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Thermal ablation for cervical lymph node metastasis from papillary thyroid carcinoma

A meta-analysis

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Abstract

Background: Traditionally, surgery has been the standard treatment for cervical lymph node metastasis in patients with papillary thyroid carcinoma (PTC). However, thermal ablation is currently recommended by several guidelines. This study aimed to evaluate the efficacy and safety of thermal ablation for lymph node metastasis in patients with PTC.

Methods: We searched PubMed, Embase, Web of Science, and China National Knowledge Infrastructure databases until March 2022 to collect studies on thermal ablation (including radiofrequency, microwave, and laser ablations) for cervical lymph node metastasis from PTC.

Results: A total of 190 patients were included, ranging from 5 to 39 in each study, with a sex ratio (male/female) ranging from 1/4 to 17/20, an average age ranging from 15.6 ± 3.0 to 62.3 ± 13.2 (yr), and a total of 270 cervical lymph nodes, ranging from 8 to 98. The follow-up results showed that thermal ablation significantly reduced the maximum diameter and volume of metastatic lymph nodes in PTC ($P < .01$). The pooled complete disappearance rate was 86% (95% confidence interval 79% to 93%). Thyroglobulin levels were significantly lower after surgery ($P < .01$). No major complications occurred, and the combined voice change rate was as low as 1% [CI 0% to 3%].

Conclusion: Our meta-analysis showed that thermal ablation is an effective and safe method for the treatment of cervical lymph node metastases from PTC. Considering the limitations of this study, more prospective, multicenter, large-sample studies are needed in the future.

Abbreviations: CLNM = cervical lymph node metastases, LA = laser ablation, MWA = microwave ablation, PTMC = papillary thyroid microcarcinoma, RFA = radiofrequency ablation, RoBANS = risk of bias for nonrandomized studies.

Keywords: laser, lymph node metastasis, microwave, radiofrequency, thyroid carcinoma

1. Introduction

Thyroid cancer is the most common endocrine cancer and one of the fastest-growing cancers in recent years.[1–4] The most common pathological subtype of thyroid cancer is papillary carcinoma, which accounts for approximately 80–85% of thyroid cancers.[2] The use of radioiodine after thyroidectomy to remove small occult lesions has been a standard treatment for patients with thyroid cancer since 1977[5], but it has become controversial recently.[6,7] Patients with low-risk papillary thyroid microcarcinoma (PTMC) are managed by active surveillance (AS) as a first-line option in Japan, Korea, and the United States,[6,8–12] which may cause anxiety among nonsurgical patients, leading to reduced quality of life and mental health problems.[13] Notably, approximately 20 to 30% of patients with PTC still develop cervical lymph node metastases (CLNM) after the first surgery.[14–16] Therefore, the 2015 American Thyroid Association guidelines recommend reoperation and/or radioiodine ablation for patients with PTC or PTMC with CLNM.[10] However, after the primary operation, the tissue plane of the operating bed develops fibrosis and undergoes deformation, resulting in a high risk of serious complications after reoperation, such as laryngeal nerve paralysis, hypoparathyroidism, and lifelong medication.[17–19]

Therefore, a noninvasive technique that is an alternative to surgical resection, with a low complication rate, needs to

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The datasets generated during and/or analyzed during the current study are publicly available.

Ethics committee approval was not required for this study because the included studies were obtained from public datasets and all patients had signed informed consent.

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be introduced to effectively eliminate PTMCs over a certain follow-up period. Thermal ablation, radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA) refer to a series of minimally invasive local treatment methods to achieve satisfactory clinical results for local tumor control in a variety of organs and have been recommended in relevant guidelines.[20] In addition, complications after thermal ablation are low.[21–24] Although thermal ablation has been effective in the treatment of PTC in recent years,[25–28] few reports exist on its efficacy and safety in CLNM from PTC, and the number of patients included in the literature is limited. Therefore, conducting a meta-analysis of thermal ablation for CLNM from PTC is necessary to provide guidance for clinical practice.

2. Method

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29]

2.1. Search strategy

PubMed, Embase, Web of Science, and China National Knowledge Infrastructure databases were searched until March 2022. The search terms included ((papillary thyroid carcinoma) OR (thyroid papillary microcarcinoma)) AND (lymph node metastasis) AND (ablation). Additionally, references were searched to identify related articles. Two reviewers independently selected potentially relevant studies by screening the retrieved literature. Disagreements were resolved through consensus.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included: patients diagnosed with CLNM from PTC or PTMC and treated with thermal ablation, RFA, MWA, or LA; prospective or retrospective studies; and treatment outcomes including diameter reduction, volume reduction, complete disappearance, thyroglobulin (TG) reduction, and complications. Studies meeting the following criteria were excluded: case reports/series; reviews and comments; studies not written in English; and overlapping studies.

