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# Recurrent papillary thyroid carcinoma in cervical lymph nodes: outcomes of radiofrequency ablation compared to radioactive iodine

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## Abstract

**Purpose**: To evaluate the effects of radioactive iodine (RAI) ablation after radiofrequency ablation (RFA) in patients with recurrent papillary thyroid carcinoma (PTC).

**Material and methods**: We conducted a retrospective cohort study involving 60 patients with documented cervical lymph node (LN) recurrent PTC. All RFA procedures were performed using the "pulling-back, moving-shot" approach under local anaesthesia. LN volume reduction ratio (VRR), thyroglobulin, and complications were analysed 6 and 12 months after RFA. This study comprised two distinct groups of patients: one group that received a combination of RFA and RAI ablation, and another group that underwent RFA alone (30 cases in each group).

**Results**: The mean age of patients was 39.8 ± 10.5 years, 68% of whom were women. VRR of LNs was significant at 6 months and 12 months after RFA (87.4% and 91.9%, respectively, $p < 0.001$). Serum thyroglobulin level decreased after 12 months (2.7 ± 5.9 to 0.6 ± 1.8, $p = 0.021$). Post-RFA complication was noted in one patient with transient hoarseness. Ten new recurrent LNs were reported in 9 patients (15%) during follow-up. No benefit was detected for the RAI treatment at the end of 12 months of follow-up in terms of structural or biochemical recurrence. Based on the non-randomised retrospective study design, this comparison is descriptive in nature and cannot be used to make any causal inference regarding the effectiveness of adjuvant RAI.

**Conclusions**: RFA has been shown to be effective in achieving volume reduction with a high success rate of 97% and with minimal complications. There was no additional benefit of adjuvant RAI. However, this result cannot be used to make any inference regarding the effectiveness of RAI due to confounding by indication. A prospective randomised trial is needed.

**Key words**: papillary thyroid carcinoma, cervical lymph node, radiofrequency ablation, radioactive iodine.

## Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer and is associated with favourable outcomes and a low mortality rate [1,2]. Even though the long-term prognosis is favourable, locoregional recurrences have been reported in up to 28% of patients [3]. Over 90% of recurrent PTC cases occur in cervical lymph

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**Authors' contribution:**
**A** Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

nodes (LNs) [1]. Conventional treatment for locoregional LN metastasis involves re-operation followed by RAI therapy [4-6]. This is especially concerning because repeated surgeries can lead to complications, such as vocal cord injury, hypoparathyroidism, and altered architectural neck tissue [1,4]. Alternative methods could be considered if patients with recurrent thyroid carcinoma are ineligible for surgery or are at risk of repeated surgery. Recently, recurrent thyroid carcinoma has been successfully treated with minimally invasive treatment methods such as laser ablation, microwave ablation, and radiofrequency ablation (RFA) [6,7].

More recently, the identification of the RFA effect has added a new dimension to the management of patients with recurrent PTC. RFA is a non-invasive, effective, and safe procedure that can be used as an alternative method to surgery in patients with recurrent PTC. Theoretically, if the RFA is considered a substitute for surgery, adjuvant therapy with RAI can be reasonable. Several studies have investigated the efficacy and safety of RFA in the treatment of benign nodules and local recurrence of PTC, but the efficacy of RFA in comparison to the combination of RFA and radioactive iodine (RAI) ablation has not been investigated [1,8]. There has been one study that evaluated the efficacy and safety of combining RFA and iodine therapy in the treatment of recurrent PTC [5].

There is no evidence to determine if RAI ablation should be performed after RFA of recurrent PTC in cervical LNs. The indication was decided mainly based on the expert opinion of the consultant endocrinologist or nuclear physician for patients in this setting. Such a comparison may deepen our understanding of the effect of RFA on the treatment of locoregional recurrent PTC, inform on the effect of the combination of RFA with RAI ablation, guide the management of recurrent PTC, and improve the patient's outcome.

We conducted this study to evaluate the effect of RFA on patients with neck nodal recurrence in PTC. Moreover, we compared the effectiveness and safety of RFA versus combining RFA with iodine therapy in the management of patients with nodal recurrent PTC.

