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# Thermal ablation for radioactive iodine refractory cervical lymph node metastasis in differentiated thyroid cancer

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## Abstract

**Objective** Therapeutic management of radioactive iodine-refractory lymph node metastasis (RAIR-LNM) in differentiated thyroid cancer remains challenging. Thermal ablation for RAIR-LNM has gained a paucity of evidence for clinical guidelines.

**Materials and methods** This multicenter retrospective study analyzed 88 patients with 182 RAIR-LNM at 5 Chinese hospitals between June 2011 and July 2022, to evaluate the effectiveness of thermal ablation for RAIR-LNM. All included patients had at least one ≤ 3 cm RAIR-LNM. The main outcomes were the technical success and disease progression rate. Secondary outcomes included volume reduction rate (VRR), tumor disappearance ratio and the complication rate. Subgroup analyses were performed by using Kaplan-Meier curves and Cox proportional hazards regression models.

**Results** The mean diameter was 1.35 ± 0.65 cm. The technical success rate was 100% and all elevated thyroglobulin (Tg) levels returned to normal after ablation. Over a mean follow-up period of 55.3 ± 31.39 months, disease progression occurred in 18.18% of patients (16 of 88). Subgroup analysis revealed significantly reduced rates of disease progression ($p < 0.05$) and new LNM development in patients with Tg ≤ 35 µg/L. Multivariable analysis identified Tg level as a predictor associated with new LNM and disease progression, whereas tumor size and ablation modality showed no statistically significant associations. LNM shrank evidently after ablation, and the disappearance rate was higher for LNM ≤ 1 cm. The overall complication rate was 10.23% (9 of 88).

**Conclusions** Thermal ablation emerges as a viable therapeutic strategy for RAIR-LNM, offering durable local tumor control and prolonged progression-free survival, especially for patients with Tg < 35 µg/L.

## Key Points

***Question*** *Whether thermal ablation for radioactive iodine refractory lymph node metastasis could achieve a long-term survival benefit.*

***Findings*** *Reduced rates of disease progression and new lymph node metastasis development were found in patients with thyroglobulin ≤ 35 µg/L.*

***Clinical relevance*** *Thermal ablation serves as a viable therapeutic strategy for patients with radioactive iodine-refractory lymph node metastasis. It offers durable local tumor control and prolonged progression-free survival, especially for patients with lower thyroglobulin levels.*


**Keywords** Lymphatic metastasis, Thyroid neoplasms, Iodine radioisotopes, Drug resistance, Ablation technique

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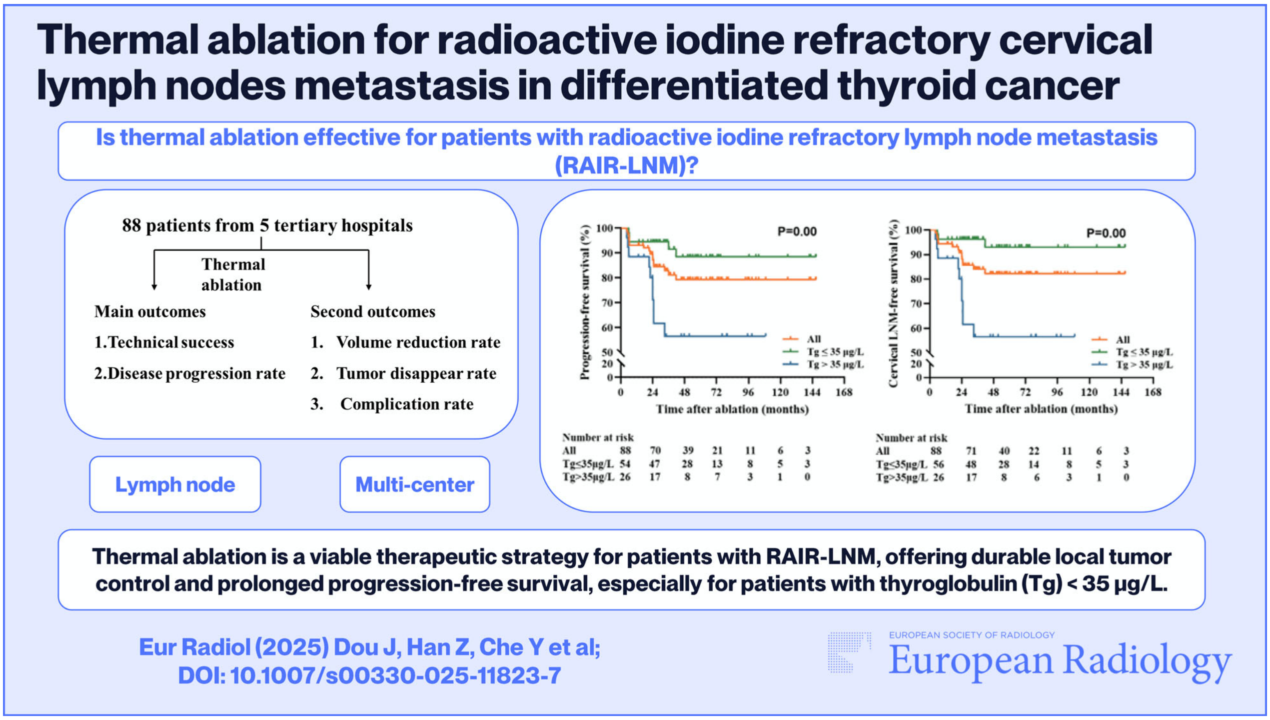
**Graphical Abstract**




## Introduction

Thyroid cancer accounted for an estimated 821,173 cases globally in 2022, ranking as the seventh most prevalent malignancy worldwide [1]. Differentiated thyroid cancer (DTC), encompassing papillary, follicular, Hürthle cell, and poorly differentiated histological subtypes, is the most common type and constitutes over 90% of all thyroid cancers [2, 3]. Clinical surveillance reveals disease recurrence in approximately 35% of DTC cases [4], and nearly 50% of metastatic DTC are eventually refractory to radioactive iodine (RAI) therapy [5]. Patients with radioactive iodine-refractory DTC (RAIR-DTC) demonstrate suboptimal prognoses, with a 5-year disease-specific survival rate of 60% to 70% and a 10-year survival rate of 10%, respectively, rendering it a major clinical concern.

Treatment options for RAIR-DTC remain constrained. Surgery persists as the primary therapeutic approach for locoregional recurrence of RAIR-DTC, though its utility is substantially limited by procedural complications and diminished efficacy in multifocal and frequently recurrent cases. External beam radiation to control cervical disease in DTC lacks robust clinical validation, constrained by treatment-related morbidity and insufficient prospective trial evidence [6]. While molecular-targeted treatments demonstrate progression-free survival (PFS) benefits in patients with RAIR-DTC, their clinical adoption is hindered by concerning adverse events, including hand-foot syndrome, hypertension, or proteinuria [7–10].

