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Comparative Efficacy and Safety of Radiofrequency Ablation and Microwave Ablation in the Treatment of Benign Thyroid Nodules: A Systematic Review and Meta-Analysis

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Objective: The current body of evidence lacks clarity regarding the comparative efficacy and safety of radiofrequency ablation (RFA) and microwave ablation (MWA) as minimally invasive treatments for benign thyroid nodules. The primary objective of this study is to clarify these concerns.

Materials and Methods: A comprehensive search was conducted using the Cochrane Library, Scopus, Europe PMC, and Medline databases until October 10th, 2023, using a combination of relevant keywords. This study incorporated literature that compared RFA and MWA for benign thyroid nodules. The primary outcome was the volume reduction ratio (VRR) from baseline to follow-up. Secondary outcomes were symptom score, cosmetic score, ablation time, major complications rate, hemorrhage, hoarseness, skin burn, cough, and sympathetic nerve injury. We used Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool to assess the risk of bias in the included studies. We employed random effects models to analyze the standardized mean difference (SMD) and odds ratio for the presentation of outcomes.

Results: Nine studies with 2707 nodules were included. The results of our meta-analysis indicated similar efficacy between RFA and MWA in terms of VRR during the 1 (SMD 0.06; 95% confidence interval [CI]: -0.13 to 0.26; $P = 0.52$) and 3 (SMD 0.11; 95% CI: -0.03 to 0.25; $P = 0.12$) months of follow-up. VRR was significantly higher in RFA than in MWA at the 6 (SMD 0.25; 95% CI: 0.06–0.43; $P = 0.008$) and 12 month of follow-up (SMD 0.38; 95% CI: 0.17 to 0.59; $P < 0.001$). There were no significant differences between RFA and MWA in symptom scores, cosmetic scores, or the incidence of complications, including hemorrhage, hoarseness, skin burn, cough, and sympathetic nerve injury.

Conclusion: RFA showed a higher VRR than MWA at 6 and 12-month follow-ups, with a comparable safety profile.

Keywords: Thyroid; Oncology; Endocrinology; Minimal-invasive; Ablation

INTRODUCTION

Thyroid nodules manifest as palpable masses in the thyroid gland located in the cervical region and represent a prevalent type of thyroid pathology that manifests in both sexes [1], The global prevalence of thyroid nodules varies according to the diagnostic method employed [1]. Specifically, the estimates indicate that the frequency ranges are 2%–6% when diagnosed through palpation, 19%–35% when diagnosed using ultrasound, and 8%–65% when diagnosed through autopsy [1]. The majority of thyroid nodules are non-malignant, with approximately 10%–15% exhibiting malignancy or are commonly referred to as cancer [1]. According to the most recent guidelines

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issued in 2023 by the European Thyroid Association (ETA), it is generally unnecessary to pursue additional interventions for asymptomatic benign thyroid nodules [2]. However, it is recommended to conduct ultrasonography evaluations every 3–5 years if the nodule size exceeds 10 mm [2]. In cases of malignancy, a fine-needle aspiration biopsy (FNAB) should be performed [2]. Nevertheless, in specific cases where individuals display symptoms of compression, have cosmetic issues, or are concerned about potential malignancies, interventional therapy may provide aid [3]. Surgical intervention is an effective approach for managing thyroid nodules; however, it is often accompanied by a range of potential complications, including hemorrhage, infection, and impairment of the recurrent laryngeal nerve [3].

To enhance safety and decrease invasiveness, many minimally invasive interventional modalities have been developed for treating thyroid nodules [4,5]. These include ethanol ablation (EA), microwave ablation (MWA), radiofrequency ablation (RFA), and laser ablations (LA) [4,5]. In a meta-analysis conducted in 2023, data from 16 studies were synthesized to compare RFA and MWA during surgery in patients with benign thyroid nodules [6]. The findings of this study indicated that both RFA and MWA demonstrated superior efficacy and safety outcomes compared with conventional surgical interventions [6]. Therefore, it is quite probable that these two minimally invasive treatments can be offered to patients who decline or are unable to undergo surgery [6]. However, the current body of evidence regarding the comparative superiority of MWA and RFA in the treatment of benign thyroid nodules remains inconclusive.

A previous meta-analysis conducted by He et al. [7] did not compare RFA and MWA in the treatment of benign thyroid nodules. Instead, this study focused on comparing RFA with placebo or EA. Concurrently, another meta-analysis by Guo et al. [8] did not provide sufficient evidence regarding the direct comparison between RFA and MWA, as they conducted subgroup analyses for RFA and MWA and presented the standardized mean difference (SMD) separately: one for RFA and one for MWA. Hence, there are gaps in the existing literature pertaining to the comparative superiority of these two approaches while ensuring the preservation of the safety profile in the management of benign thyroid nodules. The objective of this study was to evaluate the efficacy and safety of RFA compared to those of MWA for the management of benign thyroid nodules.

MATERIALS AND METHODS

Eligibility Criteria

The PROSPERO international database was used to register the study protocol (registration number: CRD42023469336). The studies included in this review were chosen based on their adherence to the following inclusion criteria formulated using the PICOS framework:

1) Population: adults clinically diagnosed with benign thyroid nodules.

2) Intervention: ultrasound-guided RFA as an intervention for benign thyroid nodules.

3) Control: received ultrasound-guided MWA for the management of benign thyroid nodules.

4) Outcome: data on

- Primary outcome = volume reduction ratio (VRR) at 1-, 3-, 6-, and 12- month follow-ups.

- Secondary outcome = symptom and cosmetic scores during the 1-, 3-, 6, and 12-month of follow-ups; duration of ablation; major complication rate; hemorrhage/hematoma; hoarseness/voice change; skin burn; cough; and sympathetic nerve injury.

5) Study design: randomized or non-randomized clinical trials, prospective or retrospective cohorts, and case-control studies.

Additionally, we eliminated papers that met the following criteria: 1) the study cohort consisted of pediatric patients, 2) the individuals included in the study were diagnosed with a malignant thyroid nodule, 3) investigations aimed to compare the effectiveness of RFA or MWA with surgical intervention, LA, or no treatment at all, 4) studies that lacked a comparison group, 5) non-primary investigations, and 6) research articles that were not accessible in their entirety or studies that did not undergo the process of publication. We wrote this article from the beginning to the end according to the guidelines published in the PRISMA statement [9,10].