## Material and methods

This study was approved by the Ethics Committee of Iran University of Medical Sciences (ethics code. IR.IUMS.REC.1403.459) and was consonant with the principles of the Declaration of Helsinki. Informed consent for RFA was obtained from all patients. This retrospective cohort study was conducted on 60 patients with PTC who experienced regional nodal recurrence. Patients had been referred to TIRAD imaging institute (Tehran, Iran) from March 2019 to March 2023 by their clinician (i.e. endocrinologist, surgeon, or nuclear physician) for RFA.

### Patient selection protocol

Patients with the following inclusion criteria were included in our study: (1) history of total thyroidectomy due to PTC, and (2) LN recurrence confirmed by one of the following two ways before RFA: cytologic findings of PTC in fine needle aspiration (FNA) of the suspicious lesion or positive FNA thyroglobulin (Tg) washout.

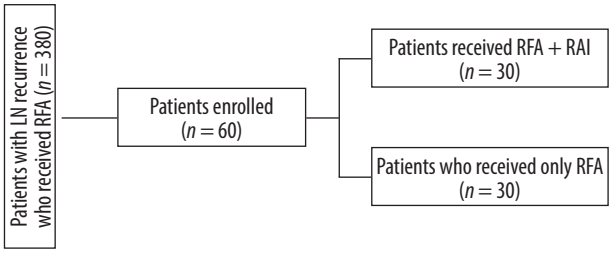
Also, the following patients were excluded from further assessment: (1) patients over 60 years old; (2) with a history of previous RAI ablation within the 12 months before RFA; (3) with the presence of distant metastasis; (4) patients with aggressive primary pathology (i.e. tall cell, columnar cell, sclerosing type, solid variant, hobnail cell variant, insular type, and poorly differentiated pathologies); (5) involvement of more than 5 LNs in the neck (perceived as nonresponsive to non-surgical approaches); and (6) patients lost to follow-up for 6 or 12 months post RFA.

### Included patients

There were 380 patients with nodal recurrence after primary PTC who received RFA. After comprehensive evaluation, 30 patients who received adjuvant RAI after RFA mentioned criteria for enrolment were included in this study. Then, 30 patients who did not receive RAI after RFA were enrolled. The process of matching was based on the chronological list of the registry of 380 patients. The first patient in the list, which was matched by age (±4 years) and number of LNs involved with the considered patient in combined group, was selected. Finally, we considered 60 patients for the analysis. Figure 1 provides a summary of the patients included in this study.

### Pre-ablation assessment

Prior to RFA, thyroid and neck ultrasound (US) was performed by two expert radiologists with approximately 15 years of experience. It was performed according to The Korean Society of Thyroid Radiology guidelines [9] using the same US (Supersonic Aixplorer® Ultimate). All characteristics of the recurrent lesions were recorded such as size, volume, vascularisation, and location.




LN – lymph node, RAI – radioactive iodine, RFA – radiofrequency ablation

**Figure 1.** Flow chart of patients enrolled in this study

Tumour volume was calculated by the use of the ellipsoid volume formula: length (cm) × depth (cm) × width (cm) × 0.524 [10].

All the patients underwent the confirmation procedure before ablation. For this purpose, US-guided FNA of the nodules including fluid Tg analysis was performed. The method of FNA has been described previously in another study [11]. To assess the Tg washout test, we employed a syringe with a needle that was rinsed with 1 $cm^3$ of normal saline, and the washout was submitted for Tg measurements. Measures over 1.0 µg/l were considered diagnostic for recurrence [12,13].

## Ablation procedure

The procedure of RFA was described in detail previously [11,14]. The patient was in a supine position with neck extension. After local anaesthesia with 2-5 cc of 2% lidocaine, ablation was done by an internally cooled 18-gauge radiofrequency 200 Watt/50 kHz supplied electrode, which had a 10 cm shaft and an appropriate 5-7 mm active tip. Initially, the LNs were dissected using constant and high-pressure injection of 5% dextrose saline around them to separate the adjacent structure when needed.

A "pulling-back, moving-shot" approach (i.e. placing the needle tip at distal tumour and heating the tumour while removing the needle) was performed. For the larger LNs, the bulk of the lesion was divided into several small ablation units, then ablated unit-by-unit. Based on the size of the tumour and the active tip of the electrode, the initial power output was adjusted between 8 and 20 W. Both the tumour's capsule and peripheral zone were ablated. Ablation continued centripetal until all tumour zones turned hyperechoic.

