

The efficacy and safety of radiofrequency ablation in papillary thyroid carcinoma: A systematic review and meta-analysis

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ABSTRACT

Introduction: Radiofrequency ablation (RFA) avoids the complications of general anaesthesia, reduces length of hospitalisation and reduces morbidity from surgery. As such, it is a strong alternative treatment for patients with comorbidities who are not surgical candidates. However, to our knowledge, there have only been 1 systematic review and 3 combined systematic review and meta-analyses on this topic to date. This systematic review and meta-analysis seeks to evaluate the efficacy and safety of RFA in the treatment of papillary thyroid carcinoma (PTC) with longer follow-up durations.

Method: PubMed, Embase and Cochrane databases were searched for relevant studies published from 1990 to 2021; 13 studies with a total of 1366 patients were included. The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and Sandelowski et al.'s approach¹ to "negotiated consensual validation" were used to achieve consensus on the final list of articles to be included. All authors then assessed each study using a rating scheme modified from the Oxford Centre for Evidence-Based Medicine.

Results: Pooled volume reduction rates (VRRs) from 1 to 48 months after RFA, complete disappearance rates (CDR) and complications were assessed. Pooled mean VRRs were 96.59 (95% confidence interval [CI] 91.05–102.13, $I^2=0\%$) at 12 months²⁻⁶ and 99.31 (95% CI 93.74–104.88, $I^2=\text{not applicable}$) at 48 months.^{2,5} Five studies showed an eventual CDR of 100%.^{2,4,7-9} No life-threatening complications were recorded. The most common complications included pain, transient voice hoarseness, fever and less commonly, first-degree burn.

Conclusion: RFA may be an effective and safe alternative to treating PTC. Larger clinical trials with longer follow-up are needed to further evaluate the effectiveness of RFA in treating PTC.

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Keywords: efficacy, otorhinolaryngology, papillary thyroid cancer, radiofrequency ablation, safety

CLINICAL IMPACT

What is New

- In the treatment of papillary thyroid carcinoma (PTC) using radiofrequency ablation (RFA), pooled mean volume reduction rates after 6 months were above 90%.
- Eventual complete disappearance rates of 100% were reported in 5 studies.

Clinical Implications

- No life-threatening complications from RFA were recorded; the most common complications were pain, transient voice hoarseness, fever and less commonly, first-degree burn.
- RFA may be an effective and safe alternative treatment choice to treat PTC, particularly for patients with comorbidities who are not surgical candidates.

INTRODUCTION

Malignant nodules account for 5–15% of all thyroid nodules and papillary thyroid carcinoma (PTC) accounts for 85% of that.¹⁰ Most guidelines recommend surgery as the first-line treatment for PTC.¹¹ However, surgery does carry a risk for complications, such as hypothyroidism and recurrent laryngeal nerve damage leading to voice hoarseness.¹²⁻¹⁷ Thus, other treatment strategies, such as active surveillance (AS)¹⁸ and thermal ablation¹⁹ have been explored.

Thermal ablation can be broadly categorised into 3 main techniques: microwave ablation (MWA), laser ablation and radiofrequency ablation (RFA). In recent years, RFA has been shown to yield successful results in the treatment of a variety of

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thyroid diseases. This paper will focus on this technique. RFA utilises an alternating current with a frequency ranging between 200 kHz and 1200 kHz to produce local thermal energy, generating temperatures between 50°C and 100°C resulting in tissue necrosis, and this process may be guided using an ultrasound.

RFA avoids complications of general anaesthesia, reduces length of hospitalisation and reduces morbidity from surgery.²⁰ It has shown promising outcomes in thyroid disease, specifically PTC.^{2,5,8,21,22} Long-term observation of RFA in the treatment of PTC showed a good volume reduction rate (VRR), low tumour recurrence and low lymph node metastasis rate. This presents a strong alternative treatment choice for patients who are not surgical candidates due to the presence of comorbidities. In fact, the 2021 Cardiovascular and Interventional Radiology Society of Europe/European Thyroid Association clinical practice guidelines²³ proposed AS and ultrasound-guided minimally invasive treatment (MIT) for suitable cases of PTC. This multidisciplinary consensus statement also states that AS and ultrasound-guided MITs may be used as an alternative management option to thyroidectomy for selected cases of papillary thyroid microcarcinoma (PTMC). It may even be considered for patients with differentiated thyroid carcinoma in the following conditions: PTMC, unresectable thyroid cancer, neck lymph node recurrence of differentiated thyroid cancer and distant metastases.²⁴

According to the 2015 American Thyroid Association clinical practice guidelines, AS is a recommended option for the management of PTMCs.¹¹ However according to the data provided by Oh et al.,²⁵ nearly half of their patient cohort with PTMC (48.3%) who accepted AS had experienced anxiety during their follow-up and underwent delayed thyroid surgery thereafter.