2.3. Data extraction

On the basis of the PRISMA guidelines,[29] a standardized form was used to extract the following data from eligible studies: study characteristics: first author, year of publication, country, study design, and duration of study; demographic and clinical characteristics of the patients: age, sample size, thermal ablation modality, lymph nodes (number, maximum diameter, and volume), and duration of follow-up; and treatment outcome: maximum diameter reduction, volume reduction, complete disappearance, TG reduction, and complications. One reviewer (blinded) extracted the data, and another (blinded) confirmed the validity of the data.

2.4. Quality assessment

Two reviewers independently extracted data from the included studies and used the Risk of Bias Assessment for Non-randomized Studies (RoBANS) tool for non-randomized controlled trials.[30]

2.5. Statistical analyses

Statistical analyses were performed using R 4.0.5 with the "meta" package (version 4.18–1) and its dependencies. Continuous variables are presented as means with standard deviations. The 95% confidence interval (CI) was calculated for each mean difference (MD). P-value < 0.05 was considered significantly different. Heterogeneity was examined using the Q-test and I^2 statistics. A random-effects model was used when studies were heterogeneous ($P < .1$ or $I^2 > 50\%$); otherwise, a

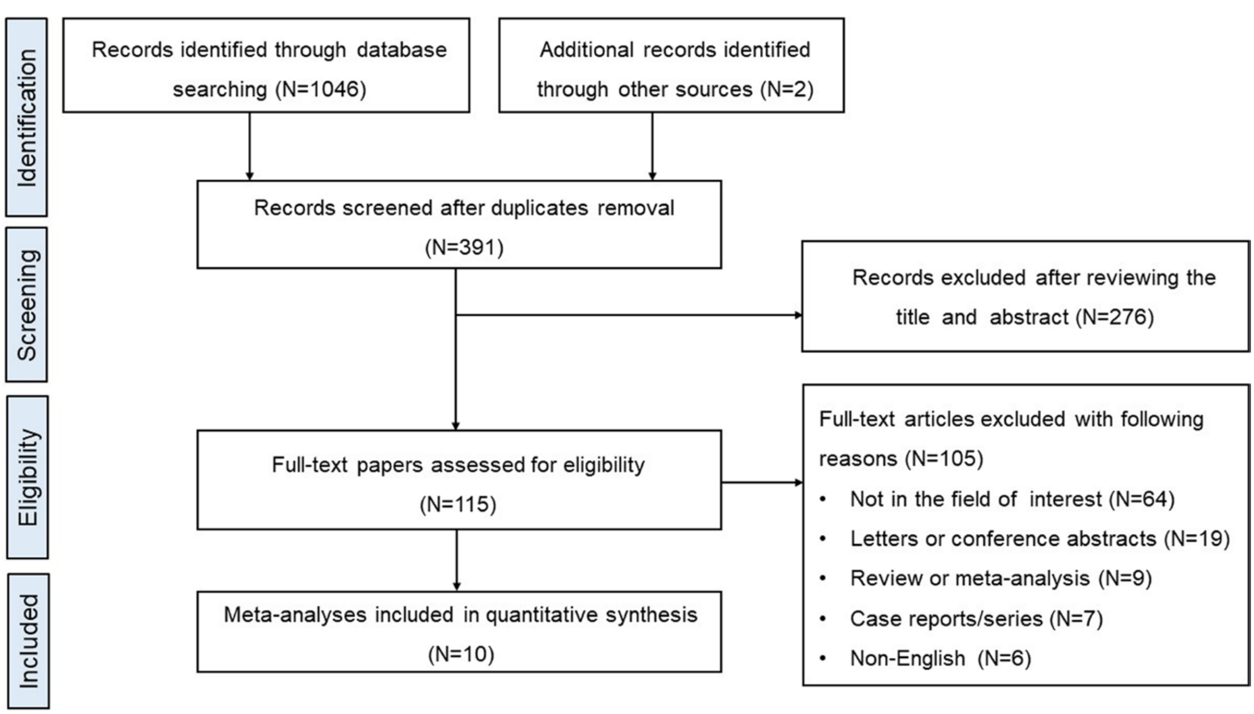

Figure 1. Procedure for the selection process of the included articles.

fixed-effects model was used.[31] In addition, subgroup analyses were conducted according to the different thermal ablations, and between-subgroup differences were tested using the *Q*-test. Statistical significance was set at $P < .05$.

