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Research article

Safety and efficacy of microwave ablation for benign thyroid nodules and papillary thyroid microcarcinomas: A systematic review and meta-analysis

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ABSTRACT

Purpose: To summarize the published literature on microwave ablation (MWA) for the treatment of benign thyroid nodules and papillary thyroid microcarcinomas, and to evaluate the effectiveness and safety of MWA as a novel treatment strategy.

Methods: Two independent authors carried out the literature search using four databases, including PubMed, Embase, Cochrane, and Web of Science. The meta-analysis included prospective and retrospective data that compared pre-treatment values to post-treatment outcomes.

Results: From the 33 original articles, seven studies met the inclusion criteria for this meta-analysis. Of these, five were retrospective studies, two were prospective trials, one was controlled study, and one was a multi-center study. The results showed significant improvements in nodule volume, clinical symptom scores, and beauty scores between the baseline and final follow-up visits. In all of the studies, the most common adverse effects were hematomas, unbearable pain, and transient or permanent voice change in 3.8%, 2.2%, and 4.6% of patients, respectively. None of these incidents resulted in hospitalization or death.

Conclusions: MWA is effective and safe for the treatment of benign thyroid nodules and papillary thyroid microcarcinomas. However, future studies should compare the efficacy of MWA, RFA, and surgical intervention.

1. Introduction

The incidence of thyroid nodules continues to rise each year worldwide. Currently, it is estimated that 20–76% of adults have one or more thyroid nodules [1]. Most thyroid nodules are benign and require no treatment. While most patients are asymptomatic for decades, the growth of benign nodules can result in compression of the surrounding anatomical structures, such as the trachea, esophagus, and neck [2–4]. In these cases, surgical excision of the nodules can rapidly alleviate the compression and discomfort. For patients with hyperfunctioning thyroid nodules, treatment strategies include surgery, radioactive iodine, and percutaneous ethanol injections (PEI) to control the disease [5]. However, a small number of these patients develop hyperthyroidism, which can adversely affect the cardiovascular and skeletal systems [6]. While surgical intervention and radioactive iodine are the most common treatments in the clinic, the surgery is considered to be high risk and is associated with several complications, such as hypocalcemia, laryngeal nerve injury, hematoma formation, and hypothyroidism in some patients. In addition, elderly patients or individuals with dysfunctional immune systems are not considered as ideal candidates for surgery.

For papillary thyroid microcarcinomas, the American Thyroid Association (ATA) recommends active monitoring without surgical intervention due to the low death rates of less than 1% [7]. However, some patients choose to undergo surgery for psychological reasons, and these patients experience low recurrence rates. The most common complication after total thyroidectomy or semi-thyroidectomy is hypothyroidism, which requires life-long thyroid hormone replacement therapy with synthetic T4 medications like levothyroxine. This can decrease the quality of life for some patients, along with a visible scar associated with the surgical procedure [8].

There are several new treatment options on the horizon, most of which are minimally invasive, such as laser ablation (LA), radiofrequency ablation (RFA), high-intensity focused ultrasound(HIFU) and microwave ablation (MWA). Microwave ablation is an important minimally invasive technique, and its appearance has expanded the selection range of non-surgical minimally invasive treatment. At present, microwave ablation can be used to treat benign and malignant tumors of liver, lung, kidney, breast, bone and thyroid [39–43]. After over a decade of clinical application, MWA technique has been proved to be effective and safe for reducing the volume of thyroid nodules [15,18,29,44–46] since the first publication by Feng et al [29] to the

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best of our knowledge. MWA has several advantages in comparison to the other modalities, including its high specificity, optimal temperature to induce cell death, larger ablation volume, ablation speed, and it has less influence on the nearby blood vessels due to the heat (*i.e.*, sink effect). MWA has been used for the treatment of benign thyroid nodules and papillary thyroid microcarcinomas with excellent results [9,10,15,29]. The purpose of this systematic review and meta-analysis was to summarize the published literature about the safety and effectiveness of MWA for the treatment of thyroid nodules, especially in patients who were not surgical candidates. Currently, there is an urgent need for a comprehensive review of MWA in the treatment of thyroid nodules.