Search Strategy and Study Selection

A comprehensive literature review was conducted, specifically focusing on papers written in English. The search encompassed a time frame up to October 10th, 2023, and was undertaken across four prominent worldwide databases: Medline, Scopus, Europe PMC, and the Cochrane Library. The search terms utilized for the literature review were as follows: “(radiofrequency ablation OR RF ablation OR RFA) AND (microwave ablation OR MWA) AND (benign thyroid nodule OR non-malignant thyroid nodule OR non-cancerous thyroid nodule OR low-risk thyroid nodule)." Supplementary Material provides additional information regarding the search approach employed for each database. The papers retrieved from the database were screened based on their titles and abstracts. Two authors independently conducted this screening and duplicate articles were promptly removed. Any primary research study that was referenced in review articles, systematic reviews, or meta-analyses but was not found during the initial search was considered for inclusion in the study, provided that it satisfied the eligibility requirements. Subsequently, the two aforementioned authors comprehensively assessed the full-text articles in their entirety. In the event of discord during the article selection process, a discussion was solicited to reconcile the disagreement.

Data Extraction

Data extraction was independently conducted by two authors. The extracted data were presented as follows: information on the first author of the study, year of publication, study design, country where the study was conducted, duration of the study, details about the tools used for RFA and MWA, sample size in each study arm, average age of the participants, sex distribution, initial volume of the thyroid nodule, and outcome of interest. Discrepancies during data extraction were resolved through discussion.

Risk of Bias Assessment

The primary objective of this study was to evaluate interventions for a specific disease. Therefore, to assess the risk of bias in each study included in our analysis, we employed the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool [11]. This evaluation was performed independently by two authors. In the event of a discrepancy during the risk of bias assessment process, discussion was solicited to reconcile the disagreement. The ROBINS-I tool encompasses seven distinct evaluation domains: confounder mitigation efforts, participant selection, intervention selection, intervention adherence, handling of missing data, outcome assessment, and selection of reported outcomes [11]. The authors' evaluations were categorized as having a "low risk," "moderate risk," or "serious risk" of bias [11].

Statistical Analysis

Continuous variable outcomes were computed using the inverse variance formula to derive the SMD with a 95% confidence interval (CI). The outcomes of the dichotomous variables were computed using the Mantel–Haenszel formula to derive the odds ratio (OR) and its corresponding 95% CI. The diverse participant characteristics and follow-up durations necessitated the consideration of a substantial amount of variability. To address this issue, random effects models were employed. The I^2 statistic was used to quantify the heterogeneity among the studies, where values exceeding 50% indicated a substantial or noteworthy level of heterogeneity [12]. The data, originally expressed as medians and interquartile ranges or medians and minimum-to-maximum ranges, were transformed into means and standard deviations for meta-analysis pooling. This conversion was performed using the formula developed by Wan et al. [13]. This study employed a restricted maximum likelihood random effects method to conduct a meta-regression analysis. This analysis aimed to examine the relationship between pre-determined variables, including sample size, study design, study quality, age, sex, and initial nodule volume, and the primary outcome. If the number of papers included in the meta-analysis exceeded ten, a funnel plot was used to evaluate the presence of publication bias. All analyses were conducted using Review Manager 5.4, a software tool developed by the Cochrane Collaboration.

RESULTS

Study Selection and Characteristics

In total, 459 studies were retrieved from the four databases used in the literature search. After eliminating all instances of duplication and subsequently evaluating publications based on their titles and abstracts, 421 articles were deemed irrelevant and excluded from further analysis. This resulted in the final selection of 38 articles for further examination. Of the 38 articles subjected to a comprehensive assessment of their full texts, 29 did not satisfy the pre-determined eligibility criteria. These articles were then excluded from our analysis based on the following specific details: 14 articles lacked a comparison group, 5 articles were identified as review articles, 5 articles conducted a comparison between RFA or MWA and conventional surgery, 3 articles utilized LA as the comparison group, and 2 articles included patients who did not have any intervention as the basis for comparison.

Finally, nine papers that satisfied the pre-determined criteria for inclusion were identified [14-22]. Consequently, these publications were selected for analysis, as shown in Figure 1. Of the nine publications under consideration, seven were retrospective studies and only two were prospective studies. China contributed four papers, Turkey contributed three, and Germany contributed two. The follow-up duration ranged from 1 to 12 months. Additional information regarding the attributes of the participants and the methodology employed for RFA and MWA is listed in Table 1.

Quality of Study Assessment

The risk of bias in the included studies was assessed using the ROBINS-I technique. Of the total number of studies, only four were found to have a "low risk" of bias across all seven assessment domains. Two studies possessed a "serious risk" of bias in the selection of the participants' domains. This was attributed to the differences in the baseline characteristics of the participants in the two groups. No subsequent measures were taken to account for this difference, thereby increasing the likelihood of bias. Three studies exhibited a "serious risk" of bias in both the confounder domain and the selection of participants. Table 2 presents a comprehensive overview of the risk of bias assessment conducted using the ROBINS-I method for each study included in the analysis.

Primary Outcome (VRR)

The findings of a meta-analysis incorporating data from nine studies indicate that, overall, the use of RFA was associated with higher reduction in the VRR of benign thyroid nodules when compared with the use of MWA (SMD 0.19; 95% CI: 0.11 to 0.28; $P < 0.001$; $I^2 = 67\%$) (Fig. 2).

Subgroup analysis, stratified by the duration of follow-up, revealed variations in VRR contingent upon the timing of the follow-up assessment (Fig. 2). There was no statistically significant difference observed in the VRR between RFA and MWA between the 1 (SMD 0.06; 95% CI: -0.13 to 0.26; $P = 0.52$; $I^2 = 55\%$) and 3 months of follow-up (SMD 0.11; 95% CI: -0.03 to 0.25; $P = 0.12$; $I^2 = 54\%$). However, beginning in the 6 months of follow-up, notable distinctions emerged,