3. Results

3.1. Literature search results

The literature screening process is shown in Fig. 1. A total of 1046 records were initially retrieved. Two related articles were obtained using other methods. After removing the duplicates, only 391 records remained. Among them, 276 records were eliminated after the title and abstract were reviewed, leaving 115 articles. After full-text reading, articles were excluded for the following reasons: not in the field of interest (N = 64), letters or conference abstracts (N = 19), reviews or meta-analyses (N = 9), case reports/series (N = 7), and non-English articles (N = 6). After searching references in the literature, no eligible studies were found. Finally, a total of 10 articles[32–41] were included, including 190 patients.

3.2. Study characteristics

The detailed characteristics of the 10 included articles[32–41] are shown in Table 1. All of the included articles were published within the last 10 years, and 70% of them were published within the last 5 years. Among the different ablation modalities, 3 articles applied RFA,[33,35,41] 4 applied MWA,[36,37,39,40] and 3 applied LA.[32,34,38] Regarding the study design, only one article was a prospective study[31] and the remainder were retrospective studies.[32–40] A total of 190 patients were included, ranging from 5 to 39 in each study, with a sex ratio (male/female) ranging from 1/4 to 17/20, an average age ranging from 15.6 ± 3.0 to 62.3 ± 13.2 (years), and a total of 270 cervical lymph nodes, ranging from 8 to 98.

As shown in Fig. 2(A, B), the quality assessment of the RoBANS showed that the overall quality of the included studies was moderate, and at least one of the studies was highly biased. The risk of bias for some items was unclear in 6 studies. Thermal ablation techniques and equipment were described in all studies.

3.3. Maximum diameter reduction of metastatic lymph nodes

A total of 7 studies[33,36–41] reported the maximum reduction in the diameter of metastatic lymph nodes after ablation. Owing to the significant heterogeneity among the studies ($I^2 = 98\%$, $P < .01$; Fig. 3), a random-effects model was used. The results showed that the maximum diameter of metastatic lymph nodes was significantly reduced after ablation than before ablation (MD = 6.92 mm; 95% CI, 2.86 to 10.98; $P = .0008 < 0.01$; Fig. 3). Subgroup analysis showed no significant differences between the groups ($P = .90$).

3.4. Volume reduction of metastatic lymph nodes

A total of 8 studies[32,33,35–39,41] reported a reduction in the incidence of metastatic lymph nodes after ablation. Owing to the significant heterogeneity among the studies ($I^2 = 90\%$, $P < .01$; Fig. 4), a random-effects model was used. The results showed that the volume of metastatic lymph nodes was significantly reduced after ablation than before ablation (MD = 271.95 mm^3; 95% CI, 173.65–370.24; $P < .01$; Fig. 4). Subgroup analysis showed no significant difference between the groups ($P = .81$).

3.5. Complete disappearance of metastatic lymph nodes

A total of 10 studies[32–41] reported the complete disappearance of metastatic lymph nodes after ablation. Owing to the significant heterogeneity among the studies ($I^2 = 86\%$, $P < .01$; Fig. 5), the random-effects model was used. As seen in Fig. 5, the results showed that the complete disappearance rate of metastatic lymph nodes after ablation reached 95% CI of 0.86 [0.79, 0.93]. In addition, subgroup analysis showed no significant differences between the groups ($P = .40$).

Table 1

Basic characteristics of the included articles in the meta-analysis.

Authors (year)	Country	Thermal ablation modality	Study design	Duration of study	No. of patients (Male/Female)	Age (years) Mean ± SD or median/range	No. of lymph nodes (Lateral/central)	Follow-up (mo) Mean ± SD or median/range
Papini et al (2013)[32]	Italy	LA	Pro	Jan 2009 to Dec 2010	5 (1/4)	53.6 ± 18.3	8 (N.R.)	12/N.R.
Lim et al (2015)[33]	Korea	RFA	Retro	Sep 2008 to Apr 2012	39 (14/25)	52.8 ± 16.7	61 (N.R.)	26.4 ± 13.7
Mauri et al (2016)[34]	Italy	LA	Retro	Sep 2010 to Dec 2013	24 (11/13)	62.3 ± 13.2	46 (43/3)	30.0 ± 11.0
Guang et al (2017)[35]	China	RFA	Retro	Jul 2013 to Aug 2014	33 (11/22)	43.7/22–67	54 (45/9)	21.0 ± 4.0
Teng et al (2018)[36]	China	MWA	Retro	May 2014 to Jun 2015	11 (3/8)	40.4 ± 10.5	24 (23/1)	32.0 ± 22.9
Zhou et al (2019)[37]	China	MWA	Retro	Jan 2017 to Apr 2018	14 (3/11)	45.1 ± 12.1	21 (15/6)	8.4 ± 4.1
Guo et al (2020)[38]	China	LA	Retro	Jun 2016 to Sep 2017	8 (3/5)	39.0 ± 11.6	18 (15/3)	12.8 ± 2.1
Cao et al (2020)[39]	China	MWA	Retro	Nov 2015 to Nov 2018	14 (3/11)	46.9 ± 11.9	38 (32/6)	23.6 ± 9.3
Han et al (2020)[40]	China	MWA	Retro	Jun 2015 to Jan 2020	37 (17/20)	43.6 ± 13.8	98 (79/19)	11.1 ± 9.2
Yan et al (2021)[41]	China	RFA	Retro	Dec 2014 to Mar 2018	5 (2/3)	15.6 ± 3.0	10 (9/1)	52.0 ± 21.4

LA = laser ablation; MWA = microwave ablation; NR = not reported; Pro = prospective; Retro = retrospective; RFA = radiofrequency ablation.