In 2023, the American Thyroid Association updated a statement on utilising ablation techniques on benign thyroid nodules²⁶—however, there has not been a statement on utilising ablation techniques on PTCs. Nevertheless, it provides a general framework of recommendations for RFA such as using a moving shot technique with hydrodissection, and guidelines on the management of periprocedural complications.

To our knowledge, there have only been 5 combined systematic review and meta-analyses on this topic to date.²⁷⁻³¹ Our systematic review and meta-analysis seeks to evaluate the efficacy and safety of RFA in the treatment of PTC, with the aim of updating the information presented in previous

studies, given the emergence of several new findings and to examine the benefits of longer follow-up durations.

METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this paper. The study team consulted a team of experts that comprised the head and neck surgical oncologists at the Department of Otorhinolaryngology of Tan Tock Seng Hospital, a tertiary care teaching hospital in Singapore.

Guided by the Population, Intervention, Comparison, Outcome and Study (PICOS) design elements of the inclusion criteria, the primary research question was determined as follows: How efficacious is RFA as a treatment for PTC? The secondary research question was determined as: How safe is RFA as a treatment for PTC? Efficacy may be defined by VRR and complete disappearance rate (CDR), which are the main outcomes examined in this study. Evaluation of safety encompassed the risk of post-procedure complications.

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and is available online with the registration number: CRD42023432383. No amendments have been made to the protocol.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review, guided by the PICOS framework are outlined in Table 1.

Search strategy

The PubMed, Embase and Cochrane databases were searched to identify articles that evaluated the efficacy and safety of RFA as a treatment for PTC.

Articles published from 1 January 1990 to 30 February 2023 were searched using the terms “radiofrequency ablation” and “papillary thyroid carcinoma”. All articles published in English or had English translations were included. The search was carried out between 5 March 2023 and 9 March 2023. The search process is summarised in the PRISMA flowchart (Fig. 1).

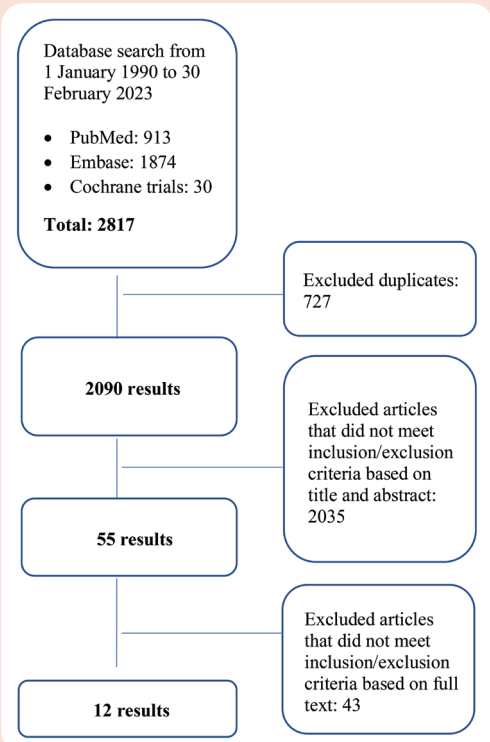
Two reviewers (WSCC and XYJA) independently assessed the titles and abstracts found in each database to compile the definitive list of articles for review. The method of “negotiated consensual validation” by Sandelowski et al. (2007)¹ was used to establish agreement on the final list of articles selected. In cases where consensus between the 2 initial reviewers was not achieved, the article

Table 1. Inclusion and exclusion criteria.