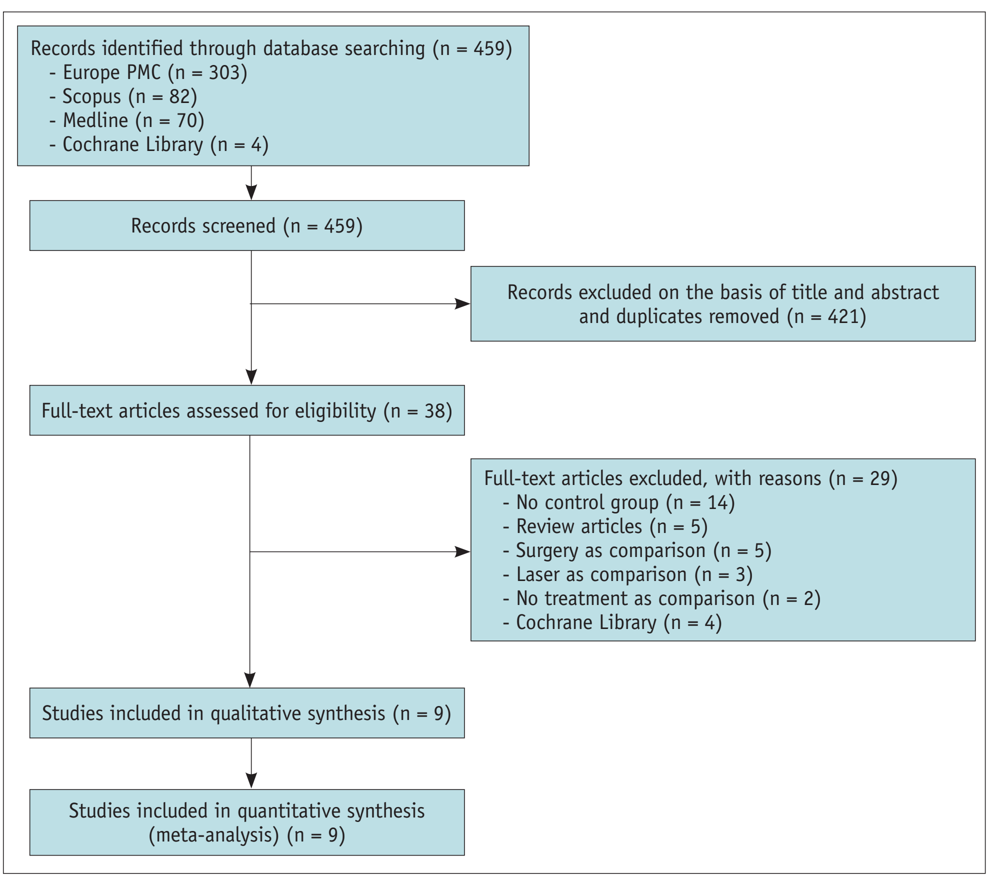

Fig. 1. PRISMA diagram depicting the detailed selection process of studies for the systematic review and meta-analysis.

Table 1. Characteristics of included studies

Study	Country	Design	RFA	MWA	Study durations (m)	Study arms	Patients (n)	Patient age (yrs)*	Male Patient (%)	Nodule volume (mL)*
Cerit et al., 2023 [14]	Turkey	Retrospective cohort	- US-guided with moving-shot technique - AMICA dual-system generator with 17-gauge cooled shift electrodes or VIVA RF generator with 19-gauge RFA needle - Power: 20–50 W	- US-guided with moving-shot technique - CANYON MWA generator with 16-gauge SURETIP antennas - Power: 20–40 W	12	RFA	37	41 ± 9	37.8	20.3 ± 16.8
						MWA	43	45 ± 11	34.8	52.2 ± 46.4
Cheng et al., 2017 [15]	China	Prospective non-randomized trial	- US-guided with moving-shot technique - VIVA RF generator with 18-gauge, monopolar, modified, internal-cooled RFA electrode - Power: 25–60 W	- US-guided with moving-shot technique - KY-2000 2450 MHz microwave system with 16-gauge, internal-cooled microwave antenna - Power: 25-50 W	12	RFA	649 (687 nodules)	47.9 ± 13.6	21.5	7.2 ± 6.7
						MWA	603 (664 nodules)	47.1 ± 12.9	22.3	7.7 ± 9.1
Hu et al., 2019 [16]	China	Retrospective cohort	- US-guided with moving-shot technique - Medsphere RF Generator S-500 with 19-gauge RFA electrode - Power: 10–20 W	- US-guided with moving-shot technique - MTC-3C microwave system with 16-gauge antenna - Power: 25–35 W	12	RFA	72	46.3 ± 16.3	34.7	10.7 ± 5.9
						MWA	100	52.0 ± 15.9	34	13.0 ± 7.9
Javadov et al., 2021 [17]	Turkey	Prospective cohort	- US-guided with moving-shot technique - VIVA RF generator with 18-gauge internal cooling bipolar system electrode - Power: not stated	- US-guided with moving-shot technique - MedWaves microwave system - Power: not stated	6	RFA	50	48.2 ± 11.3	22	19.3 ± 21.0
						MWA	50	47.8 ± 10.9	32	19.5 ± 27.3
Jin et al., 2021 [18]	China	Retrospective cohort	- US-guided with moving-shot technique - S-1500 Maide RF equipment system - Power: not stated	- US-guided with dot-to-dot technique - MTI-5DT tumor microwave therapy system - Power: not specified	18	RFA	289	49.6 ± 8.7	NR	9.3 ± 2.1
						MWA	289	49.5 ± 8.3	NR	9.3 ± 2.2
Korkusuz et al., 2018 [19]	Germany	Retrospective cohort	- US-guided with multi-shot technique - Bipolar RF with POWER system generator and cooled 15-gauge electrode or un-cooled 18-gauge electrode - Power: 9–40 W	- US-guided with multi-shot technique - MedWaves incorporated generator with cooled or un-cooled 14 to 16 gauge electrodes - Power: 24–32 W	3	RFA	40 (55 nodules)	48.0 ± 13.9	45	14.2 ± 20.7
						MWA	40 (47 nodules)	48.0 ± 13.9	47.5	23.5 ± 18.7
Sönmez et al., 2023 [20]	Turkey	Retrospective cohort	- US-guided with moving-shot technique - Apro RF generator with 18-gauge, internal-cooled electrode - Power: 40–100 W	- US-guided with moving-shot technique - ECO microwave generator - Power: 60–140 W	1	RFA	30	50.5 ± 12.7†	20†	67.2 ± 112.5
						MWA	25			20.2 ± 19.0

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Table 1. Characteristics of included studies (continued)

Study	Country	Design	RFA	MWA	Study durations (m)	Study arms	Patients (n)	Patient age (yrs)*	Male Patient (%)	Nodule volume (mL)*
Vorländer et al., 2018 [21]	Germany	Retrospective cohort	- US-guided with multiple overlapping shot technique - CelonLab POWER RF system with 18-gauge, cooled electrode - Power: maximum 250 W	- US-guided with multiple overlapping shot technique - MedWaves Avecure microwave generator with 14 or 16-gauge, internal cooled antenna - Power: 24–36 W	3	RFA	36 (40 nodules)	54 ± 12	33.3	29.4 ± 30.1
						MWA	24 (25 nodules)	57 ± 13	37.5	23.9 ± 17.3
Yue et al., 2017 [22]	China	Retrospective cohort	- US-guided with moving-shot technique - Celon AG bipolar RF generator with 15.5 or 18-gauge, internal-cooled electrode - Power: 3–5 W or 20–25 W	- US-guided with moving-shot technique - KY-2000 microwave system with 16-gauge, internal-cooled antenna - Power: maximum 100 W	12	RFA	102	46.4 ± 13.3	26.5	5.8 ± 1.3
						MWA	102	49.5 ± 10.2	27.5	5.6 ± 1.2

*Data are mean ± standard deviation, †The presented data reflect the results for both groups combined as the separate results for each group were not available. RFA = radiofrequency ablation, MWA = microwave ablation, m = month, US = ultrasonography, NR = not reported

indicating that RFA was linked to a much higher VRR than MWA (SMD 0.25; 95% CI: 0.06–0.43; P = 0.008; I^2 = 72%). Similarly, throughout the 12 month of follow-up, there was an increasing disparity in favor of RFA (SMD 0.38; 95% CI: 0.17–0.59; P < 0.001; I^2 = 78%).