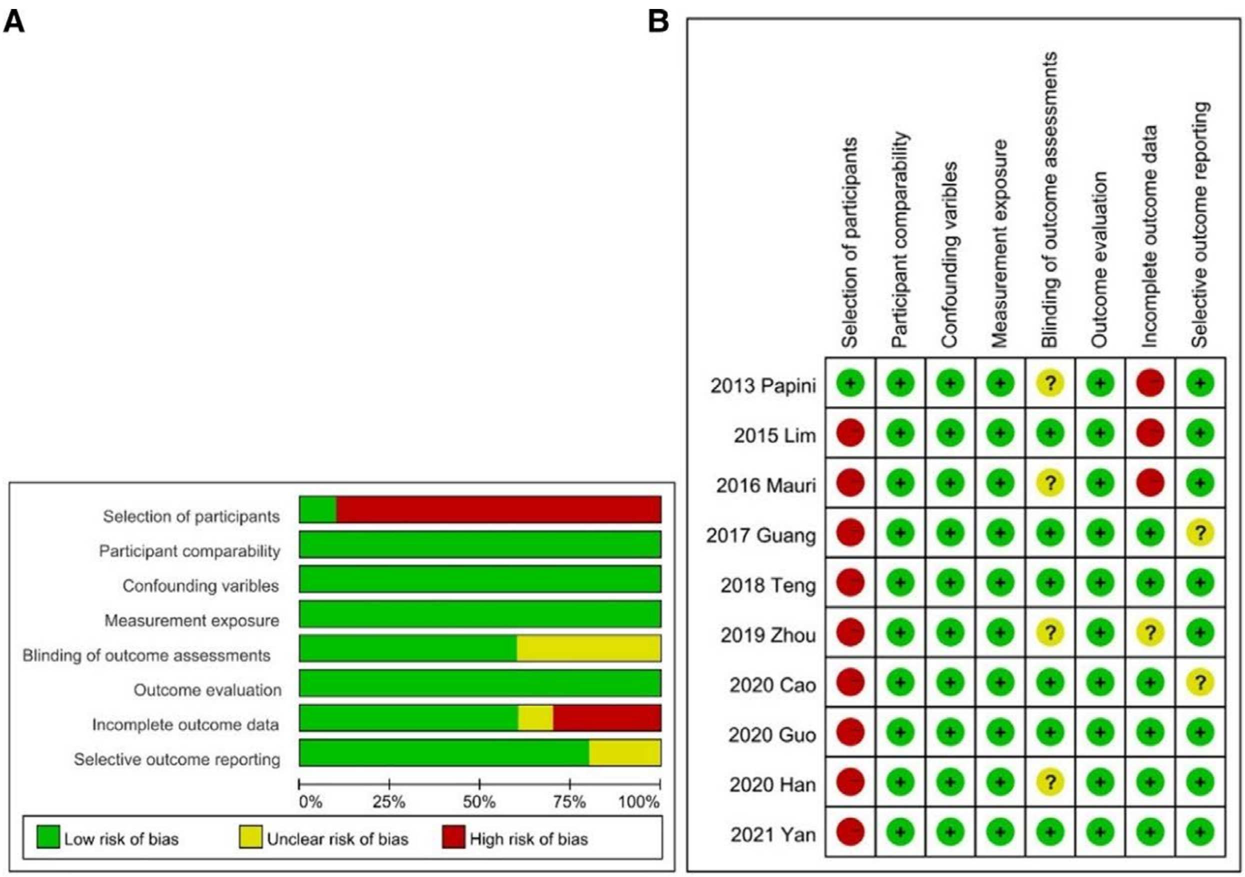

Figure 2. (A, B) The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) criteria.

