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Ten-Year Outcomes of Radiofrequency Ablation for Locally Recurrent Papillary Thyroid Cancer

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Objective: This study investigates the long-term efficacy and safety of ultrasound (US)-guided radiofrequency ablation (RFA) for treating locally recurrent papillary thyroid cancer (PTC).

Materials and Methods: We retrospectively analyzed 39 consecutive patients with 61 locally recurrent PTCs (14 males, 25 females; mean ± standard deviation age, 52.8 ± 16.7 years; range 21–92 years) who underwent US-guided RFA with curative intent between September 2008 and April 2012. A subgroup of 24 patients with 37 recurrent PTCs who had a follow-up of at least 10 years were analyzed separately. All patients were followed for changes in lesion size on US and thyroglobulin (Tg) levels at 1, 3, 6, and 12 months after RFA, with follow-up every 6–12 months thereafter. Any complications were documented during the follow-up period. Recurrence-free survival (RFS) rates were assessed using Kaplan-Meier estimates. Long-term outcomes were evaluated in patients with follow-up of at least 10 years.

Results: The follow-up period ranged from 7 to 180 months (median 133 months). The RFS rates for the 39 patients at 3, 5, and 10 years were 86.8%, 75.5%, and 60.6%, respectively. Among the 24 patients with 37 recurrent PTCs followed for more than 10 years, the volume reduction rate was 99.9% (range 96%–100%), and the complete tumor disappearance rate was 91.9%. The mean serum Tg level also decreased significantly, from 2.66 ± 86.5 mIU/L before ablation to 0.43 ± 0.73 mIU/L (P < 0.001) at the final follow-up. In 14 (58.3%) of the 24 patients, Tg levels were undetectable (below 0.08 mIU/L) at the last follow-up. No life-threatening or delayed complications were observed during the 10-year follow-up period.

Conclusion: The high RFS throughout the follow-up period, with efficacy and safety lasting beyond 10 years, supports US-guided RFA as a valuable option for local control of recurrent PTCs.

Keywords: Recurrent thyroid cancer; Papillary thyroid carcinoma; Radiofrequency ablation; Treatment outcome; Ultrasound

INTRODUCTION

The thyroid gland is the most prevalent site for primary endocrine malignancies worldwide and ranks ninth among cancers affecting women [1]. Fortunately, differentiated thyroid carcinoma (DTC), the predominant type encompassing over 95% of cases, exhibits a remarkably low mortality rate that has remained consistent over the past three decades [2,3].

Despite the generally favorable prognosis for DTC, a significant challenge arises for 20%–50% of patients who exhibit cervical lymph node metastasis at the time of diagnosis [4-6]. Repeated neck dissections for recurrent tumors become progressively more intricate due to scar tissue formation within the surgical bed. This disrupts normal tissue planes and elevates the risk of complications of fibrosis during subsequent surgery [7].

Thermal ablation techniques, particularly radiofrequency ablation (RFA), offer a promising alternative for the treatment of recurrent tumors. Compared to repeat surgery, this minimally invasive approach offers several advantages, including a reduced risk of complications, shorter hospital stays, and faster recovery times.

While previous studies investigating RFA for recurrent thyroid carcinoma have demonstrated excellent initial outcomes with high rates of complete tumor ablation [8-12],

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a critical limitation lies in their relatively short follow-up periods, typically ranging from 10.3 to 80.0 months [9-11,13-16]. Papillary thyroid cancer (PTC), the most prevalent type of DTC, is known for its slow-growing cancer, and several studies have reported a high incidence of late recurrence, with more than half of patients undergoing reoperation more than 10 years after the initial operation. This underscores the need for a long-term follow-up [17,18]. Therefore, this study aimed to evaluate the long-term therapeutic efficacy and safety of ultrasound (US)-guided RFA for locally recurrent PTC.

MATERIALS AND METHODS

Participants

This retrospective study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2023-1332), with a waiver for written informed consent due to the retrospective nature of the study.