2. Materials and methods

2.1. Literature search

Four databases, including PubMed, Embase, Cochrane, and Web of Science were systematically searched for published studies using the terms (percutaneous microwave ablation OR microwave ablation OR MWA OR MW ablation) AND (thyroid OR thyroid nodules OR benign OR benign thyroid nodules OR papillary thyroid microcarcinoma OR thyroid cancer OR thyroid cancers OR thyroid carcinoma OR thyroid malignancy OR thyroid tumor). Some additional studies were found through a manual search that included references from other studies. We screened all of the articles and excluded the articles unrelated to this study. In addition, suspected duplicate publications were also excluded from this study. After applying the exclusion criteria, seven articles remained for inclusion in this systematic review and meta-analysis.

2.2. Inclusion and exclusion criteria

The studies selected were required to meet the following inclusion criteria: (1) They were original research papers written in English. (2) The study participants were human. (3) Prospective or retrospective studies. (4) However, the selected articles were not limited to randomized controlled trials. (5) The patients underwent US-guided MWA for therapy and the study compared clinical results such as nodule volume, symptom score, cosmetic score. (6) The study demonstrated the clinical value of MWA for benign thyroid nodules and papillary thyroid microcarcinoma. (7) A follow-up of at least 3 months was performed after the treatments.

We excluded studies according to the following criteria: (1) Abstracts, case reports, case series, in vitro studies and animal studies were excluded. (2) If an author has more than one article, we exclude articles with incomplete data or that are not of the latest time. Disagreements over the inclusion of any study were resolved by discussion until a consensus was reached among the authors.

2.3. Data extraction and analysis

Data were extracted from the selected studies using standardized methods, one reviewer extracted the data from the selected studies, and two reviewers verified the accuracy of the extracted data. The outcomes were conceived and the data forms constructed before the article was reviewed. The primary outcomes of this study included changes in nodule volume, symptom scores, and cosmetic scores. Other data to be extracted include: authors, year of publication, study type, hospital or medical school, study period, number of final subjects and nodules, MWA sessions, follow-up interval, nodular component and major and minor complications. The meta-analysis utilized a pre-treatment (*i.e.*, baseline) to post-treatment comparison, with all subjects serving as their own controls. Each treatment outcome was assessed and recorded as an absolute value or change from the baseline using the last available time-point.

The included articles estimated nodule volumes using the formula for the volume of an ellipsoid:

$$V = \pi/6\ (abc)$$

where a, b, and c are the largest diameters in the x-, y-, and z-dimensions.

The meta-analysis of the selected studies with a continuous measure, or the comparison of means and standard deviations between the control and treatment groups, and dichotomous variables were performed using the Cochrane Review Manager (RevMan) Version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). For the meta-analysis, both the fixed-effects model and the random-effects model were taken into account [54]. If $P \geq 0.05$, the assumption of homogeneity was deemed valid and the fixed-effects model would be applied, or else random-effects model would be used, in which both the random variation within the studies and the variation between the different studies, were incorporated into this study. Heterogeneity within the study was estimated using the I^2 statistic [55], considering a value of 25% to illustrate low heterogeneity; 50% to illustrate moderate heterogeneity; and 75% to illustrate high heterogeneity. All statistical analyses were calculated by Stata 12.0 software. For the continuous data, the standardized mean difference (SMD) was calculated for all outcomes as all of the analyzed outcomes used the same unit scale.

We assessed the quality of the included studies in terms of risk of bias using the Cochrane Collaboration's tool [56].

2.4. Statistical analysis

A 95% confidence interval (CI) was calculated for each SMD. The odds ratio (OR) and 95% CI were calculated for one dichotomous outcome. *P*-values were considered significant if less than 0.05. When possible, subgroup analyses were performed for all outcomes for "benign thyroid nodules" and "papillary thyroid microcarcinomas".

2.5. Definitions of complications

MWA-associated complications were classified as major complications and minor complications. Major and minor complications were as defined by the Society of Interventional Radiology [57,58].The major complication is defined as, if not treated, it may threaten the patient's life, lead to severe disability or long-term hospitalization. Minor complication is defined as adverse consequences that need medication to be treated to relieve it. According to the above definition, in our study major complications included transient or permanent voice change, hypoparathyroidism, esophageal injury, dysphagia, infection and nodule rupture, while minor complications included unbearable pain(severe pain that need medication to relieve it), skin burns, hematoma and vomiting.