Secondary Outcome

Ablation Time

There were three studies which reported the ablation times of RFA and MWA for benign thyroid nodules [15,18,21]. Overall meta-analysis from these studies showed that RFA was associated with shorter time needed for ablation of benign thyroid nodule when compared to MWA (SMD -0.33; 95% CI: -0.52 to -0.13; P < 0.001; I^2 = 65%) (Supplementary Fig. 1).

Symptoms Score

A meta-analysis of four studies [15,16,20,22] revealed no statistically significant differences in symptom scores between RFA and MWA treatments for benign thyroid nodules (Fig. 3). This observation holds true over several time intervals, including the 1 (SMD -0.07; 95% CI: -0.33 to 0.20; P = 0.62; I^2 = 0%), 3 (SMD -0.08; 95% CI: -0.18 to 0.02; P = 0.14; I^2 = 0%), 6 (SMD -0.05; 95% CI: -0.17 to 0.07; P = 0.43; I^2 = 16%), and 12 months of post-treatment follow-up (SMD -0.05; 95% CI: -0.15 to 0.05; P = 0.33; I^2 = 0%) (Fig. 3).

Cosmetic Score

A meta-analysis of five studies [15-17,20,22] revealed no statistically significant difference in cosmetic scores between RFA and MWA treatments for benign thyroid nodules (Supplementary Fig. 2). This observation holds true over several time intervals, including the 1 (SMD 0.38; 95% CI: -0.50 to 1.26; P = 0.40; I^2 = 93%), 3 (SMD -0.08; 95% CI: -0.18 to 0.02; P = 0.12; I^2 = 0%), 6 (SMD -0.05; 95% CI: -0.15 to 0.04; P = 0.29; I^2 = 0%), 12 months of post-treatment follow-up (SMD -0.07; 95% CI: -0.17 to 0.03; P = 0.17; I^2 = 0%) (Supplementary Fig. 2).

Major Complications Rate

A cumulative count of eight studies was documented, each reporting major complication rates [14-16,18-22]. The findings from the aforementioned eight studies indicate that no statistically significant difference was observed between RFA and MWA in relation to the rate of major complications (OR 0.87; 95% CI: 0.63–1.20; P = 0.41; I^2 = 0%) (Table 3).

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Table 2. Risk of bias assessment for non-randomized intervention study by using ROBINS-I tool

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Cerit et al., 2023 [14]	+	X	+	+	+	+	+	X
Cheng et al., 2017 [15]	+	+	+	+	+	+	+	+
Hu et al., 2019 [16]	+	+	+	+	+	+	+	+
Javadov et al., 2021 [17]	X	X	+	+	+	+	+	X
Jin et al., 2021 [18]	+	+	+	+	+	+	+	+
Korkusuz et al., 2018 [19]	X	X	+	+	+	+	+	X
Sönmez et al., 2023 [20]	+	X	+	+	+	+	+	X
Vorländer et al., 2018 [21]	X	X	+	+	+	+	+	X
Yue et al., 2017 [22]	+	+	+	+	+	+	+	+

D1: Bias due to confounding, D2: Bias due to selection of participants, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported result.
D = domain, ROBINS-I = Risk of Bias in Non-randomized Studies - of Interventions, + = low, x = serious

Hemorrhage or Hematoma

A cumulative count of six studies was documented, each reporting the incidence of hemorrhage or hematoma [14-16,18-20]. The findings from the aforementioned six studies indicate that no statistically significant difference was observed between RFA and MWA in relation to the hemorrhage or hematoma incidence (OR 1.41; 95% CI: 0.81–2.47; $P = 0.22$; $I^2 = 0\%$) (Table 3).

Hoarseness or Voice Change

An overall meta-analysis of 5 studies [15,16,18,20,22] involving benign thyroid nodule patients showed no significant difference in the hoarseness or voice change rate between RFA and MWA (OR 0.73; 95% CI: 0.47–1.14; $P = 0.17$; $I^2 = 0\%$) (Table 3).

Skin Burn

An overall meta-analysis of 2 studies [15,18] involving benign thyroid nodule patients showed no significant difference in the skin burn incidence between RFA and MWA (OR 1.03; 95% CI: 0.22–4.94; $P = 0.97$; $I^2 = 0\%$) (Table 3).

Cough

A cumulative count of two studies was documented, each reporting the incidence of post-procedure cough [15,18]. The findings from the aforementioned two studies indicate that no statistically significant difference was observed between RFA and MWA in relation to the post-procedure cough incidence (OR 0.60; 95% CI: 0.07–4.92; $P = 0.64$; $I^2 = 0\%$) (Table 3).

Sympathetic Nerve Injury

A cumulative count of three studies was documented, each reporting the incidence of sympathetic nerve injury [14,15,21]. The findings from the aforementioned two studies indicate that no statistically significant difference was observed between RFA and MWA in relation to the sympathetic nerve injury incidence (OR 0.47; 95% CI:

