

Our meta-analysis delineated significant amelioration in compressive symptoms and aesthetic concerns subsequent to RFA and MWA, with negligible distinctions in therapeutic impact. Pertaining to complication rates, both modalities exhibited comparable safety profiles with no marked differences in the incidence of major or minor complications. However, instances of sympathetic nerve injury were exclusively associated with MWA, accentuating the exigency for operator expertise and a profound comprehension of anatomical vicinities. Given MWA's higher energy deployment, the prerequisite for operator dexterity is underscored, and the strategic employment of hydrodissection techniques may serve as a prophylactic measure to obviate complications by spatially segregating the target nodule from critical perinodular structures.

Notwithstanding the insightful revelations from our study, it is incumbent upon us to acknowledge its limitations, including the paucity of longitudinal data in certain investigations, the potential for publication bias, and the circumscribed inclusion of non-English literature. As the domain of thermal ablation for BTNs continues to evolve, subsequent meta-analyses that integrate these considerations and encapsulate a broader compendium of studies will be instrumental in distilling a more holistic comprehension of the comparative efficacy and safety of RFA and MWA in the treatment of BTNs.

5. Conclusion

In conclusion, this meta-analysis indicates that both RFA and MWA are safe and effective minimally invasive techniques for treating benign thyroid nodules, with comparable efficacy at the 3-month and 6-month follow-up stages. However, at the 12-month long-term follow-up, RFA demonstrated a higher nodule volume reduction rate (86.2% vs. 80.0%, $p = 0.036$), suggesting a slight advantage in long-term efficacy. Nonetheless, due to the limited number of studies (only five, all observational cohort studies) included in this analysis, as well as the small sample sizes and high heterogeneity, this study carries a certain risk of bias. Future research should aim to validate these findings through higher-quality, multi-center, prospective randomized controlled trials (RCTs) or IPD meta-analyses, and further explore the clinical applicability and operational optimization strategies of both techniques.

6. Acknowledgments

Conflict of Interest Statement: Authors must declare any potential conflicts of interest.

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