## RAI ablation

Thirty patients that were included in the RFA + RAI group received 100-200 mCi of RAI within a mean interval of 2-6 months after RFA. The RAI (Parsisotope, Karaj, Iran) was used orally in an in-patient setting. Before RAI therapy, pretreatment approaches such as low iodine-free diet and thyroid hormone withdrawal for 3-4 weeks were performed.

## Outcome measures and follow-up

After completion of the RFA, ablation zones were reassessed for vascularity by directional power Doppler for microvascular flow assessment. The patients were closely monitored for complications such as haematoma and voice abnormality during the procedure until discharged from the institute.

The patients were followed up 6 and 12 months after RFA. During the follow-up, thyroid and neck US were performed by the same radiologist who performed RFA previously. The number, diameters, and vascularity of the ablated lesions were collected from the follow-up US reports. The volume reduction ratio (VRR) was calculated as follows: initial nodule volume – final nodule volume × 100/initial nodule volume). RFA was considered successful when there was a reduction of more than 50% in VRR [15]. Also, the laboratory tests including serum levels of Tg and anti-Tg were evaluated before RFA and at follow-up of 6 and 12 months.

## Statistical analysis

An independent samples *t*-test was used to compare the volumes and other indices between two groups with and without RAI therapy. The change of volumes and other indices before and after therapy was analysed by paired *t*-test at two time points. General linear models were designed for analysis of covariance at three time points (i.e. before, and 6 and 12 months after RFA). SPSS IBM v23 was used for data analysis. *P*-value < 0.05 was considered significant.

# Results

A total of 60 patients were enrolled in the study. Of these patients, 68% (41) were women. The mean age of the participants was 39.8 ± 10.5 years (range 18-60 years). There were 147 cervical-involved LNs with a median number of two malignant LNs. The mean pre-RFA LN volume was 1.19 ± 1.84 $cm^3$. The VRR of LNs was 87.4 ± 15.5 % at 6 months ($p < 0.001$) and 91.9 ± 24.9 % after 12 months ($p < 0.001$). Baseline and follow-up characteristics of these 60 patients are summarised in Table 1.

**Table 1.** Characteristics of patients with lymph node (LN) recurrence of papillary thyroid carcinoma after radiofrequency ablation (RFA)

| | Before RFA | 6 months after RFA | *p*-value* | 12 months after RFA | *p*-value† |
|---|---|---|---|---|---|
| LN volume ($cm^3$) | 1.19 ± 1.84 | 0.16 ± 0.32 | < 0.001 | 0.07 ± 0.12 | < 0.001 |
| VRR (%) | NA | 87.4 ± 15.5 | NA | 91.9 ± 24.9 | NA |
| VRR > 50% (%) | NA | 98.2 | NA | 97.4 | NA |
| Serum Tg (µg/l)‡ | 2.7 ± 5.9 | 1.6 ± 8.1 | 0.595 | 0.6 ± 1.8 | 0.021 |

Continuous variables expressed as means ± standard deviation. Categorical variables expressed as percentages. VRR was calculated with pre-ablation data minus post-ablation data. $p = p$-value statistically significant if < 0.05. *$p$-value between before and 6 months after ablation, †$p$-value between before and 12 months after ablation. ‡Data of serum Tg of 53, 49, and 31 patients at baseline, 6 months, and 12 months after RFA, respectively, were analysed due to missing data.
NA – not applicable, Tg – thyroglobulin, VRR – volume reduction ratio of the nodule (pre-ablation volume – post-ablation volume)/pre-ablation volume × 100

### Comparison between two groups

Then we compared the characteristics of the patients who received RFA followed by RAI (combined group) with the patients who did not receive any adjuvant RAI after RFA (only-RFA group). Both groups were comparable in terms of size (21.9 ± 8.8 vs. 27.2 ± 11.8, $p = 0.08$), multifocality (53.8% vs. 61.5%, $p = 0.57$), extrathyroidal extension (80.8% vs. 73.1%, $p = 0.51$), and the stage of PTC ($p = 0.73$). There was no remarkable variation in the age of patients, biochemical measure, and tumour characteristics such as number and volume of LNs across the combined and only-RFA groups (Table 2). The VRR in both groups were significant in comparison with baseline data after 6 months of RFA (91.8% and 83%, respectively, $p < 0.001$) and were stable over one year of follow-up.