Data were collected retrospectively from a cohort of patients who participated in our previous short-term follow-up study (mean follow-up: 26.4 months) investigating RFA treatment with curative intent for recurrent PTC of the neck between September 2008 and April 2012 [10,11].

Patients were included in the study if they met the following criteria: no metastasis beyond the neck before RFA, no more than four metastases, recurrent PTC confirmed by US-guided fine needle aspiration biopsy (FNAB) or thyroglobulin (Tg) measurement of needle washout; follow-up period exceeding six months, and refusal to undergo surgery. The retrospective cohort comprised 61 recurrent PTCs in 39 patients (14 males, 25 females; mean age ± standard deviation: 52.8 ± 16.7 years; range: 21–92 years) (Table 1).

On average, patients underwent 1.6 ± 0.7 surgeries (range: 1–3) and received 1.1 ± 0.7 rounds of radioactive iodine therapy (range: 1–3). All patients underwent total thyroidectomy, central compartment node dissection, and lateral neck dissection. Additionally, all patients received postoperative radioiodine therapy and supplemental levothyroxine and thyrotropin suppression therapy.

Among these patients, 24 with 37 recurrent PTCs were followed up for over 10 years (Table 1). Figure 1 illustrates the patient flow. Fifteen patients discontinued follow-up before 10 years due to death from lung cancer (n = 1), tongue cancer (n = 1), pneumonia (n = 2), or loss of follow-up (n = 11).

Procedures and Follow-Up

All patients underwent pre-RFA evaluation, including US, US-guided FNAB of the recurrent tumor, contrast-enhanced neck CT, and laboratory tests. Recurrent tumors were confirmed by cytological smears and/or elevated Tg levels in FNAB samples. Tumor diameter before RFA was measured by US, and volume (V) was calculated using the formula $V = \pi abc/6$, where a is the largest diameter, and b and c are the two perpendicular diameters [19].

US-guided RFA was performed by one of two experienced staff radiologists (16 and 21 years of experience in thyroid RFA, respectively). We used a radiofrequency generator (Cool-Tip RF system, Radionics, Burlington, MA, USA; SSP-2000, Taewoong Medical, Gimpo, Korea; VIVA RF system,

Table 1. Baseline patient characteristics

Patient characteristics	n = 39	n = 24
Age, yr	52.8 ± 16.7 (21–92)	49.5 ± 14.5 (21–71)
Sex, male:female, n	14:25	11:13
Number of recurrent tumors	1.6 ± 0.9 (1–4)	1.6 ± 0.9 (1–4)
Location, n		
Central	35	21
Lateral	26	16
Initial tumor diameter, cm	0.79 ± 0.43 (0.31–2.1)	0.82 ± 0.50 (0.31–2.1)
Initial tumor volume, mL	0.20 ± 0.35 (0.01–2.32)	0.24 ± 0.44 (0.01–2.32)
Initial serum thyroglobulin level, mIU/L	1.21 ± 1.91 (0.08–18.5)	2.66 ± 5.09 (0.08–18.5)
Number of RFA sessions, n	1.1 ± 1.3 (1–2)	1.4 ± 0.3 (1–2)
1	55	32
2	6	5

Data are expressed as the mean ± standard deviation with range in parentheses, unless stated otherwise.
RFA = radiofrequency ablation