3. Results

3.1. Literature search and screening process led to seven included studies

The process for the literature search and screening are shown in Fig. 1, as required by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In total, seven articles [9–15] met the inclusion criteria (Table 1), five of which were retrospective studies, one was a prospective, multicenter, non-randomized controlled trial, and one was a prospective, randomized, and controlled trial. All of the subjects in these studies were adults. A total of 1146 subjects and 1226 nodules were treated with MWA and subsequent follow-up procedures. Of the seven selected articles, two studies utilized multiple times rounds of MWA, while a single round of MWA was used in the other studies. In six of the studies, the follow-up times were 12 months or longer, while one study had a follow-up time

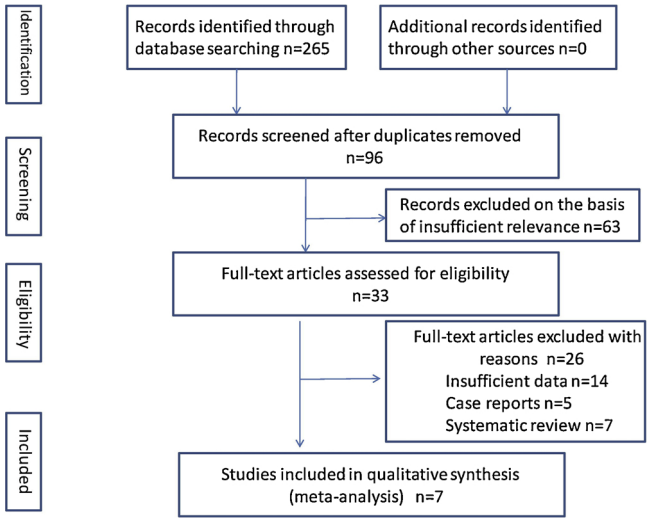

Fig. 1. PRISMA flow diagram.

of only 3 months. All post-treatment outcomes were summarized from the same follow-up visit, with the exception of adverse effects.

The risk of bias using the Cochrane Collaboration's tool was performed to assess the quality of the included studies. The summary and graphs of the risk of bias were constructed based on the investigators' judgments about each risk of bias item for each included study and represented as percentages across all the included studies (Figs. 2, Fig. 3).

3.2. MWA induces significant reductions in nodule volume in all patients

All seven studies assessed changes in nodule volume from the baseline to follow-up visits. The pooled meta-analysis demonstrated a statistically significant decrease in nodule volume both the benign thyroid nodules and papillary thyroid microcarcinomas, and the pooled proportions of the volume reduction rate (VRR) was 63% (SWD: 0.95, 95% CI: 0.84–1.06, $I^2 = 24\%$, $p < 0.00001$). The subgroup also demonstrated a significant change in volume,and the subgroup of benign thyroid nodules of proportion of VRR was 75% (SWD: 0.90, 95% CI: 0.91–1.08, $I^2 = 0\%$, $p < 0.00001$), the subgroup of papillary thyroid microcarcinomas of proportion of VRR was 59% (SWD: 0.61, 95% CI: 0.26-0.95, $I^2 = 0\%$, $p = 0.0006$), as shown in Fig. 4A, **B**, and C, respectively.