PICOS elements	Inclusion	Exclusion
Population	• Papillary thyroid cancer • Age older than 18 years	• Extra-thyroidal tissue • Benign neoplasms
Intervention	• RFA	• Other types of ablation • Non-ablative therapies
Comparison	• Comparisons of the number of nodules ablated by RFA • Mean size (volume) of ablated nodules • Amount of energy delivered per treatment • Treatment time • Complications • VRR	
Outcome	• Complete follow-up data of the number of nodules ablated by RFA • Mean size (volume) of ablated nodules • Amount of energy delivered per treatment • Treatment time • Complications • VRR	
Study design	• Articles in English or translated to English • Randomised controlled trials, cohort studies, case-control studies, cross-sectional studies • Year of publication: 1 January 1990 to 30 February 2023 • Databases: PubMed, Embase, Cochrane	• Grey literature/electronic and print information not controlled by commercial publishing • Case reports or series with 10 or fewer patients • Reviews, meta-analyses, descriptive papers, letters, editorials, conference abstracts, guidelines, consensus statements • Studies with or likely with overlapping populations of patients studied • Studies focusing on non-human subjects • Studies with insufficient data on volume reduction of treated nodules

PICOS: Population, Intervention, Comparison, Outcome and Study; RFA: radiofrequency ablation; VRR: volume reduction rate

Fig. 1. PRISMA flowchart for inclusion of selected articles in this systematic review and meta-analysis.



in question underwent review by 4 additional reviewers.

Data extraction

A standardised excel spreadsheet was used to extract data from all included articles. Data extracted is summarised in Supplementary Table S1.

Statistical analysis

The main outcomes of this study were VRR of the treated nodule at 1, 3, 6, 12, 18, 24, 30, 36 and 48 months. The CDR was analysed as well—this was defined as 100% disappearance of lesions based on ultrasound findings. Meta-analytic pooling was performed using inverse variance for calculating weights, and Der Simonian-Laird random-effects model was used to determine the pooled proportions and 95% confidence intervals (CI). The I^2 statistic for the pooled estimates was employed to determine heterogeneity among studies with $P<0.1$ indicating statistical significance. According to the Cochrane Handbook for Systematic Reviews of Interventions,³² while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not

be taken as evidence of no heterogeneity. Interpretation of the I^2 statistic may be interpreted as follows: slight (0–40%), moderate (30–60%), substantial (50–90%) or considerable (75–100%) heterogeneity.³² The $P < 0.1$ threshold was employed given the low statistical power of the chi-square test. A random-effects model was applied throughout. All statistical analyses were performed using RevMan 5.4 software (Review Manager [RevMan] [Computer program]. Version 5.4, The Cochrane Collaboration, 2020).

Risk of bias

The quality of evidence of each study was rated according to a rating scheme modified from the Oxford Centre for Evidence-Based Medicine.³³ Only studies conducted on non-palliative cases of PTC were included in this study to ensure a more uniform analysis of VRRs. However, other confounding factors, such as tumour size and location, could not be controlled as the studies did not provide specific details regarding the patient selection criteria, such as tumour size and location.

RESULTS

The search from the 3 databases retrieved 2817 articles. There were 2090 articles after the exclusion of 727 duplicates. After reviewing the titles and abstracts, 55 articles were included. The full texts of these 55 articles were retrieved. After reviewing these, 12 were included in both the systematic review and the meta-analysis (Supplementary Table S1). Of the excluded articles, 8 were suspected to have overlapping populations, 10 did not discuss the main subject, 4 had less than 10 patients, 5 were reviews, 11 could not be retrieved, 3 were case reports and 2 did not report any VRR. An additional search of their bibliographies did not return any relevant studies.

Characteristics of included studies

Supplementary Table S1 summarises the characteristics of the 13 included studies for meta-analysis. One was a prospective study and 12 were retrospective studies. All were cohort studies and from Asia. The mean total energy of RFA was 2 kJ (range 0.86 to 3.169 kJ) and the mean duration of RFA was 23.0 min (range 1.32 to 136.8 min). The mean age of patients was 45.6 (range 41 to 66 years). All nodules were confirmed as PTC by fine needle aspiration cytology. From the studies that reported mean volumes, the mean volume of the target nodules was 0.379 mL (0.03 to 156.67 mL). From the studies that reported follow-up periods, the mean follow-up period was 27.7 months.