Emerging as a mini-invasive treatment alternative, thermal ablation has gained recognition in management algorithms for symptomatic benign thyroid nodules and recurrent thyroid cancers [11–14]. Preliminary evidence from limited-scale studies and systematic reviews suggests the therapeutic potential of thermal ablation in lymph node metastasis (LNM) from papillary thyroid carcinoma (PTC) [15–21]. Notably, no studies have been conducted to validate its performance for radioactive iodine refractory lymph node metastasis (RAIR-LNM). This multicenter retrospective analysis of RAIR-LNM cases from five Chinese tertiary hospitals aims to evaluate the long-term therapeutic efficacy and clinical benefits of thermal ablation in RAIR-DTC management.

## Materials and methods

This retrospective multicenter study enrolled patients with RAIR-DTC who underwent thermal ablation across 5 tertiary hospitals in China (Table S1). The study was conducted in compliance with both the Declaration of Helsinki and the Istanbul Declaration, with protocol approval obtained from the Institutional Review Boards of all participating centers. Written informed consent was secured from all patients or their legally authorized representatives prior to procedure initiation. Patient eligibility for thermal ablation was determined by multidisciplinary evaluation by interventional radiologists, surgeons and endocrinologists. The study cohort exclusively comprised patients who either met criteria for surgical ineligibility or explicitly declined conventional surgery after comprehensive consultation.

### Patients

Data of patients with RAIR-DTC who received thermal ablation were retrospectively collected between June 2011 and July 2022. Diagnostic confirmation of RAIR-DTC required fulfillment of at least one nuclear medicine criterion by nuclear medicine physicians: (1) at least one target lesion demonstrating absent iodine-131 ($^{131}$I) uptake on therapeutic scintigraphy (2) Radiologic progression according to the Response Evaluation Criteria In Solid Tumors [7] within 12 months post-$^{131}$I therapy despite baseline avidity had progressed after a therapeutic iodine-131 administration (3) cumulative $^{131}$I dosage exceeding 600 mCi with documented disease progression (confirmed by independent radiologic review) within 13-month surveillance.

Inclusion criteria of this study were (a) age ≥ 18 years, (b) at least one Ultrasound-confirmed cervical RAIR-LNM < 3 cm in maximum diameter, (c) advanced LNM confirmed by histology, (d) Eastern Cooperative Oncology Group (ECOG) performance status score 0–2.

Exclusion criteria were: (a) LNM that planned for palliative ablation, (b) presence of distant metastasis, (c) follow-up time < 12 months and (e) severe concomitant diseases.

### Assessment

All enrolled patients underwent ultrasound, contrast-enhanced ultrasound (CEUS) and CT before ablation to delineate LNM characteristics, including the size, number, location and vascular architecture. At least one suspicious LNM underwent definitive histopathological verification through fine-needle aspiration or core-needle biopsy. Patients' demographics, comorbidity, thyroid function, thyroglobulin (Tg), tumor characteristics (size, echogenicity, location, vascularity and calcification) were recorded at baseline. Quantitative tumor volumetry, imaging acquisition and laboratory test protocols were presented in the Supplementary Methods section.

### Ablation procedures

Two techniques were implemented in this study, including microwave ablation (MWA) and radiofrequency ablation (RFA). Doctors who performed ablation in this study have more than 3-years' experience in LNM ablation. Both MWA and RFA were performed under the real-time guidance of ultrasound, as previously described [22]. Slow continuous infusion of normal saline or 5% glucose solution was administered to the space of LNM and surrounding structures to maintain a safe distance. A power of 20–30 W for MWA and 40–50 W for RFA was commonly used. A microwave antenna or radiofrequency electrode was placed into the deepest part of the LNM and remained in place for 30 to 60 s prior to being ready to reposition. The antenna/electrode might need to be repositioned to the hypoechoic area (unablated area) of the LNM and fixed for another 10 to 60 seconds if the hyperechoic ablation zone could not cover the entire tumor at the first placement. The ablation was stopped when the hyperechoic ablation zone covered the entire tumor. CEUS was performed immediately to evaluate the coagulation area after thermal ablation. Additional ablation would be conducted immediately if residual tumors were detected, as any enhancement around the ablation zone. All interventions were performed by trained interventional radiologists with a minimum of 3 years' subspecialty experience in oncologic ablation.

### Follow-up

After ablation, assessments of the thermal ablation procedure with CEUS were made 3 days after ablation. In case of any residual tumor, an additional ablation procedure was performed to achieve complete coagulation. All participants maintained thyroid-stimulating hormone (TSH) suppression therapy (target level < 0.1 mU/L) throughout follow-up [11]. Patients were requested to undergo ultrasound follow-up and laboratory tests every 3 months during the 1st year after ablation, every 6 months in the 2nd year, and every 12 months thereafter. CEUS was performed every 6 months in the first two years and every 12 months thereafter. CT was performed to detect metastasis in the neck and chest. Besides, bone scintigraphy, pelvic MRI, chest CT or PET-CT were also performed on patients who were suspended with extra-hepatic metastasis based on clinical suspicion of extra-nodal metastasis (e.g., bone pain, neurologic deficits) or unexplained Tg elevation (> 1 ng/mL during TSH suppression). US-guided biopsy was performed if local tumor progression (LTP), tumor recurrence or LNM was suspected. Final follow-up data were censored on January 31, 2024.

### Outcomes

The primary end outcome was technical success and PFS rate. Technical success was defined as the absence of any enhancement in the LNM on CEUS images within 3 days after ablation. PFS rate refers to the proportion of patients who remain free of disease progression and alive at a specific time point (e.g., 1 year, 2 years) after starting treatment. Disease progression was defined as any occurrence of LTP (biopsy-confirmed new tumor adjacent to the ablated LNM), new LNM (new recurrent LNM in other part of neck and confirmed by biopsy) or distant metastasis (metastasis outside the neck detected on CT, PET images or bone scans).

Secondary end outcomes were LNM volume changes, volume reduction rate (VRR), tumor disappearance ratio and the complication rate. The tumor volume was calculated by $V = abc \times 0.524$. $V$ is the volume, $a$ is the maximum diameter of LNM, and $b$ and $c$ are the other two perpendicular diameters of LNM. VRR was calculated as $(T - A) \times 100/T$, $T$ is initial LNM volume and $A$ is ablated LNM volume during follow-up periods. Complications were defined according to the reporting standards of thyroid ablation [23].

An excellent response rate was defined as no clinical, biochemical, or structural evidence of tumors; a structural incomplete response was local or newly identified locoregional or distant metastases.