Study or Subgroup	RFA Mean	RFA SD	RFA Total	MWA Mean	MWA SD	MWA Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 VRR at 1 month								
Cerit MN et al. [14] 2023	46.8	13.5	37	38.7	12.5	43	2.4%	0.62 [0.17, 1.07]
Hu K et al. [16] 2019	22.7	13.4	72	24	16.1	100	3.8%	-0.09 [-0.39, 0.22]
Javadov M et al. [17] 2021	42	15.3	50	46	17.9	50	2.9%	-0.24 [-0.63, 0.16]
Jin H et al. [18] 2021	15.4	2.52	289	15.3	2.48	289	5.8%	0.04 [-0.12, 0.20]
Sonmez S et al. [20] 2023	63.4	14.2	30	65.7	13	25	1.9%	-0.17 [-0.70, 0.37]
Yue WW et al. [22] 2016	24	5.9	102	22.3	9.1	102	4.2%	0.22 [-0.05, 0.50]
Subtotal (95% CI)			**580**			**609**	**21.0%**	**0.06 [-0.13, 0.26]**
Heterogeneity: Tau² = 0.03; Chi² = 11.07, df = 5 (P = 0.05); I² = 55%								
Test for overall effect: Z = 0.64 (P = 0.52)								
1.1.2 VRR at 3 months								
Cerit MN et al. [14] 2023	62.9	13.6	37	54	15.3	43	2.4%	0.61 [0.16, 1.06]
Cheng Z et al. [15] 2017	67.6	20.3	687	64.4	43.5	664	6.7%	0.09 [-0.01, 0.20]
Hu K et al. [16] 2019	56.1	19.5	72	54.8	22.8	100	3.8%	0.06 [-0.24, 0.36]
Javadov M et al. [17] 2021	56	18.53	50	64	20.57	50	2.8%	-0.41 [-0.80, -0.01]
Jin H et al. [18] 2021	48.2	3.95	289	47.9	3.57	289	5.8%	0.08 [-0.08, 0.24]
Korkusuz Y et al. [19] 2017	49.7	17.69	55	43.4	18.4	47	2.9%	0.35 [-0.05, 0.74]
Vorlander C et al. [21] 2018	51.2	16.58	40	53.5	15.4	25	2.1%	-0.14 [-0.64, 0.36]
Yue WW et al. [22] 2016	55	6.4	102	52.7	10.1	102	4.2%	0.27 [-0.00, 0.55]
Subtotal (95% CI)			**1332**			**1320**	**30.7%**	**0.11 [-0.03, 0.25]**
Heterogeneity: Tau² = 0.02; Chi² = 15.14, df = 7 (P = 0.03); I² = 54%								
Test for overall effect: Z = 1.57 (P = 0.12)								
1.1.3 VRR at 6 months								
Cerit MN et al. [14] 2023	71.6	11.9	37	59.6	12.5	43	2.3%	0.97 [0.51, 1.44]
Cheng Z et al. [15] 2017	84.1	13.5	687	78.4	49.2	664	6.7%	0.16 [0.05, 0.27]
Hu K et al. [16] 2019	77.9	21	72	68.7	19.1	100	3.8%	0.46 [0.15, 0.77]
Javadov M et al. [17] 2021	65	20.8	50	68	21.3	50	2.9%	-0.14 [-0.53, 0.25]
Jin H et al. [18] 2021	68.1	2.83	289	67.8	2.76	289	5.8%	0.11 [-0.06, 0.27]
Yue WW et al. [22] 2016	79.4	8.6	102	77.2	10.8	102	4.2%	0.22 [-0.05, 0.50]
Subtotal (95% CI)			**1237**			**1248**	**25.6%**	**0.25 [0.06, 0.43]**
Heterogeneity: Tau² = 0.03; Chi² = 17.88, df = 5 (P = 0.003); I² = 72%								
Test for overall effect: Z = 2.65 (P = 0.008)								
1.1.4 VRR at 12 months								
Cerit MN et al. [14] 2023	77.9	10.3	37	65	11.3	43	2.2%	1.18 [0.70, 1.66]
Cheng Z et al. [15] 2017	89.6	20	687	82.5	49.7	664	6.7%	0.19 [0.08, 0.30]
Hu K et al. [16] 2019	85.4	18.9	72	75.8	19.4	100	3.8%	0.50 [0.19, 0.81]
Jin H et al. [18] 2021	80.1	2.68	289	79.3	4.76	289	5.8%	0.21 [0.04, 0.37]
Yue WW et al. [22] 2016	83.6	5.2	102	81.6	8.8	102	4.2%	0.28 [-0.00, 0.55]
Subtotal (95% CI)			**1187**			**1198**	**22.7%**	**0.38 [0.17, 0.59]**
Heterogeneity: Tau² = 0.04; Chi² = 18.55, df = 4 (P = 0.0010); I² = 78%								
Test for overall effect: Z = 3.51 (P = 0.0004)								
Total (95% CI)			**4336**			**4375**	**100.0%**	**0.19 [0.11, 0.28]**
Heterogeneity: Tau² = 0.03; Chi² = 72.99, df = 24 (P < 0.00001); I² = 67%								
Test for overall effect: Z = 4.41 (P < 0.0001)								
Test for subgroup differences: Chi² = 6.26, df = 3 (P = 0.10), I² = 52.1%								

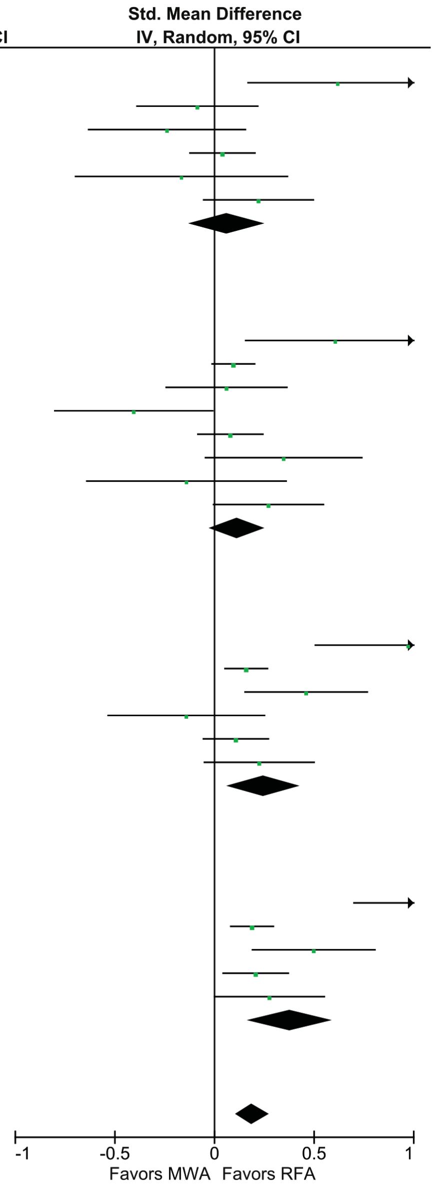

Fig. 2. Forest plot demonstrating the VRR during the 1st, 3rd, 6th, 12th, and beyond 12 months of follow-up intervals between RFA and MWA for managing benign thyroid nodules. VRR = volume reduction ratio, RFA = radiofrequency ablation, MWA = microwave ablation, Std = standard, SD = standard deviation, IV = inverse variance, CI = confidence interval

0.08–2.76; P = 0.40; I^2 = 0%) (Table 3).