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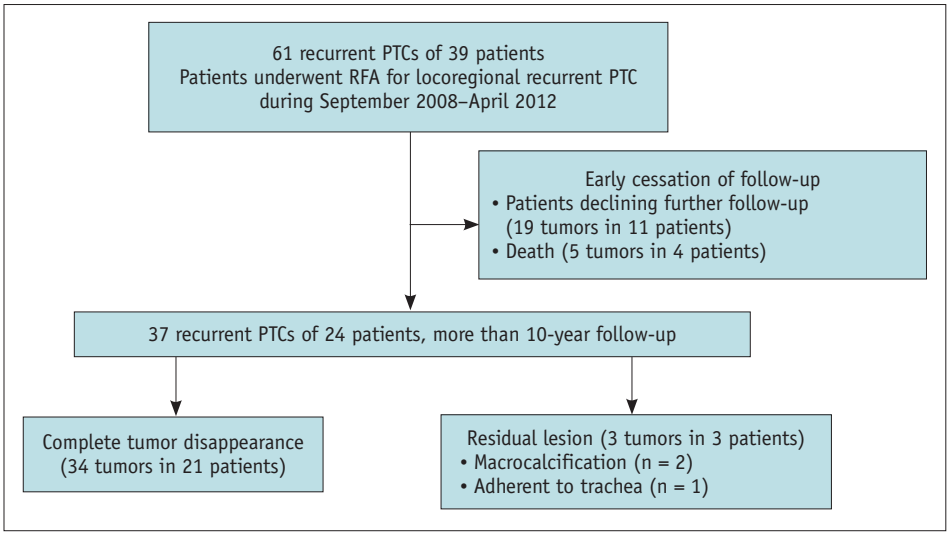

Fig. 1. Flowchart of the patient enrollment process. PTC = papillary thyroid cancer, RFA = radiofrequency ablation

STARmed, Goyang, Korea) and an 18- or 19-gauge internally cooled electrode with variable active tip sizes (0.5-, 0.7-, and 1-cm) (Cool-Tip, Radionics; Well-Point RF electrode, STARmed; VIVA, STARmed) depending on the tumor size. Local anesthesia in all the patients without analgesics, sedation, or general anesthesia were administered.

Moving shot and hydrodissection techniques were employed to ensure complete ablation, including surrounding normal tissue (usually exceeding 2 mm) to prevent marginal recurrence [11,20]. Power settings began at 10 W for the 0.5-cm tip, 15 W for the 0.7-cm tip, and 30 W for the 1-cm tip. If a transient hyperechoic zone did not form within 5–10 seconds, power was gradually increased up to 50 W in 5–10 W increments. Ablation ended when all treated tumor portions transformed into transient hyperechoic zones.

Patients were followed for at least 10 years with US and Tg level evaluations at 1, 3, 6, and 12 months, followed by assessments every 6–12 months thereafter. US examinations were performed by the same radiologists who conducted the RFA. Volume reduction rate (VRR) was calculated using the formula VRR = ([initial volume - final volume] x 100)/initial volume [21]. Additionally, the rate of undetectable serum Tg levels (<0.08 mIU/L) without thyroid-stimulating hormone stimulation was determined.

All patients underwent post-ablation contrast-enhanced CT (average time: 256 days, range: 23–2452 days). Additional RFA was performed if follow-up US indicated viable remnants (power Doppler signals) or if follow-up CT showed enhancement in a treated tumor region.

Statistical Analysis

All data were analyzed using SPSS 23 for Microsoft Windows (version 23.0; IBM Corp., Armonk, NY, USA) and R (Version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria). Recurrence-free survival (RFS) time was defined as the interval between RFA treatment and the date of tumor recurrence or death from all causes, and survival curves were plotted using the Kaplan-Meier method. The Wilcoxon signed-rank test was used to compare the largest tumor diameter, tumor volume, and serum Tg levels before RFA and at the final follow-up. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Entire Cohort

During a 10-year follow-up, recurrent disease developed in 14 patients (36.8%) of the 39 patients treated with RFA for recurrent rumors. The follow-up duration ranged from 7–180 months, with an average of 133 months. Among these patients, 10 exhibited local tumor recurrence, while four presented with lung metastasis. Notably, none of the local tumor progression occurred at the original RFA site. Seven of the ten patients with local tumor recurrence lesions underwent additional RFA treatment, two opted for surgery, and one underwent close observation. The overall RFS rates at 3, 5, and 10 years were 86.8%, 75.5%, and 60.6%, respectively (Fig. 2).