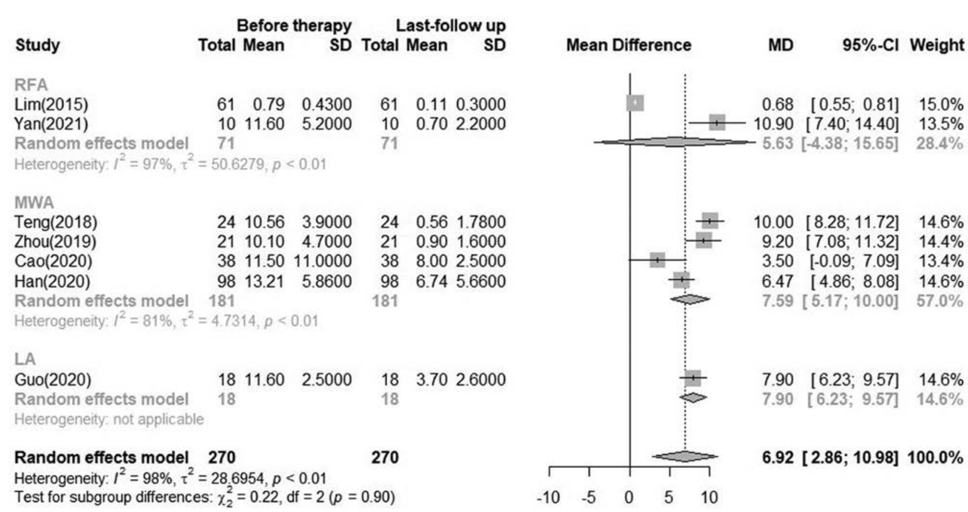

Figure 3. Forest plots of pooled estimates of the average maximum diameter reduction (mm) in the RFA, MWA, and LA subgroups. Data were analyzed using the random-effects model. LA = laser ablation, MWA = microwave ablation, RFA = radiofrequency ablation.

3.6. Decrease in serum TG

A total of 9 studies[32–39,41] reported that serum Tg levels decreased after ablation. Owing to the significant heterogeneity among the studies ($I^2 = 97\%$, $P < .01$; Fig. 6), the random-effects model was used. The results showed that the Tg level was significantly decreased after ablation than before ablation (MD = 6.91 ng/mL; 95% CI, 3.74 to 10.07; $P < .01$; Fig. 6). The subgroup analysis showed no significant difference between the groups ($P = .97$).

3.7. Subgroup analysis

Subgroup analysis was conducted for comfort and duration of the operation. The results showed that the best comfort condition was in the RFA treatment group (Table Supplementary 1, http://links.lww.com/MD/I71), followed by the MWA and LA treatment groups. The longest duration of surgery was observed in the LA group (Table Supplementary 2, http://links.lww.com/MD/I72).

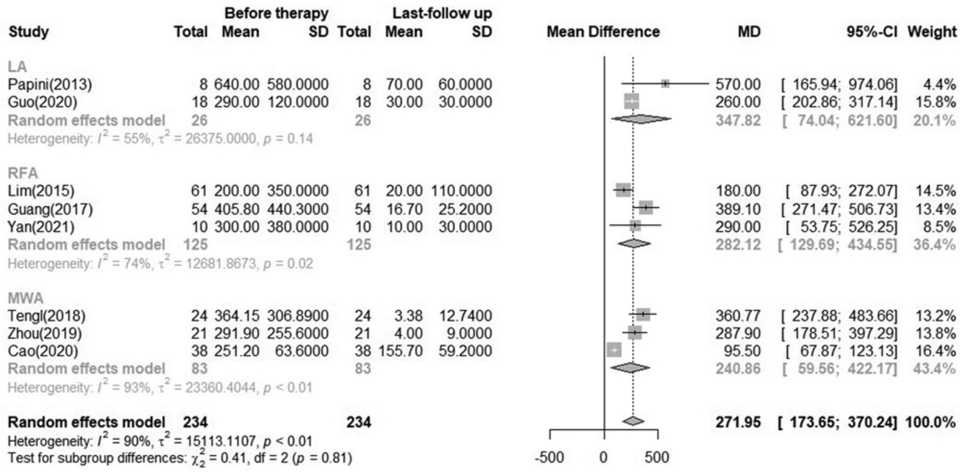

Figure 4. Forest plots of pooled estimates of mean volume reduction (mm³) in the RFA, MWA, and LA subgroups. Data were analyzed using the random-effects model. LA = laser ablation, MWA = microwave ablation, RFA = radiofrequency ablation.