Meta-Regression

The findings of the meta-regression analysis pertaining to the primary outcome measures of the VRR are presented in Supplementary Table 1 and Supplementary Figures 3–6. VRR at 1 month follow-up was significantly affected by participant age (beta coefficient: -0.0908; 95% CI: -0.1598 to -0.0218; P = 0.0099) (Supplementary Fig. 3A). The VRR at the 6-month follow-up was significantly associated with sex (beta coefficient, 0.0454; 95% CI: 0.0011–0.0897; P = 0.0447) (Supplementary Fig. 5A). VRR at the 12-month follow-up was significantly associated with study quality (beta coefficient: 0.9657; 95% CI: 0.4822–1.4493; P < 0.001), age (beta coefficient: -0.1206; 95% CI: -0.2335 to -0.0077; P = 0.0363), sex (beta coefficient: 0.0478; 95% CI: 0.0043–0.0914; P = 0.0314), and initial nodule volume (beta coefficient: 0.0330; 95% CI: 0.0172–0.0487; P < 0.001) (Supplementary Fig. 6A-D).

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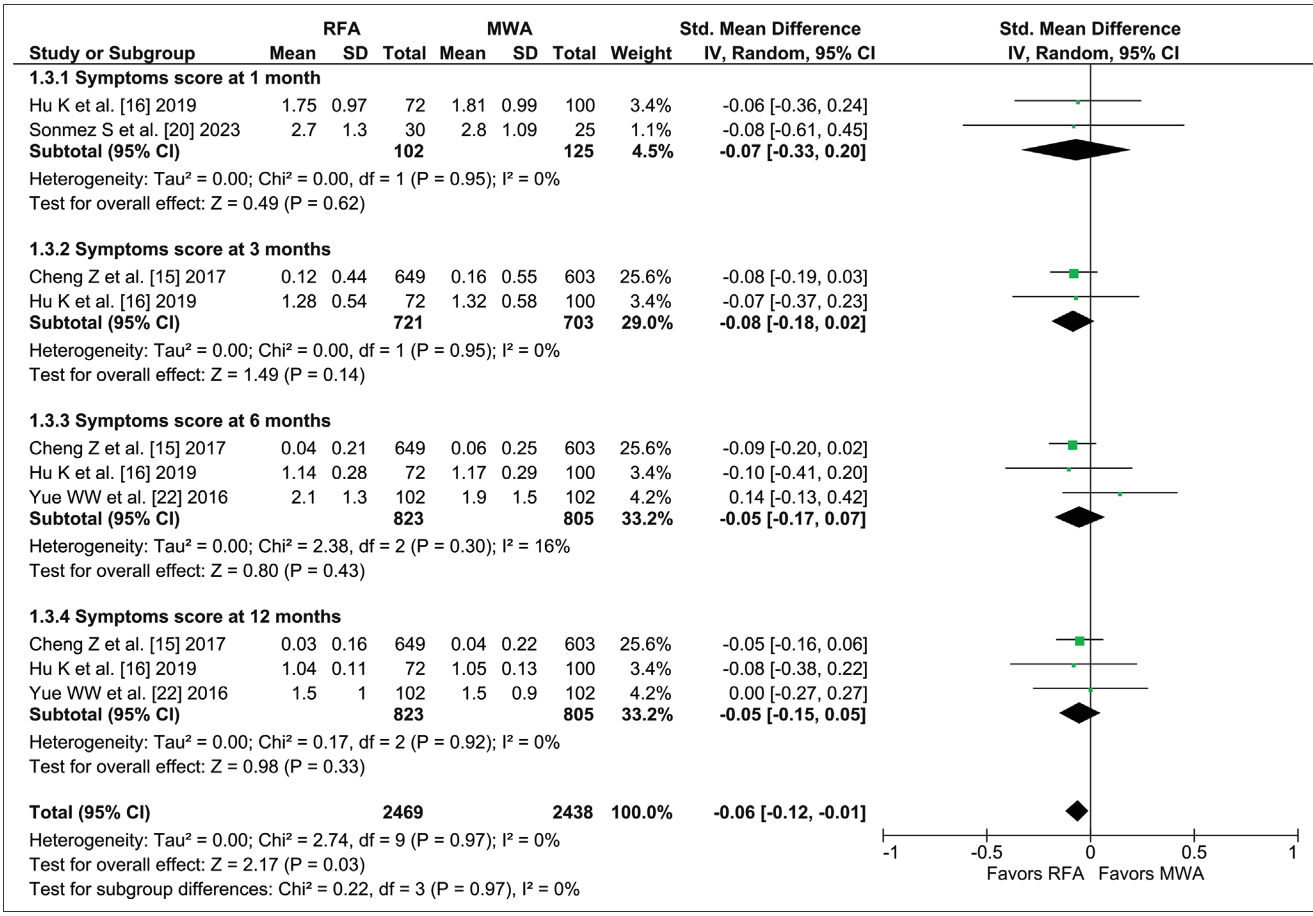

Fig. 3. Forest plot demonstrating the symptoms scores during the 1st, 3rd, 6th, 12th, and beyond 12 months of follow-up intervals between RFA and MWA for managing benign thyroid nodules. RFA = radiofrequency ablation, MWA = microwave ablation, Std = standard, SD = standard deviation, IV = inverse variance, CI = confidence interval

Table 3. Safety outcomes between RFA and MWA

Outcome	Included studies	Patients (n)		Odds ratio (95% CI)	*P*	I^2 (%)
		RFA	MWA			
Major complications	8	1255	1226	0.87 (0.63–1.20)	0.41	0
Hemorrhage/hematoma	6	1117	1100	1.41 (0.81–2.47)	0.22	0
Hoarseness/voice change	5	1142	1119	0.73 (0.47–1.14)	0.17	0
Skin burn	2	938	892	1.03 (0.22–4.94)	0.97	0
Cough	2	938	892	0.60 (0.07–4.92)	0.64	0
Sympathetic nerve injury	3	722	670	0.47 (0.08–2.76)	0.40	0

Odds ratio value < 1 favors RFA.
RFA = radiofrequency ablation, MWA = microwave ablation, CI = confidence interval

Publication Bias

Funnel plot analysis was used to assess publication bias. The present investigation did not assess publication bias because of the limited number of studies included (less than 10). Consequently, the evaluation of publication bias lacked the same level of robustness as when more than ten studies were available for analysis [23,24].

DISCUSSION

The findings of our meta-analysis indicate that RFA exhibits similar levels of efficacy and safety as MWA when used for the treatment of benign thyroid nodules. Our findings indicate that RFA exhibits certain benefits over MWA in terms of a shorter ablation duration and greater VRR

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throughout the 6- and 12-month follow-up periods. This can be explained using the fundamental principles of RFA and MWA. Due to the elevated temperature in the tissue, typically exceeding 150°C, resulting from the application of MWA, carbonization can readily develop in the ablated lesion, even at a relatively moderate power output of 30–50 W [25-27]. Nevertheless, the maximum temperature generated by RFA did not exceed 110°C, and the occurrence of carbonization in an RFA lesion is exceedingly uncommon [28]. It is crucial for the VRR elevations associated with tissue necrosis in ablated nodules to gradually disappear. The carbonized tissue in the ablated nodules proved resilient to dissolution [15]; therefore, the VRR of the ablated nodules in the RFA group showed more significant increments than that in the MWA group.