The overall complication rate was 7.7% (3/39). All three complications involved voice changes, which developed

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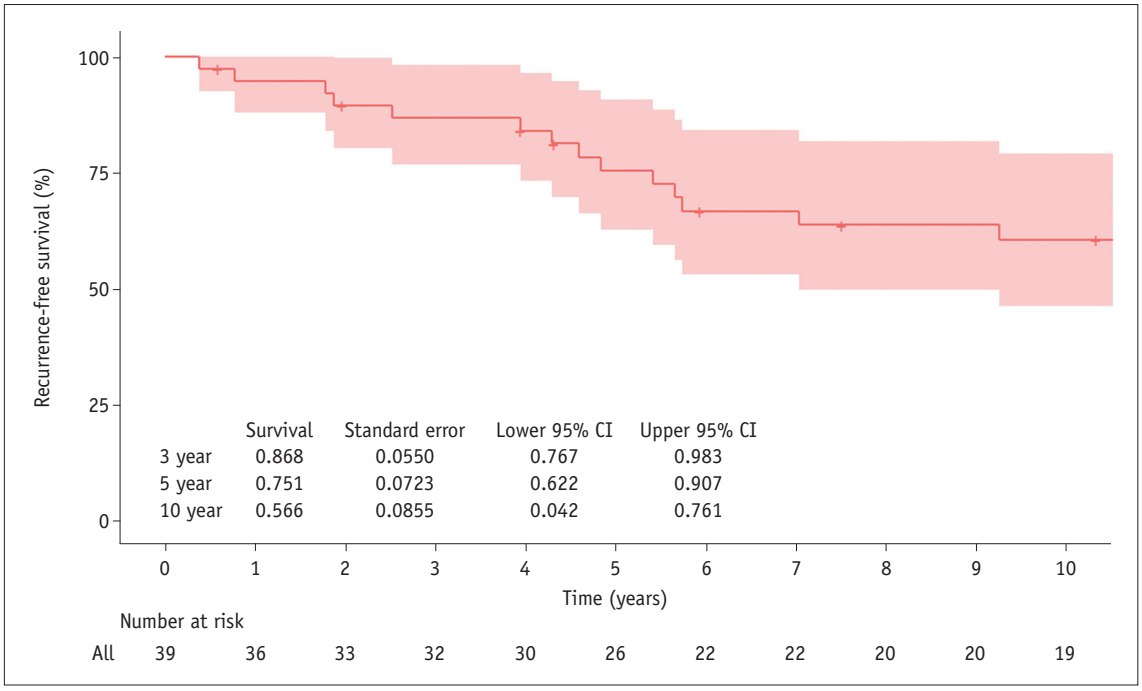

Fig. 2. Kaplan-Meier curve for recurrence-free survival rate after radiofrequency ablation for the entire cohort (n = 39). CI = confidence interval

during RFA in one patient and one to two hours after RFA in two patients. Voice changes recovered within two months in all patients. No life-threatening or delayed complications occurred during the 10-year follow-up period.

Subgroup With a Follow-Up ≥10 Years

As shown in Table 1, the baseline characteristics of the 24 patients with 37 recurrent tumors who were followed for 10 years are summarized. The study population comprised 11 males and 13 females, with a mean age of 49.5 years (range: 21–71 years). Twenty-one (56.8%) of the 37 recurrent tumors were located in the central compartment, and 16 (43.2%) were located in the lateral compartment. The mean number of recurrent tumors was 1.6 ± 0.9 (range: 1–4). The mean number of treatment sessions for each tumor was 1.4 ± 0.3 (range: 1–2), and the mean follow-up duration after RFA was 148.0 ± 15.5 months (range: 124–180 months).