### Statistical analysis

Descriptive statistics were presented as either mean ± standard deviation for continuous variables, and as frequency and percentage for categorical variables. Changes of continuous variables were analyzed by using the $t$-test and differences of categorical variables between different subgroups were analyzed by using the $x^2$ test.

For time-to-event end points, the Kaplan–Meier method was used to estimate the rates, median time, and their corresponding 95% confidence index (CI). The log-rank test was performed to compare the differences between the subgroup analyses of tumor size, Tg level and ablation technique. In addition, hazard ratios (HRs) and their 95% CI were obtained by Cox proportional hazards regression models. For binary outcomes, the Pearson method was used to calculate the 95% CIs, and the Fisher exact test was performed between subgroup comparisons.

Sensitivity analyses were performed to maximize statistical power and minimize bias that might occur if missing data were excluded. A multiple-imputation analysis was used to impute missing values. We repeated the univariable and multivariable analyses with the complete data cohort for comparison.

All statistical analyses were conducted with Empower(R) (www.empowerstats.com, X&Y solutions) and R (http://www.R-project.org). $p \leq 0.05$ indicates a significant difference.

## Results

### Demographic and tumor characteristics

183 patients received thermal ablation for LNM from DTC between June 2011 and July 2022 in 5 hospitals in China, and finally 88 RAIR-LNM patients were included (Fig. 1). The mean follow-up time was 55.3 ± 31.39 months. Of the 88 patients, 52 (58.43%) were men and 36 (41.57%) were women; mean age at baseline was 45.64 ± 13.25 years. 43 patients (48.86%) had solitary LNM, and others had multiple LNM. 45 patients had two or more lymph node metastases. 29 patients had unilateral lymph node metastases and 16 had bilateral lymph node metastases. The majority of included patients (97.72%) were diagnosed with PTC. Subgroup comparisons of demographic and tumor characteristics were summarized in Table 1 and Table S2-3. Treatment parameters were shown in Table 2.

### LNM volume changes

The mean maximum diameter of LNM was 1.35 ± 0.65 cm (range from 0.3 to 3.0 cm) before ablation. The volume of LNM shrank evidently at 1 year follow-up and remained stable in the longer follow-up period (Fig. 2a and Table S4). Smaller LNM showed quicker VRR than larger tumors in the first year after ablation ($p = 0.04$) (Fig. 2b–d). Ablation technique and Tg level did not affect the VRR (Fig. 2e, f).

At the most recent follow-up, 79 of 88 tumors (89.77%) had completely disappeared at ultrasound follow-up examination. All tumors ≤ 1 cm disappeared after thermal ablation. As shown in the Kaplan–Meier curves, tumor disappearance ratio was different in the two groups (log-rank test, $p < 0.001$) (Fig. 3). Tumors ≤ 1 cm disappeared earlier than tumor > 1 cm; in addition, the disappearance rate was higher for tumors ≤ 1 cm. No differences in tumor disappearance ratio were found in subgroups analysis of Tg level and ablation techniques (Fig. 3).

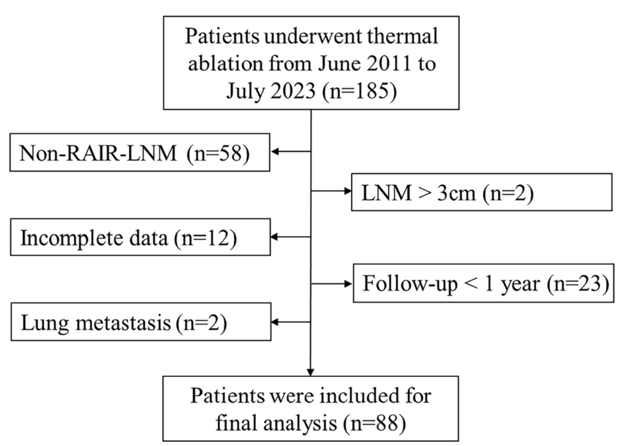



**Fig. 1** Flowchart of the included patients. RAIR-LNM, radioactive iodine refractory lymph node metastasis; LNM, lymph node metastasis

**Table 1** Baseline characteristics of total patients and the subgroup of tumor size

| Characteristic | Total ($n=88$) | ≤ 1 cm ($n=32$) | > 1 cm ($n=56$) | $p$-value |
|---|---|---|---|---|
| Age (year) | 45.64 ± 13.25 | 41.41 ± 12.53 | 46.84 ± 14.96 | 0.09 |
| SEX | | | | 0.62 |
| Female | 36 (41.57%) | 12 (37.50) | 24 (42.86) | |
| Male | 52 (58.43%) | 20 (62.50) | 32 (57.14) | |
| ECOG performance status | | | | 0.14 |
| 0 | 86 (97.72) | 31 (96.88) | 55 (98.22) | |
| 1 | 2 (2.27) | 1 (3.12) | 1 (1.78) | |
| aCCI | | | | 0.35 |
| 0–1 | 60 (68.18) | 25 (78.12) | 35 (62.50) | |
| 2–3 | 22 (22.70) | 7 (21.87) | 15 (26.78) | |
| 4–5 | 6 (6.82) | 0 (0.00) | 6 (10.72) | |
| Time since diagnosis (months) | 40.32 ± 60.66 | 38.50 ± 43.54 | 41.76 ± 69.64 | 0.82 |
| Histologic subtype | | | | 0.14 |
| Papillary | 86 (97.72) | 31 (96.88) | 55 (98.22) | |
| Follicular | 2 (2.27) | 1 (3.12) | 1 (1.78) | |
| Surgery | | | | 0.44 |
| Total thyroidectomy | 70 (79.55%) | 26 (81.25) | 44 (78.57) | |
| Subtotal thyroidectomy | 15 (17.04%) | 4 (12.5) | 11 (19.64) | |
| Missing | 3 (3.41) | 2 (6.25) | 1 (1.79) | |
| Number of RAI administrations pro prior to enrollment | 1.47 ± 0.11 | 1.42 ± 0.10 | 1.49 ± 0.14 | 0.56 |
| Prior therapy | | | | 0.14 |
| Targeted therapy | 2 (2.27) | 1 (3.12) | 1 (1.78) | |
| None | 86 (97.72) | 31 (96.88) | 55 (98.22) | |
| Thyroid function | | | | |
| fT3 | 4.79 ± 1.17 | 4.7 ± 1.24 | 4.88 ± 1.03 | 0.56 |
| fT4 | 18.61 ± 3.29 | 19.00 ± 3.74 | 18.07 ± 3.2 | 0.05 |
| TSH | 0.59 ± 1.22 | 0.76 ± 1.45 | 0.54 ± 1.07 | 0.51 |
| Maximum cervical lymph node diameter (cm) | 1.35 ± 0.65 | 0.96 ± 0.29 | 1.66 ± 0.49 | 0.00 |
| Maximum cervical lymph node volume (mL) | 0.97 ± 1.49 | 0.31 ± 0.50 | 1.34 ± 1.72 | 0.00 |
| Lymph node number | 182 | 65 | 117 | 0.36 |
| Cervical lymph node location | | | | 0.35 |
| 1 | 1 (2.25) | 0 (0.00) | 1 (1.79) | |
| 2 | 23 (25.84) | 8 (25.00) | 15 (26.79) | |
| 3 | 25 (28.09) | 8 (25.00) | 17 (30.36) | |
| 4 | 19 (21.35) | 8 (25.00) | 11 (19.64) | |
| 5 | 5 (5.62) | 2 (6.25) | 3 (5.36) | |
| 6 | 15 (16.85) | 6 (18.75) | 9 (16.07) | |
| Tg | 31.6 ± 129.4 | 42.78 ± 184.78 | 15.08 ± 36.62 | 0.38 |