Additional regression analysis revealed that age, sex, and initial nodule volume significantly influenced the associations between RFA, MWA, and VRR. Age is a significant factor that frequently affects the efficacy of medical procedures including nodule ablation [29-31]. Elderly individuals frequently experience frailty and multimorbidity, which increase the likelihood of procedural complications or diminish their response to medical intervention [29-31]. In addition to age, sex is a significant factor that is frequently considered while performing medical procedures [31,32]. Prior researches indicate that sex exerts a notable influence on the efficacy of RFA procedures, with male exhibiting a higher likelihood of success than female [32]. Additionally, prior research has substantiated the impact of the initial volume of nodules on the increase in the VRR [32,33]. These studies have demonstrated that RFA is more likely to achieve success in nodules with smaller dimensions than in those with larger dimensions [32,33]. Unfortunately, the precise mechanism by which these factors affect the response to RFA and MWA remains unknown and warrants further investigation in future studies. Nevertheless, no statistically significant differences were observed between RFA and MWA in terms of changes in symptom scores, cosmetic scores, and the occurrence of various complications such as bleeding, hoarseness, skin burns, post-procedure cough, and sympathetic nerve injury.

The findings of our meta-analysis align with those of prior meta-analysis conducted by Guo et al. [8]. The meta-analysis conducted by Guo et al. [8] also reached the conclusion that both RFA and MWA exhibit comparable levels of effectiveness and safety when utilized for the treatment of benign thyroid nodules. Nevertheless, disparities exist between the meta-analysis conducted by Guo et al. [8] and the present investigation.

First, the meta-analysis conducted by Guo et al. [8] incorporated a limited number of studies, specifically five, for the purpose of analysis. In contrast, our meta-analysis incorporated a greater number of investigations, specifically, nine studies, to generate more robust and substantiated data.

Furthermore, of the five investigations [15,16,19,21,22] incorporated in the meta-analysis conducted by Guo et al. [8] that were also incorporated in our current meta-analysis, none were randomized trials. However, Guo et al. [8] continued to use the tool provided by the Cochrane Collaboration in RevMan 5.3 [34], which was unsuitable for the five studies included in their analysis. This tool was specifically developed to evaluate the risk of bias in randomized controlled trials (RCTs) [34]. Moreover, despite the use of imprecise or inappropriate tool, Guo et al. [8] concluded a 'low-risk' of bias in the random sequence generation for the four studies included in their analysis; regardless of the fact that none of those studies employed randomization of participants. Three [16,21,22] of them had retrospective cohort designs that did not allow the randomization of participants. This can be considered as a fatal error. Hence, in the present meta-analysis, we chose to use a more appropriate instrument, the ROBINS-I tool [11], which was created to evaluate the potential for bias in non-randomized interventional trials.

Finally, it should be noted that the study conducted by Guo et al. [8] did not include a direct comparison between RFA and MWA in terms of VRR, symptoms scores, and cosmetic scores, but rather treated RFA and MWA as distinct sub-groups for analysis. They presented the data of these outcomes in both groups separately and, thus, whether the differences in these values were significant cannot be ascertained. [8] This approach is deemed inappropriate because the difference between RFA and MWA, as assessed by these outcomes in the form of a SMD or *P*-value, which are essential for assessing statistical significance, remains unobservable. Hence, the data reported by Guo et al. [8] were less meaningful when comparing RFA and MWA for benign thyroid nodules. In contrast, the present meta-analysis conducted a direct comparison between RFA and MWA in terms of VRR, symptom scores, and cosmetic scores. This comparison was made by designating one of the interventions as the reference group. Therefore, it was possible to calculate the SMDs and their accompanying *P*-values for these outcomes.

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Although in line with a previous meta-analysis by Guo et al. [8], the findings of our meta-analysis contradict those of another meta-analysis conducted by Chorti et al. [35], which found no difference between RFA and MWA in terms of VRR. The difference in findings can be attributed to variations in research methodology; Chorti et al. [35] used a network meta-analysis, whereas our study employed a traditional meta-analysis approach. As this was a network meta-analysis, Chorti et al. [35] did not directly compare RFA with MWA. Indeed, RFA and MWA are operator-dependent medical treatments, meaning that the degree of success or efficacy achieved is significantly affected by the operator's level of experience [36,37]. If the data used for the comparison between RFA and MWA do not originate from the same study and are not performed by the same operator, it will inevitably influence the outcomes. In addition, data regarding RFA and MWA that do not originate from the same study will affect the different characteristics of the participants involved in the study, which may affect the outcomes. Therefore, we conducted a traditional meta-analysis with head-to-head data to compare RFA and MWA to ensure the same baseline characteristics of the participants and same levels of operator experience for both procedures.

The current study has some limitations. First, it is worth noting that a considerable proportion of the studies included in the analysis exhibit a retrospective design, which may be susceptible to the influence of selection bias and confounding variables. The risk of bias assessment findings indicated the presence of serious bias in several studies included in our analysis. Consequently, it is imperative to exercise caution when interpreting the conclusions of our study. Second, a notable degree of heterogeneity was observed in the various outcomes of interest within this study, which can be attributed to differences in baseline characteristics among participants, variations in the techniques and instruments employed in RFA and MWA, and differences in the level of expertise among surgeons performing the ablation procedures. Furthermore, it is important to note that the sample size of each study included in this analysis is quite small, with less than 100 participants. Consequently, the generalizability of the findings of this study is limited. Finally, the studies included in the analysis lacked data regarding variations in the total cost associated with each ablation procedure, thereby limiting the ability to conduct further analysis on this aspect. Nevertheless, we argue that the results obtained from our extensive examination and meta-analysis provide useful insights into the management of benign thyroid nodules.

In conclusion, our comprehensive systematic review and meta-analysis suggests that RFA exhibits comparable levels of efficacy and safety compared with MWA in the treatment of benign thyroid nodules. Additionally, we observed a marginal advantage of RFA over MWA in terms of a shorter duration of tissue ablation and a higher alteration in VRR at the 6-month and 12-month follow-up intervals. Both minimally invasive techniques may be viable alternatives for managing benign thyroid nodules, particularly in individuals who decline or are unable to undergo surgical intervention. Furthermore, it is strongly recommended that precisely designed RCTs with substantial sample sizes be conducted in order to corroborate the results of our study.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.1004.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Formal analysis: all authors. Funding acquisition: Hendra Zufry. Investigation: all authors. Methodology: Timotius Ivan Hariyanto. Resources: Timotius Ivan Hariyanto. Supervision: Hendra Zufry. Writing—original draft: Timotius Ivan Hariyanto. Writing—review & editing: Hendra Zufry.