Changes in the largest tumor diameter observed at each follow-up evaluation are shown in Figure 3. The volume of the recurrent tumors decreased significantly from 0.24 ± 0.44 mL before ablation to 0.002 ± 0.01 mL (P < 0.001) at final evaluation, with a mean tumor VRR of 99.9% ± 0.55% (range: 96%–100%). The mean serum Tg level also decreased significantly from 2.66 ± 5.09 mIU/L before ablation to 0.43 ± 0.73 mIU/L (P < 0.001) at the final follow-up, with levels below the detection limit (0.08 mIU/L) observed in 14 (58.3%) of the 24 patients. Initial serum Tg levels >0.08 were found in 20 patients (83.3%). Among these patients, the mean serum Tg level also decreased significantly from 3.2 ± 5.5 mIU/L before ablation to 0.4 ± 0.7 mIU/L, with levels below the detection limit observed in 10 (50.0%) at the last follow-up.

Of the 37 tumors that were monitored for more than 10 years, 34 (91.9%) completely disappeared without recurrence (Fig. 4). The mean duration of the complete disappearance of the treated tumor was 8.7 months ± 8.1 (range: 1–36 months). Among the three residual lesions, two manifested solely as macrocalcifications on US and CT, lacking a vascularized solid component and without displaying a change in size over 157 and 168 months of follow-up, respectively (Fig. 5). One of these two macrocalcified lesions was confirmed to be negative for malignancy using core needle biopsy. The other residual lesion, situated at the thyroidectomy site, shrank after RFA. However, a portion of the residual lesion remained adherent to the trachea, with residual enhancement on CT. There was no change in the tumor size over 146 months after RFA.

DISCUSSION

This study evaluated the long-term outcomes of RFA for recurrent PTC in 39 consecutive patients. The RFS rates

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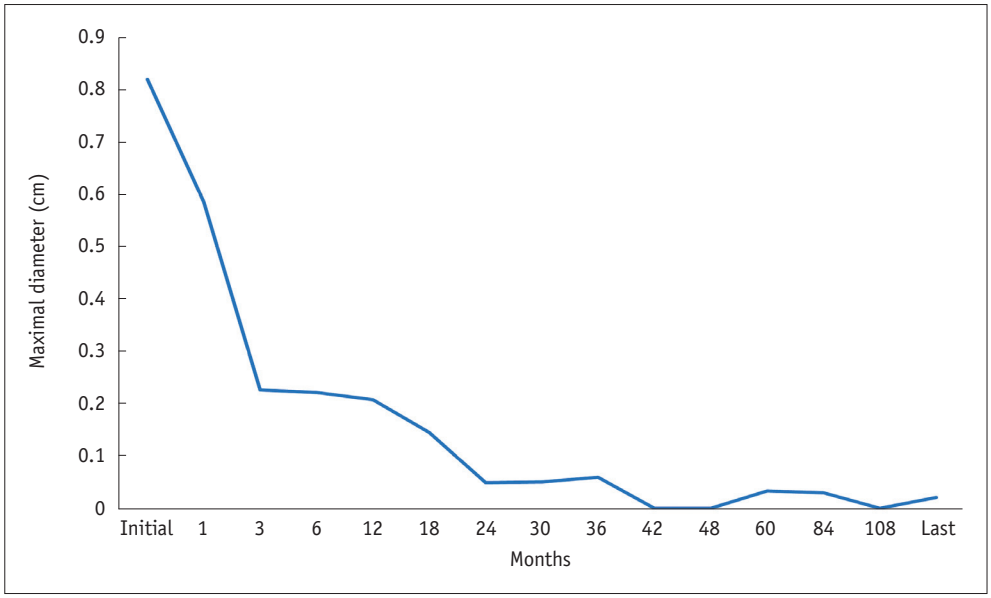

Fig. 3. Changes in the largest diameter of recurrent tumor before radiofrequency ablation and at each follow-up in patients with a follow-up ≥10 years (n = 24).