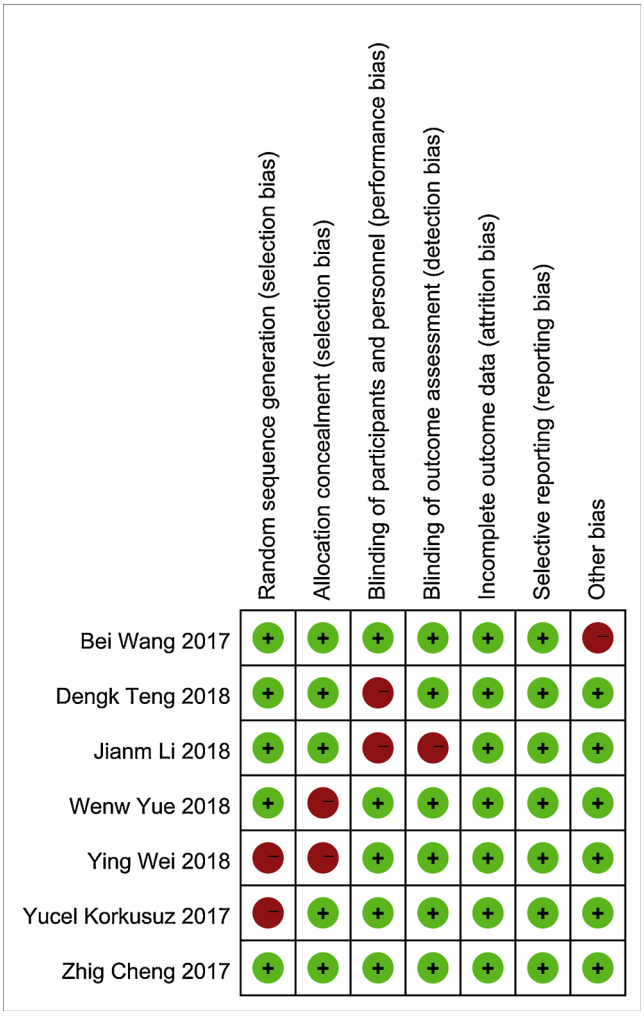

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

3.3. Symptoms and cosmetic scores

Three articles were evaluated clinically and symptomatically. Two of the studies were trials and the symptoms were rated by the subject using the 10-point VAS (visual analog scale). In three trials, a physician scored the cosmetic outcomes from 1 to 4 with minimal differences in the rating system descriptions between the trials. Changes in the

Table 1
Articles satisfying inclusion criteria.

Author, Year	Study Type	Affiliation (study period)	No. Final Subjects, Nodules	MWA Sessions	Follow-up Interval, mo	Nodular component
Bei Wang, 2017 [13]	Retrospective trial	PLA General Hospital,China(2013-2015)	110, 110	1 or 2	12	cyst, solid, mixed
Wenw Yue, 2018 [12]	Retrospective trial	Tenth People's Hospital and Yantai Affiliated Hospital,China (2012-2015)	102, 102	1	12	cyst, solid, mixed
Zhig Cheng, 2017 [10]	Prospective, multicenter non-randomized trial	Eight Hospitals#,China(2013-2016)	603, 664	1 or 2	12	cyst, solid, mixed
Ying Wei, 2018 [11]	Retrospective trial	Beijing Friendship Hospital,China(2013-2017)	230, 236	1	12	cyst, solid, mixed
Yucel Korkusuz, 2017 [14]	Retrospective observational trial	-	40, 47	1	3	cyst, solid, mixed
Jianm Li, 2018 [9]	Retrospective trial	Beijing Friendship Hospital,China(2014-2017)	46, 46	1	12	cyst, solid, mixed
Dengk Teng, 2018 [15]	Prospective, control randomized trial	The 208th Hospital of PLA,China(2013-2014)	15, 21	1	12	cyst, solid, mixed

#: The eight hospitals are:The First Affiliated Hospital of Dalian Medical University; Tianyou Hospital Affiliated to Wuhan University of Science & Technology; Chinese PLA General Hospital; Yantai Affiliated Hospital of Binzhou Medical University; Chinese PLA No. 208 Hospital; Shanghai Tenth People's Hospital; Fujian Provincial Hospital; Peking University Shenzhen Hospital.

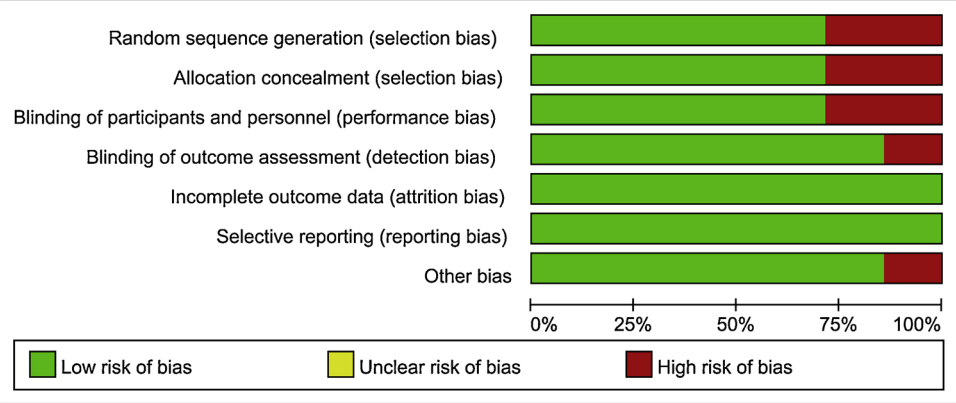

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

symptom scores on the VAS were statistically significant with a mean of SMD of 1.51 and 95% CI of -0.40 to 3.42 (Fig. 5A). In addition, the changes in cosmetic scores were also statistically significant with a mean of SMD of 1.20 and 95% CI of 0.87 to 1.52 (Fig. 5B).