During the duration of the 12-month follow-up, the volume and VRR did not exhibit any significant differences between the groups (all $p > 0.05$). However, VRR was higher in those who were not treated with RAI at 6 months ($p = 0.033$). The similar trends of volume reduction in both groups are presented in Figure 2.

### Complications and new recurrence rate

We observed one case of transient hoarseness during RFA that resolved immediately after injection of cold dextrose water around the ablated lesion. No other complicated cases were found during the ablation or follow-up.

Ten new recurrent LNs were reported in 9 patients (15%) during follow-up. Eight of these patients had 1 LN, and one patient had 2 new lesions over 9 months after RFA. In these cases, 4 patients had not received RAI (44.4%), and 5 cases had ablated with adjuvant RAI (55.5%), which was similar between the two groups ($p = 0.317$).

## Discussion

In this retrospective cohort study, we sought to expand knowledge regarding the usefulness of RFA in the management of patients with recurrent nodal PTC. The volume of recurrent lesions decreased significantly after 6 months and remained stable for up to 12 months. In addition, serum Tg levels decreased significantly after 12 months. These findings emphasise that RFA can be considered in patients with nodal recurrent PTC. These findings are consonant with other studies regarding favourable long-term outcomes of RFA in this setting [1].

In this regard, Yang *et al.* [8] conducted a retrospective study on 32 patients with 58 local recurrence PTC lesions after RFA without any adjuvant RAI therapy. They reported a 72.90% reduction in LN volume at 12 months after RFA, respectively, which is lower than our findings in the current study, with a reduction rate of 91%. In another retrospective study by Ahmad *et al.* [1] on 8 patients

**Table 2.** Comparison of characteristics between the two groups

| | No adjuvant RAI ($n = 30$) | Adjuvant RAI ($n = 30$) | *p*-value between the two groups |
|---|---|---|---|
| Age (years) | 40 ± 9.5 | 39.5 ± 11.5 | 0.845 |
| Number of malignant LN | 2.4 ± 1 | 2.6 ± 1.2 | 0.497 |
| Baseline LN volume ($cm^3$) | 1.2 ± 2.2 | 1.1 ± 1.3 | 0.9 |
| VRR (%) | | | |
| 6 months later | 91.8 ± 1.7 | 83.0 ± 17.0 | 0.033 |
| 12 months later | 94.5 ± 10.0 | 89.0 ± 34.4 | 0.495 |
| Tg (µg/l) | | | |
| Baseline ($n = 53$) | 2.2 ± 3.7 ($n = 27$) | 3.3 ± 7.5 (n = 26) | 0.482 |
| 6 months later ($n = 49$) | 0.3 ± 0.4 ($n = 26$) | 0.3 ± 0.8 ($n = 23$) | 0.250 |
| 12 months later ($n = 31$) | 0.3 ± 0.4 ($n = 13$) | 0.9 ± 2.4 ($n = 18$) | 0.364 |

Continuous variables expressed as means ± standard deviation. Categorical variables expressed as percentages. VRR was calculated with pre-ablation data minus post-ablation data. *P*-value between the two groups was considered statistically significant if $p < 0.05$. $cm^3$ – cubic centimetres, LN – lymph node, RIA – radioiodine ablation, Tg – thyroglobulin, VRR – volume reduction ratio of the nodule (pre-ablation volume – post-ablation volume)/pre-ablation volume × 100