*ECOG* Eastern Cooperative Oncology Group, *aCCI* age-adjusted Charlson Comorbidity Index, *RAI* radioactive iodine, *fT3* free triiodothyronine, fT4 thyroxine, *TSH* thyroid-stimulating hormone, *Tg* thyroglobulin

### Treatment efficacy

The technical success rate was 100% for all included nodes. 15.91% (74 of 88) developed new LNM and 2.27% (two of 88) developed LTP at 3 years follow-up (Table 3). Two patients were found to have distant metastasis to the lung and mediastinal lymph nodes. The PFS rate was 84.09% at 3 years and 81.82% at 5 years. The excellent response rate was 81.82% (72 of 88 patients), and 18.18% of patients showed structural incomplete response. Patients showed an increased disease progression rate with an extended follow-up period.

The PFS rates of tumors ≤ 1 cm and > 1 cm were 84.37% (27 of 32 patients) and 80.36% (45 of 56 patients) at 5 years follow-up, respectively. The PFS curves in the above

**Table 2** Treatment parameters and complications

| Parameter | Total | ≤ 1 cm ($n = 32$) | > 1 cm ($n = 56$) | $p$-value[a] |
|---|---|---|---|---|
| Ablation time | 198.49 ± 178.10 | 124.34 ± 86.24 | 236.24 ± 201.24 | 0.00 |
| Power (W) | 20–35 | 20–30 | 20–35 | 0.78 |
| Energy (KJ) | 15–60 | 15–60 | 15–60 | 0.85 |
| Hydrodissection ($n$, %) | 82 (93.18) | 30 (93.75) | 52 (94.55) | 0.88 |
| Cost (yuan) | 17,749.90 ± 5191.75 | 16,241.14 ± 4433.82 | 18,335.46 ± 5424.33 | 0.12 |
| Complication | | | | 0.57 |
| Voice hoarseness | 5 (5.68) | 2 (6.25) | 3 (5.36) | 0.86 |
| Hematoma | 1 (1.34) | 0 | 1 (1.79) | |
| Horner syndrome | 1 (1.34) | 0 | 1 (1.79) | |
| Vagus reflex | 1 (1.34) | 0 | 1 (1.79) | |
| Skin burn | 1 (1.34) | 1 (3.13) | 0 | |

[a] Tumors ≤ 1 cm versus tumor > 1 cm

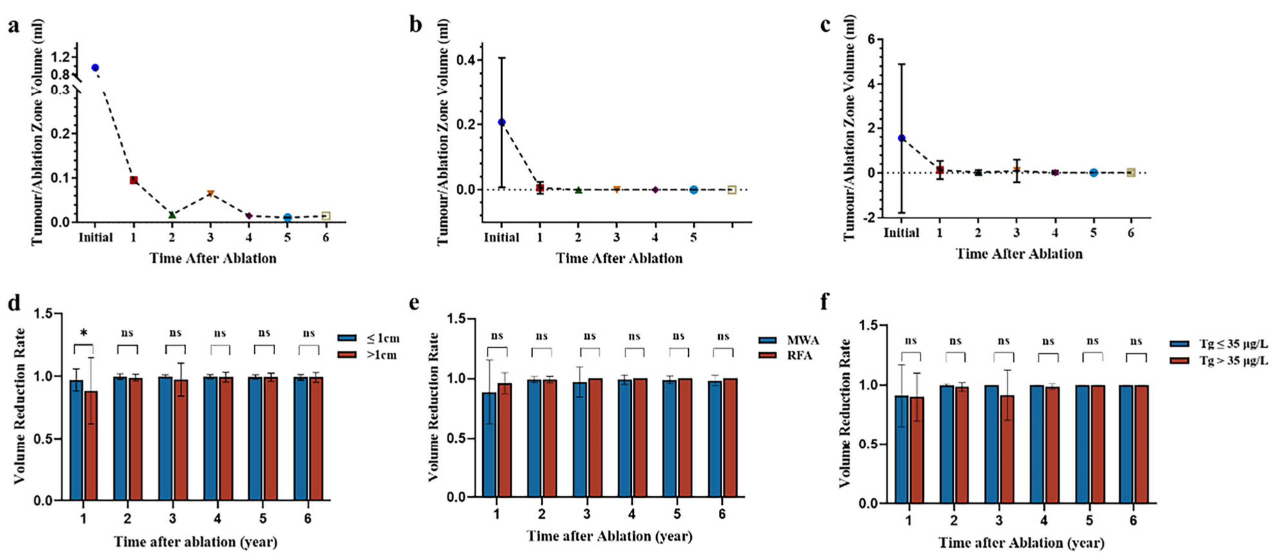



**Fig. 2** Tumor volume changes (**a** all LNM; **b** LNM ≤ 1 cm; **c** LNM > 1 cm) and volume reduction rate (**d** subgroup comparisons of tumor size; **e** subgroup comparisons of ablation techniques; **f** subgroup comparisons of Tg level) after thermal ablation. MWA, microwave ablation; RFA, radiofrequency ablation; LNM, lymph node metastasis

two groups were not different ($p = 0.86$) (Fig. 4). Similar results were found in the LNM rate between the above two groups. 9.25% patients (5 of 54 patients) with Tg ≤ 35 μg/L and 27.27% patients (3 of 11 patients) with Tg > 35 μg/L showed disease progression. The DFS curves in the above two groups were significantly different ($p < 0.05$), so were the LNM curves (Fig. 4). No differences in objective response were found in the subgroup analysis of MWA and RFA.

In multivariable analysis, Tg was found to be associated with LNM (HR: 6.77, 95% CI: 1.20, 38.09) (Table 4). Tg was also found to be associated with disease progression (HR: 3.85, 95% CI: 1.14, 12.98) (Table 4). Sensitivity analysis after multiple-imputation was shown in supplementary materials (Table S5–6).