Efficacy

Follow-up schedules of these studies were not standardised—not all had studied VRRs for the same duration of follow-up. There were 7 studies that reported VRRs at 1, 3, 6 and 12 months. Only 4 studies reported VRRs at 18 months, 6 studies reported VRRs at 24 months, 2 studies reported VRRs at 30 months, 6 studies reported VRRs at 36 months and 2 studies reported VRRs at 48 months. This review pooled mean VRRs over common follow-up durations found across each study. The pooled mean VRRs at 1, 3, 6, 12, 18, 24, 30, 36 and 48 months were 60.52% (95% CI 36.45–84.58, $I^2=27\%$) (Fig. S1), 83.47% (95% CI 68.34–98.59, $I^2=0\%$) (Fig. S2), 92.23 (95% CI 81.61–102.86, $I^2=0\%$) (Fig. S3), 96.59% (95% CI 91.05–102.13, $I^2=0\%$) (Fig. S4), 98.95% (95% CI 95.76–102.14, $I^2=0\%$) (Fig. S5), 99.47% (95% CI 97.89–101.05, $I^2=0\%$) (Fig. S6), 98.43% (95% CI 93.85–103.02, $I^2=0\%$) (Fig. S7), 99.70% (95% CI 98.32–101.08, $I^2=0\%$) (Fig. S8) and 99.31% (95% CI 93.74–104.88, $I^2=\text{not applicable}$) (Fig. S9), respectively. Reported I^2 statistics indicate little heterogeneity across all studies. Five studies recorded 100% complete disappearance of the nodules^{2,4,7–9} between the periods of 24 months and 48 months. One study⁸ divided nodules into 2 groups by their T stage and another study divided nodules into groups by age of patients.²¹ Each group was analysed separately. One study reported a recurrence rate of 1%.³ Publication bias was not evaluated due to the small number of included studies.

Cost

Three papers also reported that patients undergoing RFA incurred lower costs compared to patients undergoing surgical resection.^{21,34,35}

Factors affecting efficacy

Staging

There is an association between earlier stages of tumours and higher disappearance rates. Xiao et al. (2021)⁸ showed that the CDRs for T1a tumours were higher than that of T1b tumours (81.7% and 52.7%, respectively). This may be because the volume of coagulative necrosis was larger in the T1a group than in the T1b group. Moreover, Xiao et al. also in 2021,⁴ studied the efficacy of RFA on T2N0M0 tumours and reported that tumour size reduced significantly with a VRR of 93.7% at 30-month follow-up after RFA and a disappearance rate of 16.7%.

Wu et al. (2020) reported that RFA is effective in reducing the VRR of multiple malignant

nodules as well.³⁶ There were 6 patients who had 2 PTMC nodules at the same time and all nodules were successfully treated.

Safety

No studies recorded life-threatening complications. The most common complication was transient voice hoarseness^{2,3,5,7,9,22,34-37} though none of the studies reported permanent voice changes. This is usually caused by thermal damage to the recurrent laryngeal nerve, with damage occurring in 0.75% to 17.39% of patients. Other complications include the development of pain,^{5,21,36} transient hypoparathyroidism,³⁴ hyperthyroidism post-operation 2.9%,⁹ hypothyroidism post-operation 1.9%,⁹ haematoma,^{2,22,37} fever³ and first-degree burns.^{2,22}

Temporary thyroid function abnormalities (both hyper- and hypothyroidism)⁹ also occurred as thyroid follicular cells are destroyed during the treatment. Thus, thyroid hormones are released into the blood, causing thyroid function abnormalities.⁹ In Zhu et al. (2021), 2 out of 102 patients (1.9%) who underwent RFA developed hypothyroidism post-operation and 3 out of 102 patients (2.9%) developed hyperthyroidism.⁹

Moreover, 4 papers reported a higher quality of life associated with RFA compared to surgical resection^{5,21,35,38} in view of the reduced rate of complications, such as recurrent laryngeal nerve paralysis, hypoparathyroidism and hypothyroidism. The studies did not report the differences in outcomes of procedures performed by operators of varying experiences, hence no definite conclusion can be drawn on the association between operator experience and complication rate.

DISCUSSION

The management of PTC has traditionally revolved around surgical interventions, such as total thyroidectomy or lobectomy. However, the recent clinical practice guidelines proposed by the Cardiovascular and Interventional Radiological Society of Europe/European Thyroid Association²³ have introduced AS and MIT options for suitable cases of PTC.