3.4. Adverse effects

A list of the MWA-associated adverse effects is shown in Table 2. Transient or permanent voice change and hematomas were the most common adverse effects, while the least common was skin burns.

4. Discussion

In recent years, clinicians have become more inclined to use minimally invasive approaches to treat benign thyroid nodules and papillary thyroid cancer [16–20]. Currently, the primary methods include PEI, LA, RFA, HIFU and MWA. Ablation uses thermal energy to cause ischemia-induced coagulation and necrosis of the local tissues [21–24]. PEI is one of the most straightforward thermal ablation techniques [25], which has a unique effect on benign cystic thyroid nodules [26]. However, PEI is ineffective for treating solid thyroid nodules due to the uneven dispersion of ethanol within the tumors [2728]. Compared to PEI, LA technology has less possibility to affect the surrounding structures and has lower side effects [48–50].Alternatively, RFA can effectively treat benign thyroid nodules with fewer complications than LA [2930]. Because the principles of MWA and RFA are different, in comparison to RFA, MWA is faster, can generate higher energy, and can ablate larger tumor volumes, making it the optimal choice for the treatment of large thyroid nodules. High intensity focused ultrasound (HIFU)is an emerging thermal ablation technology. Compared with other thermal technologies, it has the advantages of without needing needle puncture and skin penetration and could induce a focused thermal tissue destruction up to 85 ℃ [52]. Therefore, high intensity focused ultrasound ablation can be considered as a truly minimally invasive surgery. The technology has been successfully applied to a wide variety of benign and malignant tumors in the liver, prostate,