## Safety

The overall complication rate in the present study was 10.23% (9 of 88 patients); of these, 5.68% (5 of 88 patients) developed voice hoarseness, 1.14% (1 of 88 patients) developed hematoma, 1.14% (1 of 88 patients) developed Horner syndrome, 1.14% (1 of 88 patients) developed vagus reflex, and 1.14% (1 of 88 patients) experienced skin burn. Voice hoarseness, Horner syndrome, and vagus reflex occurred as major complications, whereas the others were minor complications.

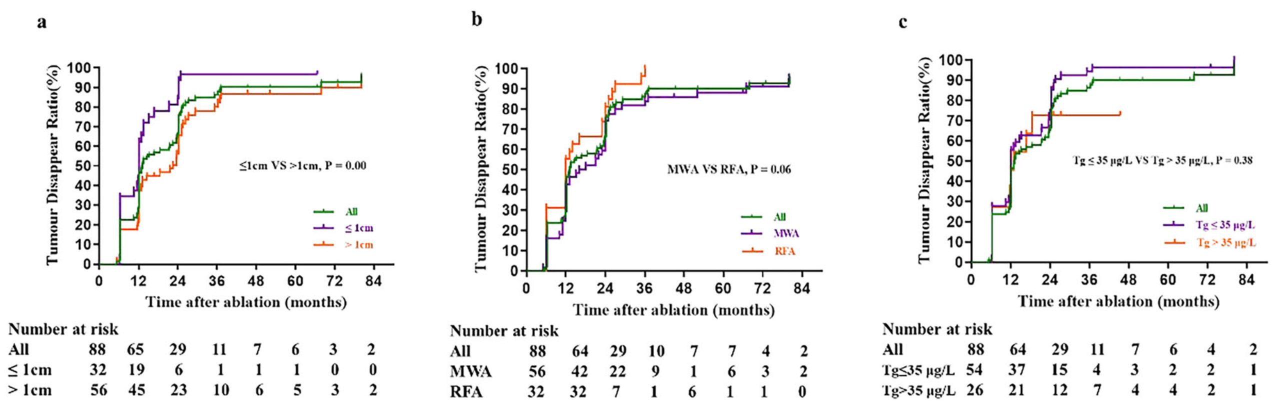



**Fig. 3** Tumor disappearance ratio in subgroup analysis (**a** tumor size; **b** ablation techniques; **c** Tg level). MWA, microwave ablation; RFA, radiofrequency ablation

The complication rates in tumors ≤ 1 cm and > 1 cm were 11.54% (3 of 26 patients) and 9.68% (6 of 62 patients), respectively. The complication rate in tumors ≤ 1 cm was similar to that in > 1 cm ($p = 0.61$) (Table 2). MWA showed an equivalent complication rate with RFA (Fig. 5). Voice hoarseness accounted for the majority of complications in this study. All patients with voice hoarseness completely recovered within 6 months. Vagus reflex was monitored during the ablation and was well controlled by atropine. The patient with Horner syndrome had slight ptosis during follow-up. None of these complications was life-threatening.

## Discussion

This retrospective cohort study demonstrates that thermal ablation confers substantial clinical benefits for patients with RAID-LMN. The disease progression rate after thermal ablation was 18.18%, predominantly manifesting as new cervical lymph node metastases. The overall complication rate in the present study was 10.23%, with transient voice hoarseness representing the most frequent adverse event. Eight patients included in this study have been reported in our previous study [22].

Our study exhibited a higher PFS rate compared to other studies of targeted therapies [8–10, 24, 25]. We only included patients who had cervical RAID-LMN without distant metastasis. All patients had total thyroidectomy with ≥ 1 neck dissection. So the disease stage in this study was lower than in other studies relating to target therapies. Besides, all suspicious LNM were ablated during thermal ablation in this retrospective study, due to the convenience and safety of thermal ablation, despite the fact that at least one LNM was diagnosed with pathology results. The above might be the reasons why we achieved such favorable results in this retrospective study with a long-term follow-up period. Notably, patients with distant metastases were excluded from this therapeutic paradigm, warranting further investigation into the role of thermal ablation in metastatic disease management.

For some RAIR-LNM cases, LNM might remain stable or slowly progress for years. These patients might also maintain a normal life under active surveillance and TSH-suppressive thyroid hormone therapy, especially for small LNM ≤ 1 cm [26]. Once a local recurrence or metastasis occurs, therapies are recommended [27]. In this study, small LNM detected by ultrasound were also treated during thermal ablation. Patients refused active surveillance for psychological anxiety or were ineligible for surgery. After thermal ablation, patients had a long tumor-free survival with high life quality. Thermal ablation did not show a survival benefit due to the indolent nature of PTC in this study, so the long-term treatment benefit of thermal ablation for minor LNM also needs further validation.

In this study, we found that patients with lower Tg levels before ablation achieved better PFS and lower LNM. Higher Tg level always indicates persistent or recurrent disease after total thyroidectomy and RAI therapy [28, 29]. Previous studies have shown the predictive role of Tg after surgery in patients with thyroid carcinoma [30–32]. All patients in this study showed normal Tg levels after ablation, but the higher Tg levels before ablation indicated a higher possibility of recurrence. Tg production from subclinical cancer foci might appear in the future as new LNM [33], as it is hard to detect subclinical cancer foci by medical image before ablation. Neither tumor size nor ablation method was found to have an influence on disease progression in this study. We only included patients with DTC, and the tumor size was small. Previous studies have validated that age, distant metastasis and radioactive iodine nonavidity