The findings of this study provide compelling evidence supporting the efficacy of RFA in the volume reduction of PTC. The pooled VRRs after 6 months were above 90%. Mean VRRs at 6, 12, 18, 24, 30, 36 and 48 months were 92.23 (95% CI 81.61–102.86, $I^2=0\%$) (Fig. S4), 96.59% (95% CI 91.05–102.13, $I^2=0\%$) (Fig. S5), 98.95% (95% CI 95.76–102.14%, $I^2=0\%$) (Fig. S6), 99.47% (95% CI 97.89–101.05, $I^2=0\%$) (Fig. S7), 98.43% (95% CI 93.85–103.02, $I^2=0\%$) (Fig. S8), 99.70%

(95% CI 98.32–101.08, $I^2=0\%$) (Fig. S9) and 99.31% (95% CI 93.74–104.88, I^2 not applicable) respectively, indicating significant tumour shrinkage. Moreover, the eventual CDRs of 100% reported in 5 studies^{2,5,8,21,22} further underscore the potential of RFA to effectively eradicate PTC. These results align with previous systematic reviews, highlighting the ability of RFA to achieve tumour control and reduction in PTC volume.

The lack of heterogeneity can be explained by our selective inclusion criteria—only papers citing RFA as a treatment for curative purposes for PTC were included. Moreover, most of the studies also included fewer than 200 patients, which may have contributed to the homogeneity and overestimate treatment efficacy.

The bio-pathophysiological mechanism of RFA in the treatment of PTC further enhances our understanding of its efficacy. RFA utilises thermal energy generated by an alternating current to induce localised tissue destruction.³⁹ The hyperthermic effects of RFA cause coagulative necrosis, protein denaturation, disruption of cell membranes and destruction of blood vessels within the tumour. Additionally, RFA triggers an immune response within the tumour microenvironment, promoting the clearance of residual tumour cells and enhancing the antitumor immune response.⁴⁰

Importantly, the safety profile of RFA appears favourable, with no life-threatening complications recorded in the included studies. The reported adverse events, including pain, transient voice hoarseness,^{2,3,5,7,9,22,34-37} fever³ and first-degree burns,^{2,22} were generally manageable and of a transient nature. The lower incidence of complications after RFA may be due to accurate tumour targeting under ultrasound guidance, the protection of vital organs via the hydrodissection technique and the abundant experience of the ultrasound physician.⁵ However, the safety margin of RFA (defined as margins of adjacent tissue to be ablated) has not yet been described. Xiao et al. (2022)⁸ reported that all patients in their cohort had solitary low-risk tumours and that the safe margin of RFA was ≥ 3 mm.⁸

The introduction of minimally invasive therapeutic options for suitable cases of PTC in the latest clinical practice guidelines reflects a growing recognition of the benefits of non-surgical approaches. RFA, as a minimally invasive technique, offers several advantages over surgery. This includes the avoidance of complications—risks of general anaesthesia, damage to the recurrent laryngeal nerve, scarring, hypothyroidism, hypoparathyroidism and the requirement for lifelong medication. Additional advantages comprise shorter hospital

stays and decreased morbidity. These advantages make RFA an attractive option for patients who are not surgical candidates due to the presence of comorbidities or personal preferences.

There exist alternative non-invasive options to treat PTC as well. This includes MWA and high-intensity focused ultrasound. There are currently no definitive guidelines that describe how these methods should be used to treat PTCs and few studies have compared these therapies as well.

In a systematic review by Tong et al. (2019)³⁰ studying MWA, laser ablation and RFA, the efficacy of these 3 methods was found to be similar.³⁰ There were no life-threatening complications resulting from these ablation methods; the pooled proportions of complications of RFA (1.7%), MWA (6.0%) and laser ablation (0.92%) were low and there was also no significant difference among these ($P>0.05$). However, it was noted that MWA resulted in more transient voice changes compared to RFA. This may be attributed to the fact that the temperature in RFA increases slowly and heat is readily removed. This limits the coagulation zone size of RFA. MWA, on the other hand, depends less on tissue impedance and rapidly increases in temperature, resulting in coagulative necrosis that can inactivate tumours quickly. However, for PTCs eligible for RFA, they are usually small in size and it may not be easy for operators to manipulate MWA, which may result in a larger zone of active heating than necessary, increasing the likelihood of adjacent nerve injury.