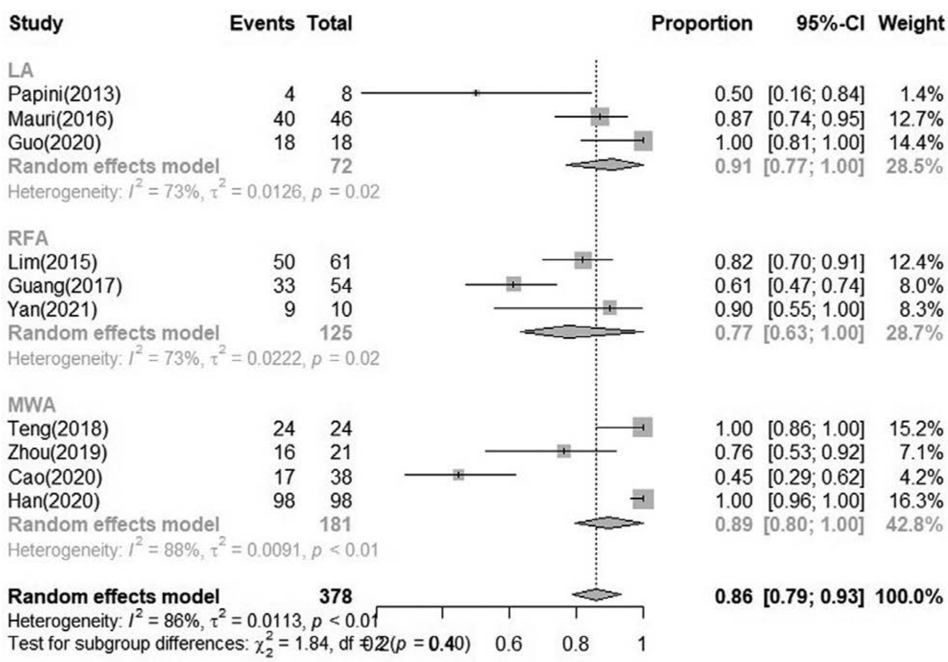

Figure 5. Forest plots of pooled proportions of the voice change in the RFA, MWA, and LA subgroups. Data were analyzed using the random-effects model. LA = laser ablation, MWA = microwave ablation, RFA = radiofrequency ablation.

3.8. Complications

No major complications were reported in any of the studies included. A total of 10 studies[32–41] reported the occurrence of voice changes after ablation. The heterogeneity of the studies was relatively low ($I^2 = 0\%$, $P = .78 > 0.01$; Fig. 7), and a fixed-effects model was used. As shown in Fig. 7, the results showed that the incidence of voice change after ablation was 1% [0%, 3%]. The group analysis showed no significant difference between the groups ($P = .65$).

4. Discussion

Thermal ablation is considered an intermediate state between reoperation and AS, without the disadvantages of both. It is considered a suitable treatment for CLNM because of its efficacy and safety in controlling small lesions. Furthermore, according to the 2021 European guidelines in malignant thyroid disease,[42] thermal ablation may be considered in patients with low-risk PTMC and in those with refractory thyroid cancer metastases who are not candidates for surgery.

The results of this meta-analysis showed that thermal ablation is an effective method for the treatment of CLNM from PTC. The pooled data showed that, after thermal ablation, the maximum diameter and volume of the metastatic lymph nodes were significantly reduced than those before ablation ($P < .01$), the percentage of metastatic lymph nodes that disappeared completely was as high as 80%, the serum TG level was significantly reduced, and there was no statistical difference in each index between the groups ($P > .05$). In terms of safety, the most common reported complication was transient voice change, with pooled data showing an incidence rate of only 1%. Notably, none of the included studies reported major complications such as permanent laryngeal nerve palsy and hypocalcemia. Thus, thermal ablation is an effective and safe treatment for metastatic lymph nodes from PTC.