**Table 3** Confirmed objective response to thermal ablation

| Response rate | All ($n = 88$) | ≤ 1 cm ($n = 32$) | > 1 cm ($n = 56$) | *p*-value | Tg ≤ 35 μg/L ($n = 54$) | Tg > 35 μg/L ($n = 26$) | *p*-value | MWA ($n = 56$) | RFA ($n = 32$) | *p*-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Excellent response | 72 (81.82%) | 27 (84.37) | 45 (80.36) | 0.64 | 49 (90.74) | 15 (57.69) | 0.00 | 45 (80.36) | 27 (84.38) | 0.64 |
| Structural incomplete response | 16 (18.18) | 5 (15.62) | 11 (19.64) | 0.64 | 5 (9.26) | 11 (42.30) | 0.00 | 11 (19.64) | 5 (15.62) | 0.64 |
| LTP | 2 (2.27) | 1 (3.12) | 1 (1.78) | | 1 (1.85) | 1 (3.84) | | 2 (3.57) | 0 | |
| New identified LNM | 14 (15.91) | 4 (12.5) | 10 (17.86) | 0.94 | 3 (5.55) | 10 (38.45) | 0.00 | 9 (16.07) | 5 (15.62) | 0.96 |
| Distant metastasis | 2 (2.27) | 2 (6.25) | 0 (0.00) | | 2 (3.70) | 0 (0.00) | | 1 (1.78) | 1 (1.78) | |
| PFS rate | | | | 0.86 | | | 0.01 | | | |
| 12 months | 82 (93.18) | 31 (96.87) | 51 (91.07) | 0.25 | 51 (94.44) | 23 (88.46) | 0.21 | 49 (90.74) | 29 (90.62) | 0.98 |
| 36 months | 74 (84.09) | 28 (87.50) | 46 (82.14) | 0.62 | 50 (92.59) | 16 (61.53) | 0.00 | 48 (85.71) | 28 (87.5) | 0.59 |
| 60 months | 72 (81.82) | 27 (84.37) | 45 (80.36) | 0.64 | 49 (90.74) | 15 (57.69) | 0.00 | 45 (80.36) | 27 (84.38) | 0.64 |
| OS rate | 100 | 100 | 100 | | 100 | 100 | | 100 | 100 | |

*LTP* local tumor progression, *LNM* lymph node metastasis, *PFS* progression-free survival, *OS* overall survival

were associated with disease progression [32]. In this study, we did not find that age was a factor associated with disease progression, but Tg before ablation was the associated factor.

This study revealed a notably higher complication rate compared with previous studies. While the complication rate associated with thermal ablation for PTC ≤ 1 cm was about 1.1% to 6.5% [34–37], the present study demonstrated a significantly elevated complication rate of 10.23%. Nerve injury was the major complication in thermal ablation for RAIR-LNM. This increased risk may be attributed to the fact that all enrolled patients had undergone at least one prior surgery, resulting in postoperative adhesions that potentially compromised the effectiveness of the hydro-dissection technique in nerve isolation. Specifically, adhesions between LNM and the neural structures may render hydro-dissection insufficient to maintain an adequate insolation distance to protect the nerve. Furthermore, the inherent limitation of ultrasonographic visualization of the recurrent laryngeal nerve poses additional challenges in nerve protection during hydro-dissection, particularly in post-surgical cases. These technical difficulties likely contributed to the elevated complication rate observed in this cohort. One case of Horner syndrome was documented following ablation, presumably due to thermal impact on cervical sympathetic ganglia. All patients with voice hoarseness completely recovered within 6 months. Vagus reflex could be monitored during the ablation and managed through atropine administration. These findings underscore the critical importance of meticulous hydro-dissection and thorough anatomical assessment during thermal ablation for RAIR-LNM.

Our study has several limitations. First, the retrospective design introduces potential selection bias and restricts control over confounding variables, which may compromise the validity of our findings. Second, the patient number limits the statistical power of our analyses and may reduce the generalizability of the results. To address this, large-scale, multicenter studies are essential to validate our conclusions and explore broader applicability. Third, despite the use of multiple imputation to account for missing data (e.g., Tg levels), residual inaccuracies or unmeasured confounding might affect the reliability of subgroup analyses. In light of these considerations, prospective studies with rigorously collected data are warranted to corroborate our findings and generate more definitive evidence in this field.

## Conclusion

Thermal ablation provides an effective and safe treatment method for patients with RAIR-LNM, who could benefit from satisfactory local tumor control and PFS, especially for patients with Tg < 35 μg/L.

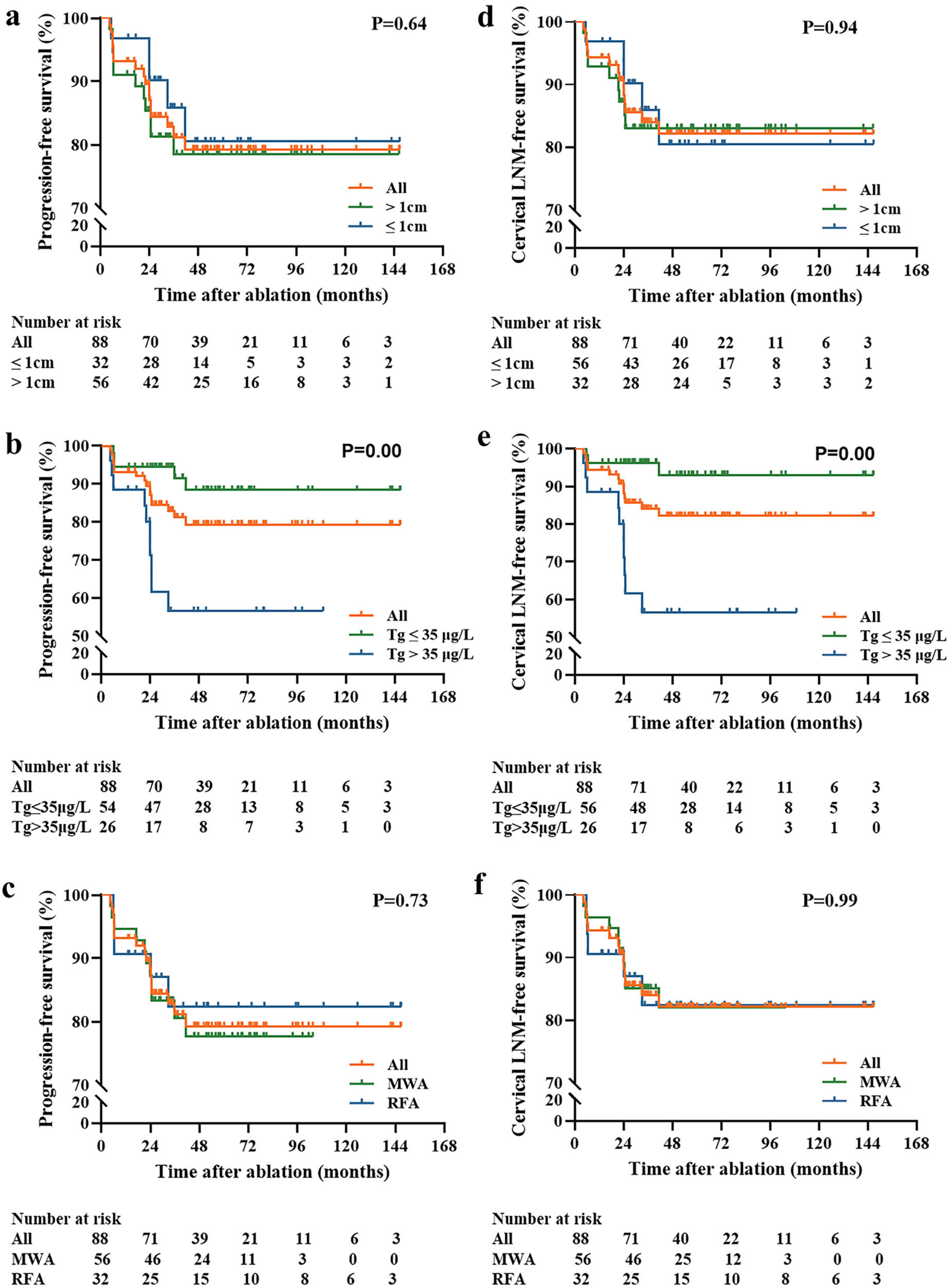



**Fig. 4** Subgroup analysis of disease progression (**a** tumor size; **b** Tg level; **c** ablation techniques) and new LNM (**d** tumor size; **e** Tg level; **f** ablation techniques) after thermal ablation