One question remains: how can healthcare policies in Singapore promote the adoption of RFA in treating PTC? First, health insurance providers should recognise RFA as a reimbursable procedure so as to encourage more healthcare facilities to adopt the technology. Second, clinical guidelines should be established specifically for RFA. Third, policies that allocate resources for training healthcare professionals in RFA techniques will enhance the competency of providers, making them more likely to incorporate this method into their practice. Last, policies that support research initiatives or provide funding for studies on RFA might encourage more medical facilities to implement RFA, as positive outcomes and evidence could help alleviate concerns about its efficacy and safety.

Limitations

It is essential to acknowledge the limitations of this study. The number of studies included in the analysis was relatively small, which may limit the generalisability of the findings. A larger number

of studies would provide a more robust and comprehensive analysis of the efficacy and safety of RFA in the treatment of PTC.

The studies did not provide specific details regarding the patient selection criteria, such as tumour size and location. This lack of standardised criteria makes it difficult to determine the ideal candidates for RFA and compare its efficacy with surgical interventions in specific subsets of PTC patients.

Our study also relied on published literature and may be susceptible to publication bias, as studies with positive or significant results are more likely to be published. This bias may affect the overall assessment of the efficacy and safety of RFA in treating PTC.

The duration of follow-up in the included studies was relatively short, ranging from 1 to 60 months. Durations of follow-up were also not standardised. Only 1 study reported a recurrence rate of 1%. Longer-term follow-up is essential to evaluate the sustained effectiveness of RFA in tumour control and recurrence rates. This is especially so as recurrence for PTC usually takes many years. Ywata et al. (2021) reported the median time of recurrence to be 56.8 months.⁴¹ Additionally, long-term data would provide valuable insights into the durability of the treatment and potential late complications.

The publications included also focused primarily on Asian cohorts. One may postulate that this may be due to a wider acceptance of MITs in East Asia, though no studies have been done on why this is so. More prospective randomised trials that compare RFA directly with surgery in low-risk versus high-risk patients should be conducted as well. There were also no randomised controlled trials in the field of RFA for PTC. There is a need for multicentre trials with Asian populations to validate the generalisability of these findings.

The included studies only evaluated the efficacy of RFA on low-risk PTCs (defined as a PTMC without extrathyroidal extension, vascular invasion or metastases).¹¹ More studies need to be conducted on higher-risk PTCs. The studies also did not address lymph node metastases, for which the standard treatment remains to be surgical resection according to current guidelines. However, it was found in 3 studies (not included in our study in view of the inclusion criteria) that volume reduction rates were high for metastatic cervical lymph nodes ablated by RFA.⁴²⁻⁴⁴

Only Chen et al. (2022)³⁵ and Chung et al. (2021)⁷ utilised RFA on recurrent tumours after surgery. We were unable to analyse the differences in VRR

between recurrent and primary PTCs as Chung et al. did not report VRRs at specific intervals, leaving only 1 such study³⁵ for our comparison. Nevertheless, it should be noted that at 6 months, VRR was 86.6 ± 22.2 as reported by Chen (2022),³⁵ which is comparatively lower than that of the other studies.

CONCLUSION

In conclusion, our meta-analysis provides a summary of the current literature on the efficacy and side effects of RFA on PTC. The results suggest that RFA may be an effective and safe alternative treatment modality. However, it is not yet a standard treatment due to the lack of long-term data. Larger clinical studies and randomised controlled trials with longer follow-up durations are needed to evaluate the recurrence rate of this treatment.

Further studies with larger populations are required to assess the risks and benefits of using different combinations of energy depending on the size, type and location of the nodule. Comparative analyses can be done with other methods of ablation such as MWA. These findings may provide a deeper insight into the efficacy and safety associated with RFA, and help guide future management of PTC using RFA as a treatment modality.

Supplementary materials

Table S1. Characteristics of included studies.

Fig. S1. Volume reduction rate (VRR) 1 month.

Fig. S2. VRR 3 months.

Fig. S3. VRR 6 months.

Fig. S4. VRR 12 months.

Fig. S5. VRR 18 months.

Fig. S6. VRR 24 months.

Fig. S7. VRR 30 months.

Fig. S8. VRR 36 months.

Fig. S3. VRR 48 months.

Ethics statement

The protocol is registered in PROSPERO (CRD42023432383).

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Availability of data and materials

All data generated or analysed during this review are included in this published article and its supplementary files.

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