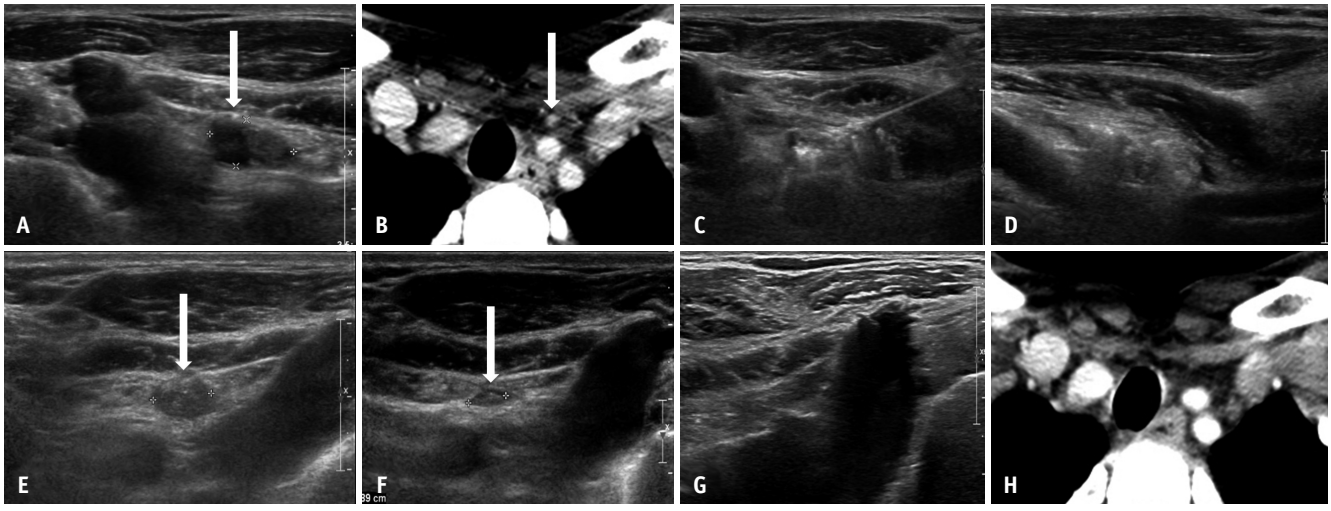

Fig. 4. A 39-year-old male with recurrent papillary thyroid cancer at left supraclavicular area after thyroidectomy and radioactive iodine therapy. **A, B:** Transverse US image, a 1.2-cm-sized heterogeneous echoic metastatic lymph node in the left supraclavicular area (arrow, **A**). The lymph nodes show strong enhancement on arterial-phase contrast-enhanced CT (arrow, **B**). **C, D:** An internally cooled electrode with a 0.5-cm-sized active tip is inserted into the metastatic lymph node **(C)**. After completion of RFA, the hyperechoic ablated zone is larger than the initial tumor size **(D)**. **E, F:** One and seven months after RFA, transverse US scans show that the treated tumor gradually decreased in size (arrows). **G, H:** At 126 months after RFA, the treated tumor was not observed on US or CT. US = ultrasound, RFA = radiofrequency ablation

at 3, 5, and 10 years were 86.8%, 75.5%, and 60.6%, respectively, with a mean follow-up of 108 months. Among the 24 patients with 37 recurrent PTCs followed up for over 10 years, the VRR was 99.9% and the complete tumor disappearance rate was 91.9%. This represents the longest reported follow-up on the efficacy and safety of RFA for recurrent thyroid cancer. Furthermore, no serious or life-threatening complications were identified during the long-term follow-up. These findings support the long-lasting efficacy and safety of RFA for treating recurrent PTC beyond 10 years, solidifying its role as a viable treatment option for local control of recurrent PTCs.