**Table 4** Factor analysis for new LNM and disease progression after thermal ablation

| Variable | New LNM | | | | Disease progression | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| Gender | 0.42 (0.15, 1.17) | 0.09 | 0.50 (0.16, 1.50) | 0.70 | 0.42 (0.16, 1.10) | 0.08 | 0.49 (0.18, 1.36) | 0.17 |
| Age | 1.06 (0.38, 2.93) | 0.91 | | | 1.04 (0.40, 2.70) | 0.94 | | |
| aCCI | 1.38 (0.44, 4.34) | 0.58 | | | 1.13 (0.37, 3.49) | 0.82 | | |
| TSH | 3.05 (0.67, 13.99) | 0.15 | | | 1.38 (0.47, 3.99) | 0.55 | | |
| Hashimoto | 0.49 (0.11, 2.18) | 0.34 | | | 0.41 (0.09, 1.85) | 0.23 | | |
| LNM number | 0.81 (0.53, 1.26) | 0.36 | | | 0.99 (0.73, 1.37) | 0.98 | | |
| LNM diameter | 2.37 (1.04, 5.40) | 0.04 | 0.93 (0.17, 5.21) | 0.94 | 2.03 (0.92, 4.48) | 0.08 | 1.68 (0.32, 8.69) | 0.54 |
| Surgery LNM | 1.31 (0.28, 6.08) | 0.73 | | | 1.08 (0.32, 3.58) | 0.90 | | |
| Ablation time | 1.00 (1.00, 1.01) | 0.01 | 1.00 (0.99, 1.01) | 0.16 | 1.00 (1.00, 1.01) | 0.01 | 1.00 (0.99, 1.01) | 0.27 |
| Tg | 8.64 (2.37, 31.52) | 0.00 | 7.86 (1.77, 38.83) | 0.01 | 5.15 (1.76, 15.11) | 0.00 | 3.85 (1.14, 12.98) | 0.03 |

*aCCI* age-adjusted Charlson Comorbidity Index, *TSH* thyroid stimulating hormone, *LNM* lymph node metastasis, *Tg* thyroglobulin

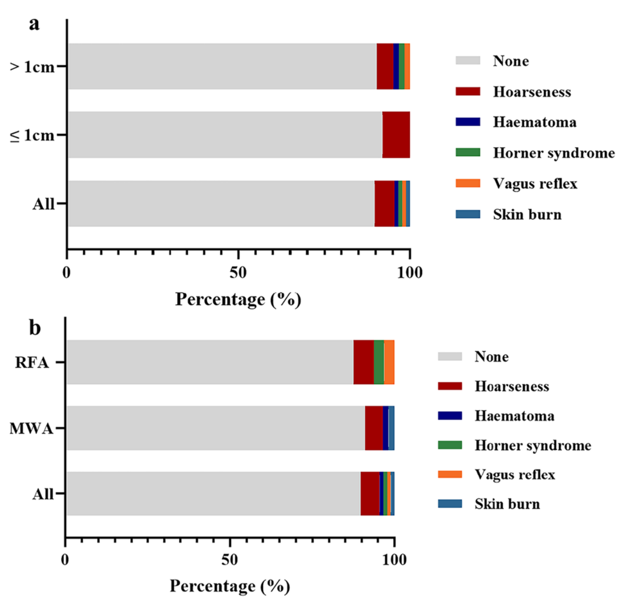



**Fig. 5** Complications of subgroup analysis of tumor size (**a**) and ablation methods (**b**). MWA, microwave ablation; RFA, radiofrequency ablation

**Abbreviations**

| | |
|---|---|
| CEUS | Contrast-enhanced ultrasound |
| CI | Confidence index |
| DTC | Differentiated thyroid cancer |
| ECOG | Eastern Cooperative Oncology Group |
| HRs | Hazard ratios |
| LNM | Lymph node metastasis |
| LTP | Local tumor progression |
| MWA | Microwave ablation |
| PFS | Progression-free survival |
| PTC | Papillary thyroid carcinoma |
| RAI | Refractory to radioactive iodine |
| RAIR-DTC | Radioactive iodine refractory DTC |
| RAIR-LNM | Radioactive iodine refractory lymph node metastasis |
| RFA | Radiofrequency ablation |
| Tg | Thyroglobulin |
| TSH | Thyroid-stimulating hormone |
| VRR | Volume reduction rate |

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## Compliance with ethical standards

**Guarantor**
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The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry**
No complex statistical methods were necessary for this paper.