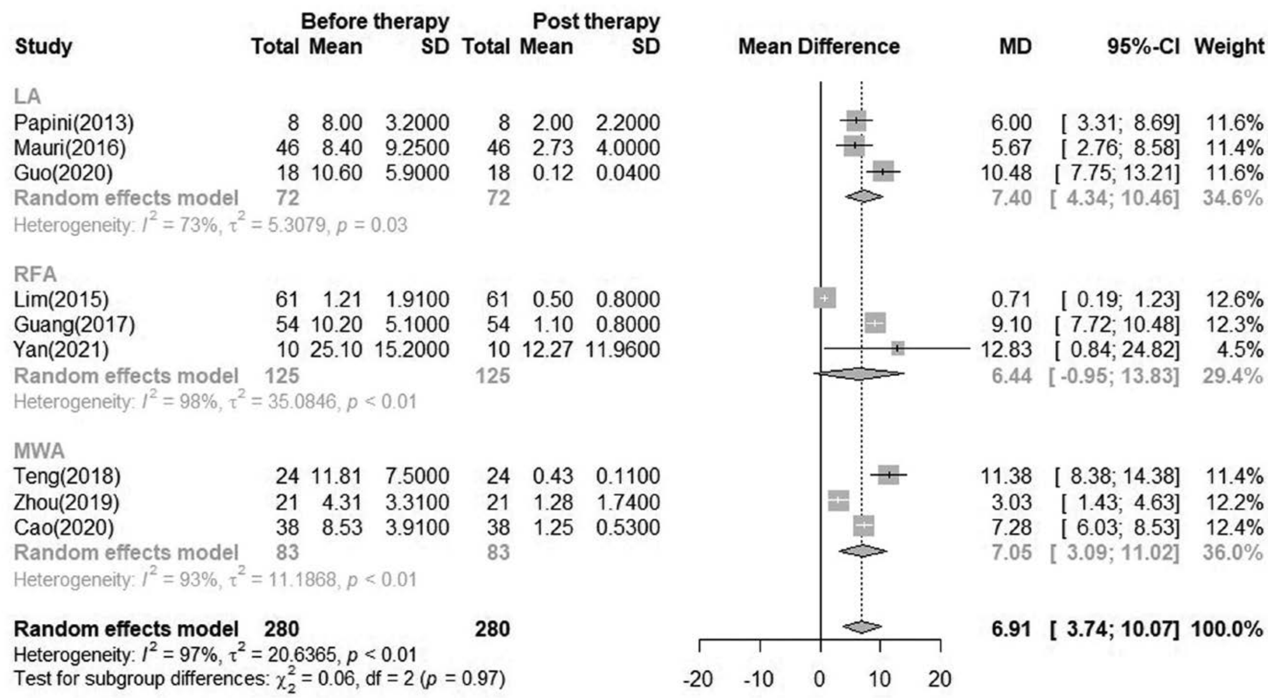

Figure 6. Forest plots of pooled estimates of the decreasing in serum Tg (mm) in the RFA, MWA, and LA subgroups. Data were analyzed using the random-effects model. LA = laser ablation, MWA = microwave ablation, RFA = radiofrequency ablation.