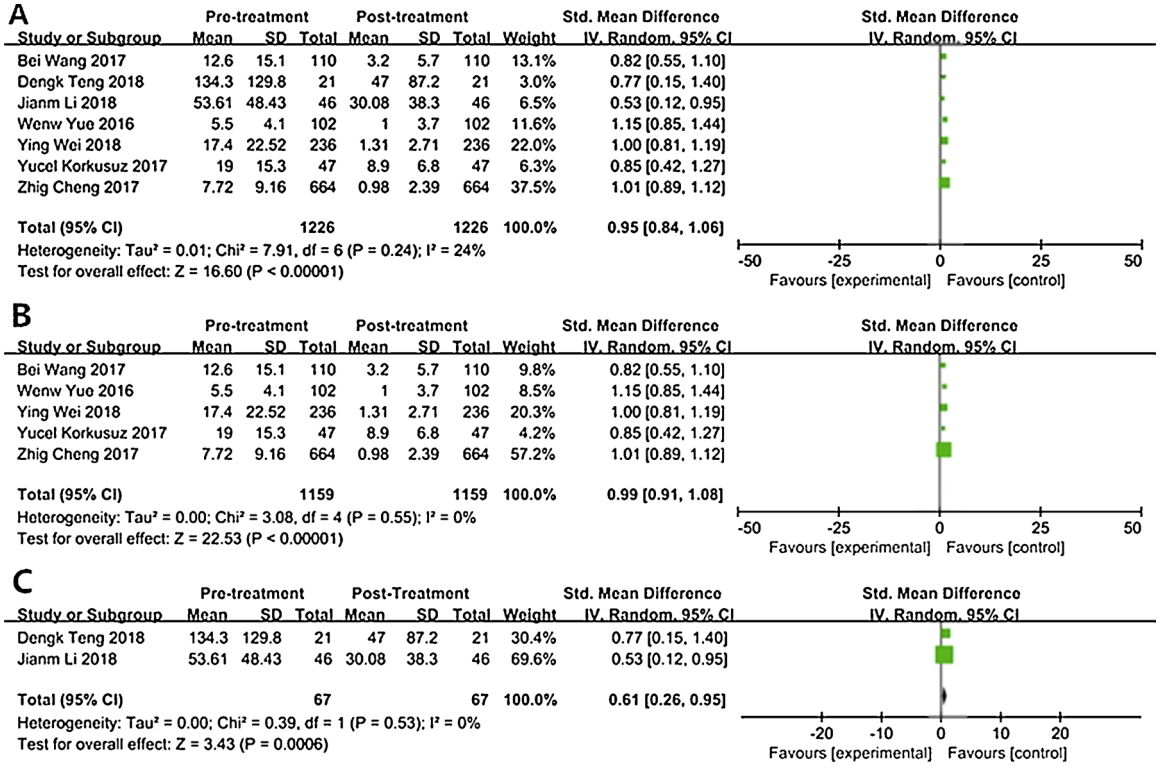

Fig. 4. A. Pooled nodule volume change. B. Benign nodule subgroup volume change.C. Malignant nodule subgroup volume change.

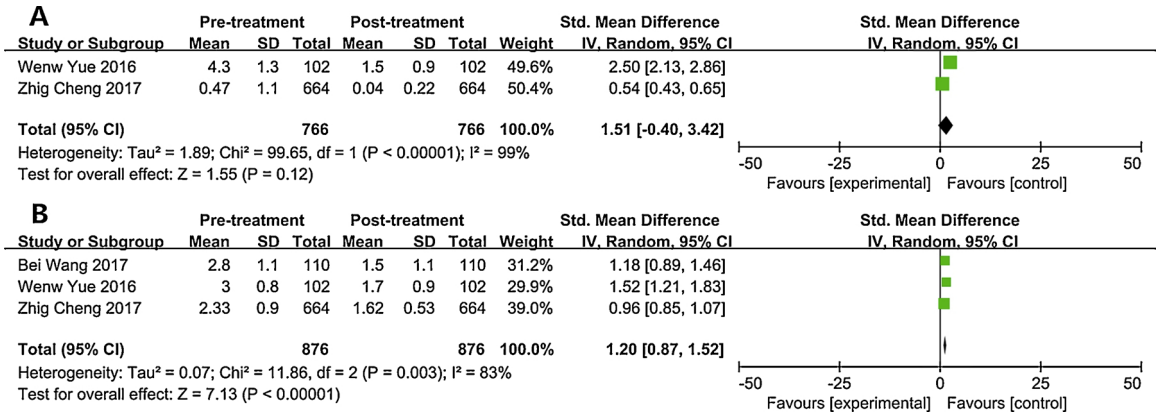

Fig. 5. A. Symptom score change. Visual analog scale score change. Values scored on a 10-point scale (0–10) of severity of symptoms related to neck mass. B.Cosmetic score change. Physician-rated cosmetic score change. Values scored on a 4-point scale (1–4).

Table 2
Summary of complications.

Classification	Complication	Number	Proportion (%)
	Transient or permanent voice change	58	4.6
	Hypoparathyroidism	0	0
Major Complications	Esophageal injury	0	0
	Dysphagia	0	0
	Infection	0	0
	Nodule rupture	6	0.5
	Unbearable pain	28	2.2
Minor Complications	Skin burns	1	0.08
	Hematoma	46	3.8
	Vomiting	0	0

bone, breast and thyroid [51–53]. Pain, discomfort, skin redness and mild subcutaneous swelling are common complications, but they usually recover quickly or in 1–2 weeks.