**Informed consent**
Written informed consent was obtained from all subjects (patients) in this study.

**Ethical approval**
Institutional Review Board approval was obtained.

**Study subjects or cohorts overlap**
Study subjects or cohorts have not been previously reported.

### Methodology

- Retrospective
- Prognostic study
- Multicenter study

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### References

1. Bray F, Laversanne M, Sung H et al (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74:229–263
2. Schlumberger M, Leboulleux S (2021) Current practice in patients with differentiated thyroid cancer. Nat Rev Endocrinol 17:176–188
3. Boucai L, Zafereo M, Cabanillas ME (2024) Thyroid cancer: a review. JAMA 331:425–435
4. Cheng F, Xiao J, Shao C et al (2021) Burden of thyroid cancer From 1990 to 2019 and projections of incidence and mortality until 2039 in China: findings from global burden of disease study. Front Endocrinol 12:738213
5. Aashiq M, Silverman DA, Na'ara S, Takahashi H, Amit M (2019) Radioiodine-refractory thyroid cancer: molecular basis of redifferentiation therapies, management, and novel therapies. Cancers (Basel) 11:1382
6. Arida AK, Papaleontiou M (2022) To radiate or not to radiate? Adjuvant external beam radiation therapy for nonanaplastic thyroid cancer. Endocr Pract 28:732–733
7. Brose MS, Nutting CM, Jarzab B et al (2014) Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 384:319–328
8. Schlumberger M, Tahara M, Wirth LJ et al (2015) Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 372:621–630
9. Lin Y, Qin S, Yang H et al (2023) Multicenter randomized double-blind phase III trial of donafenib in progressive radioactive iodine-refractory differentiated thyroid cancer. Clin Cancer Res 29:2791–2799
10. Lin Y, Qin S, Li Z et al (2022) Apatinib vs placebo in patients with locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer: the REALITY randomized clinical trial. JAMA Oncol 8:242–250
11. Haugen BR, Alexander EK, Bible KC et al (2016) 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid 26:1–133
12. Kim JH, Baek JH, Lim HK et al (2018) 2017 Thyroid Radiofrequency Ablation Guideline: Korean Society of Thyroid Radiology. Korean J Radiol 19:632–655
13. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L (2020) 2020 European Thyroid Association Clinical Practice Guideline for the use of image-guided ablation in benign thyroid nodules. Eur Thyroid J 9:172–185
14. Yang Z, Zhang M, Yan L et al (2024) Value of radiofrequency ablation for treating locally recurrent thyroid cancer: a systematic review and meta-analysis for 2-year follow-up. Endocrine 85:1066–1074
15. Ding Z, Chen J, Chen Z et al (2022) Efficacy and safety of thermal ablation for treating lymph node metastasis from papillary thyroid carcinoma: a systematic review and meta-analysis. Front Oncol 12:738299
16. Ahmad S, Aljammal J, Orozco I et al (2023) Radiofrequency ablation of cervical thyroid cancer metastases-experience of endocrinology practices in the United States. J Endocr Soc 7:bvad066
17. Offi C, Misso C, Antonelli G, Esposito MG, Brancaccio U, Spiezia S (2021) Laser ablation treatment of recurrent lymph node metastases from papillary thyroid carcinoma. J Clin Med 10:5295
18. Tang W, Tang X, Jiang D et al (2022) Safety and efficacy of thermal ablation for cervical metastatic lymph nodes in papillary thyroid carcinoma: A systematic review and meta-analysis. Front Endocrinol 13: 967044
19. Chlorogiannis DD, Charalampopoulos G, Kontopyrgou D et al (2024) Emerging indications for interventional oncology: a comprehensive systematic review of image-guided thermal ablation for metastatic non-cervical lymph node disease. Curr Oncol Rep 26:1543–1552
20. Upadhyaya A, Upadhyaya SA, Chang L, Yuanyuan L, Xi W (2025) Ultrasound-guided percutaneous radiofrequency and microwave ablation for cervical lymph node metastasis from papillary thyroid carcinoma: a systematic review and meta-analysis of clinical efficacy and safety. Acad Radiol 32:2533–2544
21. LaForteza A, Persons E, Hussein M et al (2024) Treatment outcomes in patients with papillary thyroid cancer undergoing radiofrequency ablation of metastatic lymph nodes. Gland Surg 13:1752–1758
22. Han ZY, Dou JP, Cheng ZG et al (2020) Efficacy and safety of percutaneous ultrasound-guided microwave ablation for cervical metastatic lymph nodes from papillary thyroid carcinoma. Int J Hyperthermia 37:971–975
23. Mauri G, Pacella CM, Papini E et al (2019) Image-guided thyroid ablation: proposal for standardization of terminology and reporting criteria. Thyroid 29:611–618
24. Dotinga M, Vriens D, van Velden FHP et al (2022) Reinducing radioiodine-sensitivity in radioiodine-refractory thyroid cancer using lenvatinib (RESET): study protocol for a single-center, open label phase II trial. Diagnostics (Basel) 12:3154
25. Leboulleux S, Do Cao C, Zerdoud S et al (2023) A phase II redifferentiation trial with dabrafenib-trametinib and 131I in metastatic radioactive iodine refractory BRAF p.V600E-mutated differentiated thyroid cancer. Clin Cancer Res 29:2401–2409
26. Vaisman F, Tala H, Grewal R, Tuttle RM (2011) In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. Thyroid 21:1317–1322
27. Yu Q, Zhang X, Li L, Zhang C, Huang J, Huang W (2023) Molecular basis and targeted therapies for radioiodine refractory thyroid cancer. Asia Pac J Clin Oncol 19:279–289
28. Giovanella L, Ceriani L, Garo ML (2022) Is thyroglobulin a reliable biomarker of differentiated thyroid cancer in patients treated by lobectomy? A systematic review and meta-analysis. Clin Chem Lab Med 60:1091–1100
29. Watanabe K, Igarashi T, Uchiyama M, Ishigaki T, Ojiri H (2024) Retrospective case-control study examining the relationship between recurrence-free survival and changes in pre- and post-radioiodine therapy serum thyroglobulin levels in patients with differentiated thyroid cancer. Jpn J Radiol 42:391–397
30. Signore A, Lauri C, Di Paolo A et al (2023) Predictive role of serum thyroglobulin after surgery and before radioactive iodine therapy in patients with thyroid carcinoma. Cancers (Basel) 15:2976
31. Giovanella L, Castellana M, Trimboli P (2019) Unstimulated high-sensitive thyroglobulin is a powerful prognostic predictor in patients with thyroid cancer. Clin Chem Lab Med 58:130–137
32. Ywata de Carvalho A, Kohler HF, Ywata de Carvalho CCG, Vartanian JG, Kowalski LP (2024) Predictors of recurrence after total thyroidectomy in 1,611 patients with papillary thyroid carcinoma: postoperative stimulated serum thyroglobulin and ATA initial and dynamic risk assessment. Arch Endocrinol Metab 68:e220506
33. So YK, Seo MY, Son YI (2012) Prophylactic central lymph node dissection for clinically node-negative papillary thyroid microcarcinoma: influence on serum thyroglobulin level, recurrence rate, and postoperative complications. Surgery 151:192–198
34. Cao XJ, Wang SR, Che Y et al (2021) Efficacy and safety of thermal ablation for treatment of solitary T1N0M0 papillary thyroid carcinoma: a multicenter retrospective study. Radiology 300:209–216

35. Han ZY, Dou JP, Zheng L et al (2023) Safety and efficacy of microwave ablation for the treatment of low-risk papillary thyroid microcarcinoma: a prospective multicenter study. Eur Radiol 33:7942–7951
36. Wei Y, Niu WQ, Zhao ZL et al (2022) Microwave ablation versus surgical resection for solitary T1N0M0 papillary thyroid carcinoma. Radiology 304:704–713
37. Wang MH, Liu X, Wang Q, Zhang HW (2022) Safety and efficacy of ultrasound-guided thermal ablation in treating T1aN0M0 and T1bN0M0 papillary thyroid carcinoma: a meta-analysis. Front Endocrinol 13:952113

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