The standard treatment for recurrent locoregional PTCs involves surgery, followed by radioactive iodine and thyroid

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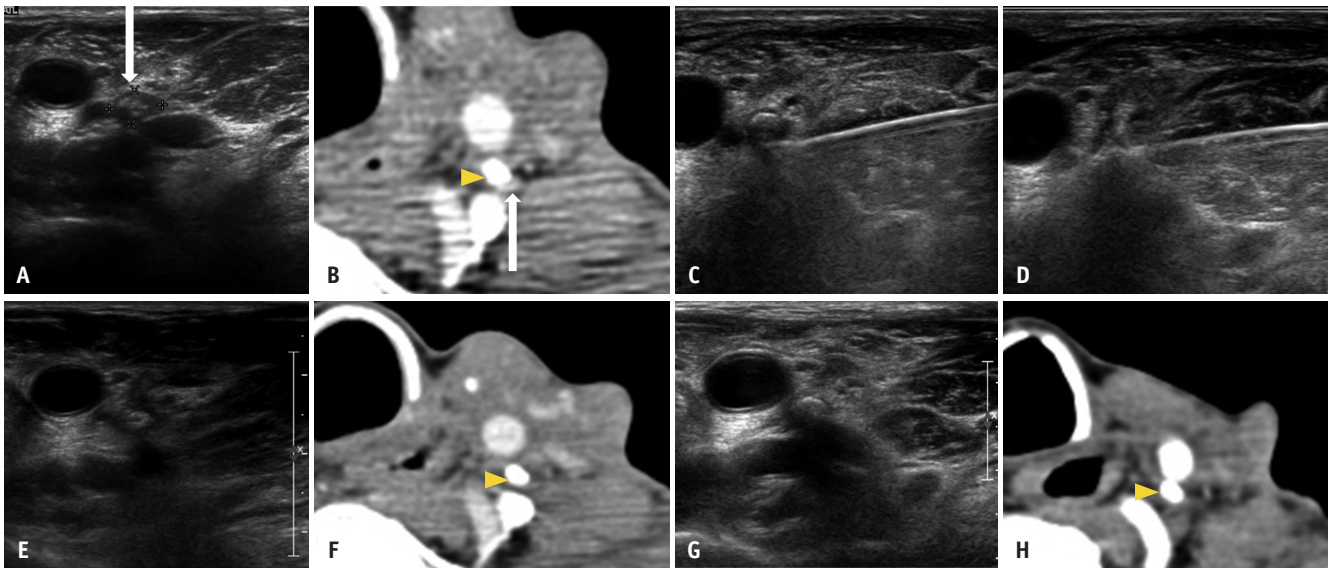

Fig. 5. A 38-year-old male with recurrent papillary thyroid cancer at left neck level IV after thyroidectomy and RI therapy. **A, B:** Transverse US image shows a 0.6-cm-sized hypoechoic metastatic lymph node with macrocalcification at left neck level IV (arrow, **A**). The lymph node exhibits a strongly enhancing component at the posterior aspect of the calcified lymph node (arrowhead, **B**) on arterial-phase contrast-enhanced CT (arrow, **B**). **C, D:** An internally cooled electrode with a 0.5-cm-sized active tip is inserted into the metastatic lymph node. **E, F:** One month after RFA, transverse US scans **(E)** showed that the treated tumor had decreased in size with residual macrocalcification. On CT **(F)**, there is no visible enhancing solid component in the posterior aspect of the calcified lymph node (arrowhead). **G, H:** At 120 months after RFA, the treated tumor remained macrocalcified (arrowhead, **H**), without a demonstrable solid component on US and CT. RI = radioactive iodine, US = ultrasound

hormone suppression therapy [22]. However, reoperation presents challenges due to scar tissue formation and potential distortion of normal tissues in the surgical area [23]. Additionally, poor lung function and multiple comorbidities in elderly patients can make surgery risky. In such cases, thermal ablation, a minimally invasive treatment approach, offers an alternative treatment modality for controlling local recurrence. Previous studies have shown promising results for RFA in terms of local tumor control, with a mean VRR of 95.1%–100% and complete disappearance rates of 82.0%–100% of treated tumors [9-11,13-16,24]. Reflecting these findings, recent guidelines recommend RFA for recurrent thyroid cancer in high-risk surgical patients or those who decline surgery [21,25-27]. Our previous five-year follow-up reported a complete disappearance rate of 91.3%, consistent with the 91.9% observed at the 10-year mark [10]. Notably, no delayed tumor recurrence was observed among patients with complete disappearance in the five-year follow-up. These findings are significant as they demonstrate the sustained effectiveness of RFA for recurrent PTC beyond 10 years.