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REFERENCES

1. Dean DS, Gharib H. Epidemiology of thyroid nodules. *Best Pract Res Clin Endocrinol Metab* 2008;22:901-911
2. Durante C, Hegedüs L, Czarniecka A, Paschke R, Russ G, Schmitt F, et al. 2023 European Thyroid Association clinical practice guidelines for thyroid nodule management. *Eur Thyroid J* 2023;12:e230067
3. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: a review. *JAMA* 2018;319:914-924
4. Gharib H, Hegedüs L, Pacella CM, Baek JH, Papini E. Clinical review: nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. *J Clin Endocrinol Metab* 2013;98:3949-3957
5. Hegedüs L, Frasoldati A, Negro R, Papini E. European Thyroid Association survey on use of minimally invasive techniques for thyroid nodules. *Eur Thyroid J* 2020;9:194-204
6. Ding J, Wang D, Zhang W, Xu D, Wang W. Ultrasound-guided radiofrequency and microwave ablation for the management of patients with benign thyroid nodules: systematic review and meta-analysis. *Ultrasound Q* 2023;39:61-68
7. He L, Zhao W, Xia Z, Su A, Li Z, Zhu J. Comparative efficacy of different ultrasound-guided ablation for the treatment of benign thyroid nodules: systematic review and network meta-analysis of randomized controlled trials. *PLoS One* 2021;16:e0243864
8. Guo DM, Chen Z, Zhai YX, Su HH. Comparison of radiofrequency ablation and microwave ablation for benign thyroid nodules: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2021;95:187-196
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71
10. Park HY, Suh CH, Woo S, Kim PH, Kim KW. Quality reporting of systematic review and meta-analysis according to PRISMA 2020 guidelines: results from recently published papers in the Korean Journal of Radiology. *Korean J Radiol* 2022;23:355-369
11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560
13. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135
14. Cerit MN, Yücel C, Cerit ET, Yalçın MM, Şendur HN, Oktar SÖ. Comparison of the efficiency of radiofrequency and microwave ablation methods in the treatment of benign thyroid nodules. *Acad Radiol* 2023;30:2172-2180
15. Cheng Z, Che Y, Yu S, Wang S, Teng D, Xu H, et al. US-guided percutaneous radiofrequency versus microwave ablation for benign thyroid nodules: a prospective multicenter study. *Sci Rep* 2017;7:9554
16. Hu K, Wu J, Dong Y, Yan Z, Lu Z, Liu L. Comparison between ultrasound-guided percutaneous radiofrequency and microwave ablation in benign thyroid nodules. *J Cancer Res Ther* 2019;15:1535-1540
17. Javadov M, Karatay E, Ugurlu MU. Clinical and functional results of radiofrequency ablation and microwave ablation in patients with benign thyroid nodules. *Saudi Med J* 2021;42:838-846
18. Jin H, Fan J, Lu L, Cui M. A propensity score matching study between microwave ablation and radiofrequency ablation in terms of safety and efficacy for benign thyroid nodules treatment. *Front Endocrinol (Lausanne)* 2021;12:584972
19. Korkusuz Y, Gröner D, Raczynski N, Relin O, Kingeter Y, Grünwald F, et al. Thermal ablation of thyroid nodules: are radiofrequency ablation, microwave ablation and high intensity focused ultrasound equally safe and effective methods? *Eur Radiol* 2018;28:929-935
20. Sönmez S, Önder E, Navdar Başaran M, Çalışkan H, Topçu Y, Genç S, et al. A comparison of the 2 thermal ablation procedures for the management of benign thyroid nodules. *Endokrynol Pol* 2023;74:392-397
21. Vorländer C, David Kohlhase K, Korkusuz Y, Erbelding C, Luboldt W, Baser I, et al. Comparison between microwave ablation and bipolar radiofrequency ablation in benign thyroid nodules: differences in energy transmission, duration of application and applied shots. *Int J Hyperthermia* 2018;35:216-225
22. Yue WW, Wang SR, Lu F, Sun LP, Guo LH, Zhang YL, et al. Radiofrequency ablation vs. microwave ablation for patients with benign thyroid nodules: a propensity score matching study. *Endocrine* 2017;55:485-495
23. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000;53:207-216
24. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. *Stat Med* 2003;22:2113-2126
25. Ahmed M, Brace CL, Lee FT Jr, Goldberg SN. Principles of and advances in percutaneous ablation. *Radiology* 2011;258:351-369
26. Knavel EM, Brace CL. Tumor ablation: common modalities and general practices. *Tech Vasc Interv Radiol* 2013;16:192-200
27. Yue W, Wang S, Wang B, Xu Q, Yu S, Yonglin Z, et al. Ultrasound guided percutaneous microwave ablation of benign thyroid nodules: safety and imaging follow-up in 222 patients. *Eur J Radiol* 2013;82:e11-e16
28. Shin JH, Baek JH, Ha EJ, Lee JH. Radiofrequency ablation of thyroid nodules: basic principles and clinical application. *Int J Endocrinol* 2012;2012:919650
29. Boccardi V, Marano L. The geriatric surgery: the importance of frailty identification beyond chronological age. *Geriatrics (Basel)* 2020;5:12
30. Lin HS, Watts JN, Peel NM, Hubbard RE. Frailty and post-operative outcomes in older surgical patients: a systematic review. *BMC Geriatr* 2016;16:157
31. Stabile G, Bertaglia E, Pappone C, Themistoclakis S, Tondo C,

Zorzi A, et al. Influence of age and gender on complications of catheter ablation for atrial fibrillation. *J Atr Fibrillation* 2015;7:1197
32. Motaghed Z, Chegeni H, Mosadeghkhah A, Azimi Aval M, Gerami R, Ebrahiminik H. Effect of ultrasound parameters of benign thyroid nodules on radiofrequency ablation efficacy. *BMC Med Imaging* 2023;23:85
33. Deandrea M, Trimboli P, Mormile A, Cont AT, Milan L, Buffet C, et al. Determining an energy threshold for optimal volume reduction of benign thyroid nodules treated by radiofrequency ablation. *Eur Radiol* 2021;31:5189-5197
34. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928
35. Chorti A, Bontinis V, Tzikos G, Bontinis A, Ioannidis A, Michalopoulos A, et al. Minimally invasive treatments of benign thyroid nodules: a network meta-analysis of short-term outcomes. *Thyroid* 2023;33:950-964
36. Pagano L, Durante C, Tufano RP. Editorial: radiofrequency ablation as an alternative to conventional treatment. *Front Endocrinol (Lausanne)* 2022;13:883809
37. Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol* 2010;21(8 Suppl):S192-S203