Every study in this review has shown that tumor volume, clinical symptom scores, and cosmetic scores of thyroid nodules significantly improve after MWA. The review underscores existing evidence that MWA is a safe and effective option for the treatment of both benign thyroid nodules and papillary thyroid microcarcinomas, especially in patients who may be poor surgical candidates. In the comparison of MWA, size reductions of the cystic nodules were substantially larger than the solid nodules or nodules with solid components, which may be due to the easy handling, absorption greater heat conduction effect [29] and the less heat sink effect of cystic components [37]. However, most nodules do not entirely disappear after MWA in most of the cases. This may be due to a delay in the immune system, as the immune cells must travel to the site of ablation to assist in the process, which can take time. One meta-analysis of the efficacy of LA and RFA demonstrated the difference in the rate of volume reduction (RFA, 77.8%, 95% CI: 67.7–88.0, vs. LA, 49.5%, 95% CI: 26.7–72.4) [47], which is also different from the results of microwave ablation for thyroid nodules this paper(63%, 95% CI: 0.84–1.06). Recently, Yue et al. [12] published an article on a direct comparison of the effects of radiofrequency ablation and microwave ablation on benign thyroid nodules. The results show that VRR of RFA group did not differ significantly from that of MWA group (79.4 vs. 77.2% and 83.6 vs. 81.6% at 6-month and 12-month follow-up) in a propensity-matched population. However, Cheng et al. [10] consider that for VRR, no significant differences were found after 3 months between the two groups, while the RFA group achieved better results than the MWA group at the 6th and 12th month and the last follow-up. In Complication, Sae Rom Chung et al. [59] giving a pooled proportion of 2.38% for overall RFA complications and 1.35% for major RFA complications, while the statistical results of this article show that a pooled proportion of 11.5% for overall complications and 5.1% for major complications after microwave ablation. In other aspects, such as anaesthetic procedure and pain control during procedure, the difference of RFA and MWA is not obvious. Although the comparison data of RFA and MWA in the current literatures are different, MWA has the following advantages: higher energy generation, larger ablation area, shorter treatment time, more thorough tumor inactivation, and more obvious effect in the treatment of thyroid nodules with larger volume. Therefore, it is widely used at present. In the aspect of number of rounds of treatment, both will encounter multiple ablations so as to achieve the goal of complete inactivation. Compared with surgery, MWA is still a minimally invasive method despite multiple ablations, and the incidence of some complications such as hemorrhage and postoperative infection is significantly reduced although there are a few nodules with multiple microwave ablation. The occurrence of multiple ablations is partly due to the scope of ablation is sometimes confined to the nodules to avoid injury to the adjacent structures, and on the other hand, especially for larger nodules, which may require multiple ablations to achieve the goal of thorough inactivation. As far as we know, there is no direct comparison about the effects between LA and MWA as well as a meta-analysis of RFA and MWA. In the end, which one is more effective still needs large sample clinical randomized controlled trials and further meta-analysis.

To ensure complete ablation of the entire nodule, physicians can increase the ablation timed or treatment area, yet this may increase the risk of damaging adjacent healthy tissues. A balance should be reached between the treatment efficacy and risk of complications [3132]. For example, Jeong et al. [31] found that approximately 33% of nodules require 2–6 rounds of ablation for complete treatment. In another study, Liu et al. [33] found that 11% of benign nodules require two rounds of MWA, while 2% of nodules require three rounds to achieve complete inactivation. Currently, 3–6 months post-treatment is recommended as the optimal time to supplement the ablation of residual tissues. This is likely due to the small size of the nodules by this time, which makes it simpler to remove.

Recurrent laryngeal nerve injury is the most common serious complication [34–36] during microwave ablation and surgery. Previous studies [12,38] have shown that artificial liquid isolation-assisted ablation is safe and effective for thyroid nodules near the trachea or esophagus. This method prevents the ablation heat from stimulating the trachea and esophagus, and also decreases the risk of coughing and pain often associated with the procedure. In addition, it also protects the laryngeal nerve from injury. In the prospective study conducted by Cheng et al., patients treated with RFA were used as the control group [10]. The results revealed that the advantages of both therapies (RFA and MWA) in treating benign thyroid nodules were not apparent. However, this was attributed to a carbonization issue, which may be

overcome by reducing the output power of the laser by 30–50 Watts to 20–30 Watts. However, additional studies are needed to verify this finding.

There are some limitations to this article. First, it lacks a control group as only some of the studies had control groups and none of the controls were consistent across all of the studies. Some studies used the operation group as the control, while others used RFA as the control group. Secondly, the articles meeting the inclusion criteria were more concentrated in one geographic area with less diversity and some overlapping of authorship. This could bring some degree of bias into this meta-analysis. These studies were removed to ensure the objectivity of this analysis. In addition, we excluded some articles with high heterogeneity to provide an objective standard. Based on the above two points, the number of articles that met our inclusion criteria was smaller than initially anticipated, which could limit the applicability of our findings.

5. Conclusions

MWA is a safe and effective treatment for benign thyroid nodules and papillary microcarcinomas. However, there is a strong need for a comparative analysis of MWA, RFA, HIFU and surgical intervention. We believe that this topic is promising for future research and has practical clinical significance.

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Disclosure

The authors declare they have no conflicts of interest.

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