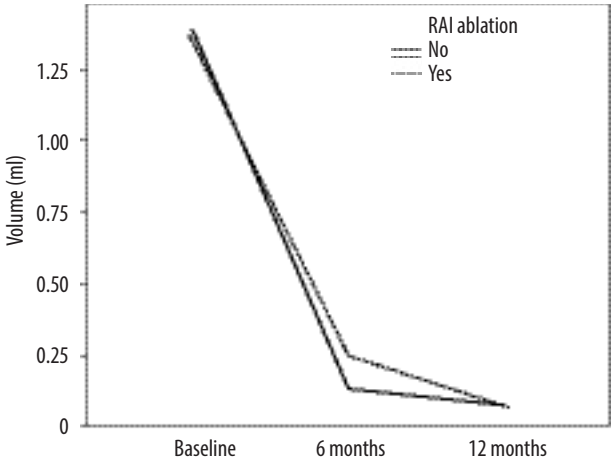



**Figure 2.** The trend of lymph node (LN) volume reduction after radiofrequency ablation (RFA) in patients with and without radioactive iodine (RAI) adjuvant therapy. This figure shows the trend of LN reduction in both groups after 6 and 12 months of RFA. The solid line shows the volume changes of the LN reduction in patients who received RAI ablation. The dashed line shows the changes in patients who did not receive RAI. The volume decreased in patients with or without adjuvant radioiodine therapy (within-group statistics: $p < 0.001$; partial eta squared = 0.33; and observed power = 0.98), and no difference in the trend of reduction was determined between the two groups (between groups with and without RAI: $p = 0.914$, partial eta squared = 0.00 and observed power 0.05)

with PTC, who had 11 cervical metastatic LNs, the patients underwent RFA. They presented that RFA resulted in a complete response in 81.8% of lesions at a median follow-up of more than one year; however, the sample size was small [1].

The VRR of LNs in both the combined (RFA + RAI ablation) and RFA-only groups were remarkable after 6 and 12 months of follow-up. No advantage was detected for the prescription of adjuvant RAI at the end of 12 months of follow-up in terms of structural or biochemical recurrence. Surprisingly, there was a significant VRR in patients who had not ablated with RAI after 6 months of follow-up. However, the combined group achieved a reduction rate of LNs that was nearly equivalent to that observed in the RFA-only group at the conclusion of the follow-up period. The impact of adjuvant RAI therapy following RFA remains uncertain, and to our knowledge, there is only one study addressing this entity. A prospective study conducted by Long *et al.* [5] involved 12 patients with PTC who underwent RFA, followed by RAI ablation 2 weeks later, with a follow-up period of 6 months after treatment. The findings indicated that the combination of RFA and RAI is an effective method for managing local recurrence in PTC; however, the study faced certain limitations, including the absence of a control group and a small sample size. Although the effectiveness of RFA in patients with PTC has been investigated [6], previous research did not compare the effectiveness and safety of RFA in patients who received RAI ablation versus those who did not. To our knowledge, this current study presents the first insights on this setting.

In this study, the complication rate associated with RFA was found to be low and not serious. There was an acceptable recurrence rate of about 15% during a one-year follow-up. Notably, the incidence of new LN recurrence rate in a study by Yang *et al.* [8] was 28.13%. Additionally, another study indicated that lesions with a volume exceeding 1.1 $cm^3$ had a lower response rate and even experienced regrowth [1].

This study was conducted using a retrospective design with its indigenous limitations. Above all, the decision to use adjuvant RAI was made based on the opinion of the responsible physician and based on the clinical data of patients (including the initial recurrence risk of primary pathology and trend of the disease aggressiveness), which may be ignored in the current study. Also, it seems that a longer follow-up period is needed to better compare the results. Nevertheless, this study includes a larger number of followed patients when compared to other research efforts.

## Conclusions

This study shows that RFA is a safe and effective treatment for selected patients with recurrent PTC involving cervical LNs. The achieved outcomes include a 97% reduction in target volume of more than 50% and a 15% rate of recurrence at one year; however, these outcomes are dependent on strict selection criteria and thus are not applicable to the general population. In relation to the comparison of RFA treatment alone and RFA treatment combined with RAI, although descriptive, these results are only hypothesis-generating. In addition, the fact that no benefit was found does not exclude the efficacy of RAI treatment, because treatment decisions were based on clinical risk assessment, without randomisation, controlling for confounders, or long-term results. To identify specific groups that may benefit from such treatment, prospective randomised studies or studies using propensity score matching are needed.

## Disclosures

1. Institutional review board statement: This study was approved by the Ethics Committee of Iran University of Medical Sciences (ethics code.IR.IUMS.REC.1403.459) and was consonant with the principles of the Declaration of Helsinki. Informed consent for RFA was obtained from all patients.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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