The overall RFS rate in our study was 86.8%, 75.5%, and 60.6% at 3, 5, and 10 years, respectively. By some definitions, the complete response rate to reoperation for recurrent thyroid cancer ranges from 46% to 53% [28-31], with a mean follow-up duration of five years. It is important to note that our study focused on a selective group of patients with locoregional recurrence limited to the neck area, making direct comparison with reoperation studies challenging due to different patient selection criteria. However, the efficacy of RFA in these selected patients with locoregional recurrence appears comparable to reoperation. Additionally, studies comparing the efficacy of RFA and reoperation have reported no significant difference in RFS [13,14].

Patient selection is crucial for achieving successful RFA outcomes [21]. According to the guidelines established by the Korean Society of Thyroid Radiology, favorable outcomes are achieved when the following criteria are met: the number of locally recurrent tumors is limited to less than three or four per patient, the greatest tumor diameter is smaller than 1.5–2.0 cm, and the lesions should be completely treated with RFA [21]. In our study, three out of 37 tumors were still visible and did not completely disappear. Two of these tumors had macrocalcifications. But lacked a non-calcified solid component as seen on US and CT, and remained stable during the follow-up period exceeding 10 years after RFA. Similar findings of complete disappearance of recurrent tumors with macrocalcifications were reported by Yang

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et al. [16] and Yoo et al. [32]. These findings suggest that macrocalcification within a recurrent tumor is not a contraindication for RFA.

One residual tumor in our study adhered to the trachea. Previous studies have shown that the likelihood of tracheal wall invasion increases with a wider angle between the tumor and trachea, and the VRR after RFA in such cases is significantly lower [33]. Therefore, crucial pre-procedural evaluation for potential invasion of surrounding tissues is essential for optimal patient selection and successful RFA with curative intent.

The limitations of this study are twofold. First, its retrospective design inherently carries the risk of selection bias. Patients with better outcomes might be more likely to have complete follow-up data, potentially inflating the observed success rates. Second, the data originated from only two specialists. This raises concerns about generalizability to real-world settings where practitioners' expertise may vary. Success rates could be lower in community hospitals with less expertise in PTC management.

In conclusion, this study demonstrated high RFS rates after RFA for locally recurrent PTC over a 10-year follow-up. The mean tumor VRR of 99.9% and complete tumor disappearance rate of 91.9% in patients followed for at least 10 years strongly suggest the long-lasting efficacy and safety of RFA for treating recurrent PTC beyond 10 years. These findings solidify RFA as a viable treatment option for local control of recurrent PTCs.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jung Hwan Baek and Jeong Hyun Lee, who hold respective positions as Editorial Board Member and Section Editor of the *Korean Journal of Radiology*, were not involved in the editorial evaluation or decision to publish this article.

Author Contributions

Conceptualization: Jung Hwan Baek. Data curation: Jung Hwan Baek, Jeong Hyun Lee. Formal analysis: Sae Rom Chung. Investigation: Young Jun Choi, Sae Rom Chung. Methodology: Sae Rom Chung, Jung Hwan Baek. Project administration: Jung Hwan Baek. Resources: Jung Hwan Baek. Software: Jung Hwan Baek. Supervision: Jung Hwan Baek. Validation: Jung Hwan Baek. Visualization: Sae Rom Chung. Writing—original draft: Sae Rom Chung. Writing—review & editing: all authors.

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