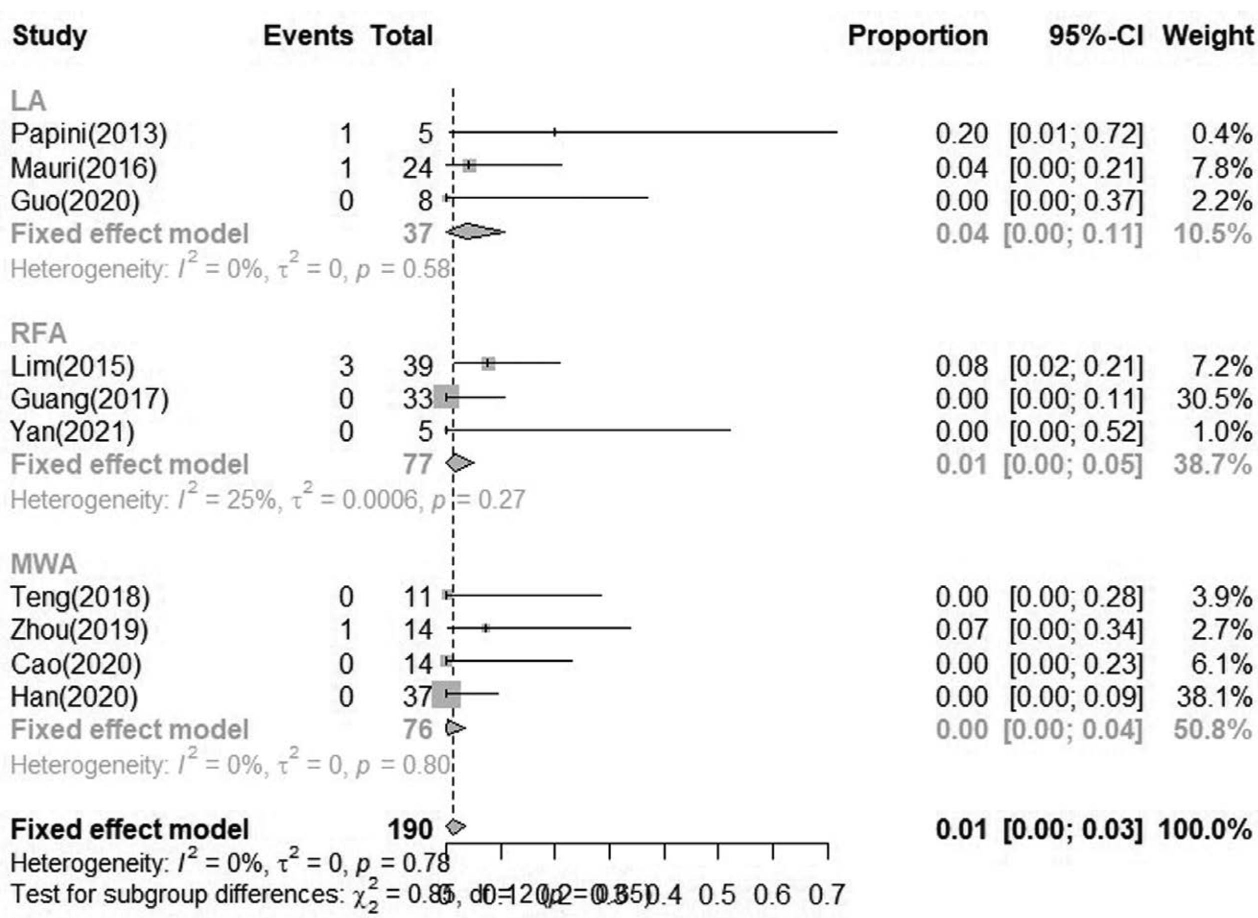

Figure 7. The incidence of voice change after ablation.

Volume reduction is one of the most important indicators for evaluating ablation efficacy. Ablation success was defined as a tumor volume reduction > 50%.[43] A large population study involving 236 patients with thyroid nodules reported an 84.8% reduction in nodule volume at 1-year follow-up.[44] In another study, Lim et al reported[33] that the volume reduction rate of metastatic lymph nodes in thyroid cancer reached 95.1 ± 12.3% 1 year after ablation. Although the effect of volume reduction mentioned in the above literature is similarly to that in this study, the heterogeneity among the studies was relatively high ($I^2 > 50\%$), which may be related to insufficient follow-up time in some of the included studies, resulting in inaccurate statistical results. For example, the follow-up period of Zhou et al[37] was only 8 months. Of note, cosmetic problems also improved in some patients after thermal ablation, and symptoms of compression of the surrounding tissues were reduced, which relieved the patients' anxiety.[37,45] In patients who respond well to ablation, enlarged nodules or metastatic lymph nodes may be completely absorbed and disappear during follow-up. In addition, the statistical results of this meta-analysis showed that the complete disappearance rate of metastatic lymph nodes reached 80%. Some patients had residual calcifications or cicatrice-like lesions after lymph node ablation, and no enhancement was observed on enhanced angiography; this was not included in the index of complete lymph node disappearance, resulting in certain statistical errors.

Serum TG is a large glycoprotein produced only by normal thyroid tissue or well-differentiated thyroid cancers.[46] Therefore, serum TG levels after thyroidectomy can be used to predict tumor recurrence and metastasis. Owing to the good cure rate after thyroidectomy and adjuvant administration of radioactive iodine ablation, most patients had no obvious clinical symptoms during follow-up, and serum TG remained at a very low level, which was consistent with the findings of this meta-analysis. For patients with recurrent thyroid cancer or CLNM, a more sensitive and specific detection method is required to obtain an early intervention at the follow-up stage. Therefore, postoperative serum TG monitoring is necessary to detect potential lymph node metastases.[47]

Voice change is one of the most common complications of thermal ablation and may result from recurrent laryngeal nerve dysfunction due to thermal effects and bleeding.[48] The results of this study showed that the complication rates of the 3 thermal ablation methods were relatively low, with no significant difference ($P > .05$), which may be related to the frequency of ablation, type of equipment, operator experience, and technology. Although only 6 patients in this study had temporary voice changes, some measures could still be taken to avoid injury. For example, during RFA treatment, the moving shot technique, trans-isthmic approach, and undertreatment of the danger triangle may minimize recurrent laryngeal nerve injury. In addition, during thermal ablation, real-time ultrasound (US) guidance and the hydrodissection technique have been introduced as safe techniques to prevent thermal damage to the nerve.[49]

This study had some limitations. First, the follow-up periods of the included studies were insufficient. Moreover, the length of the follow-up varied among the included studies. Second, the ablation methods (MWA, RFA, or LA) and the methods used to confirm successful ablation (Doppler US or contrast-enhanced US) were not identical in each study, which may have affected accuracy. Third, most of the included studies were concentrated in Asia, and the results are not universal. Finally, the sample sizes of the included studies were relatively small, and most were retrospective. Despite these limitations, we applied a robust approach using currently available evidence and demonstrated that RFA, MWA, and LA are effective therapies for the management of PTMC in terms of efficacy and safety.

5. Conclusion

In summary, the results of our meta-analysis showed that thermal ablation is an effective and safe method for the treatment of CLNM from PTC. Considering the limitations of this study, more prospective, multicenter, large-sample studies are needed in the future.

Acknowledgments

Author contributions

YZ and XX were the main researchers in this study and took part in the study conceptualization, literature review, data extraction, analysis, and writing of the manuscript. YW, FL, and QW revised the manuscript editing. XX, YZ, and YL planned the study and revised the manuscript. All authors read and approved the final manuscript.

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Writing—original draft: Xiaoyi Xiao.

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