



Long-term follow-up of the radiofrequency ablation of benign thyroid nodules: the value of additional treatment

ULTRASONOGRAPHY

Hyun Jin Kim¹, Jung Hwan Baek², Woojin Cho³, Jung Suk Sim⁴

¹Department of Radiology, Daejin Medical Center, Bundang Jesaeng General Hospital, Seongnam; ²Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ³Department of Otolaryngology-Head and Neck Surgery, Withsim Clinic, Seongnam; ⁴Department of Radiology, Withsim Clinic, Seongnam, Korea

Purpose: This study aimed to evaluate the efficacy of additional radiofrequency ablation (RFA) treatment for benign thyroid nodules.

Methods: Electronic medical records at a single institution from September 2008 to August 2016 were searched, and consecutive patients treated with RFA due to benign thyroid nodules with cosmetic or symptomatic problems were enrolled. All patients were followed up for at least 30 months. The nodules were divided into three groups: group 1 included nodules that met the criteria for additional treatment and underwent additional treatment, group 2 included nodules that met the criteria but did not undergo additional treatment, and group 3 included nodules that did not meet the criteria. The ablation results were compared among the three groups in terms of the initial ablation ratio (IAR) and volume reduction ratio (VRR).

Results: Ninety nodules from 88 patients were included in the study. At the last follow-up, group 1 showed a significantly smaller nodule volume and larger VRR (2.5 mL and 84.6%, respectively) than group 2 (8.1 mL and 39.8%, respectively, $P < 0.001$), but did not present a significant difference from group 3 (0.9 mL, $P = 0.347$, and 92.8%, $P = 0.238$). The IAR was significantly higher in group 3 (94.5%) than in the other two groups (group 1, 81.1%; group 2, 82.8%; $P < 0.001$).

Conclusion: Multiple treatment sessions achieve greater VRR. Therefore, additional treatment could be considered for patients who meet the corresponding criteria.

Keywords: Radiofrequency ablation; Thyroid nodule; Thyroid gland

Key points: These results demonstrate the efficacy of additional treatment in radiofrequency ablation of symptomatic benign thyroid nodules. Additional treatment may achieve greater volume reduction.

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Correspondence to:

Jung Suk Sim, MD, Department of Radiology, Withsim Clinic, 353 Hwangsaeul-ro, Bundang-gu, Seongnam 13590, Korea

Tel. +82-31-708-3444

Fax. +82-31-704-8179

E-mail: jungsuk.sim@gmail.com

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Introduction

Various studies have demonstrated that thermal ablation (TA) is an effective and safe treatment

for benign thyroid nodules in patients with cosmetic problems or compressive symptoms [1–5]. However, several studies with long-term follow-up periods have shown that treated thyroid nodules can regrow after 2 to 3 years [6–8]. Even if regrowth occurs, some studies have suggested that a single treatment is sufficient because the primary purpose of TA is to improve compressive symptoms or cosmetic problems rather than to provide complete ablation [1,9]. At the same time, other studies have suggested that additional treatment is needed to achieve long-lasting effects without recurrence after TA [6]. With increasing awareness of the effectiveness and safety of TA, patients may choose a minimally invasive TA procedure to avoid scarring in the anterior neck area and to reduce the risk of surgical complications [10,11]. Therefore, to be considered as an alternative to surgery, TA procedures should be effective for the treatment of larger nodules, and the effects should be sustainable for longer periods [12].

Although there has been debate regarding the necessity of additional treatment, no study has investigated the efficacy of additional treatment. In addition, the proper timing and indications of additional treatment of radiofrequency ablation (RFA) for benign thyroid nodules remain unclear. Therefore, the present study aimed to evaluate the efficacy of additional treatment.

Materials and Methods

Compliance with Ethical Standards

The national public institutional review board designated by the Korean Ministry of Health and Welfare approved this retrospective study (P01–202102-21–009), and the requirement for informed consent was waived because the patient data were evaluated retrospectively. However, all patients provided written informed consent for RFA.

Patients

Electronic medical records were searched from September 2008 to August 2016, and consecutive patients who were treated by ultrasonography (US)-guided RFA due to benign thyroid nodules were enrolled. The eligibility criteria for inclusion in this study were patients with benign thyroid nodules and cosmetic or symptomatic problems [13] and a follow-up period of at least 30 months after initial RFA. Nodules were divided into three groups according to whether they met the criteria for additional treatment and whether they underwent additional treatment. Group 1 included nodules that met the criteria for additional treatment and underwent additional treatment. Group 2 included nodules that met the criteria but did not undergo additional treatment. Group 3 included nodules that did not meet the criteria. The detailed criteria for additional

treatment were as follows: (1) the patient's symptoms or cosmetic problem had not been resolved or recurred; (2) regrowth or an increase in the viable volume (Vv) was observed; (3) the initial ablation ratio (IAR) was <70%; (4) increased vascularity with or without volume increase was observed. Both persistent vascularity and newly developed vascularity within nodules were included within the category of increased vascularity. The decision for additional treatment was made after discussion with each patient.

The following parameters were collected: age, sex, patients' symptoms or cosmetic problems, the date of treatment, the initial nodule volume (mL), and the composition of the nodules at the initial examination.

Pre-ablation Assessment

A radiologist with 18 years of experience with thyroid imaging and US-guided procedures performed the US examinations, US-guided fine needle aspiration cytology (FNAC) or core needle biopsy (CNB), and RFA [14,15]. RFA was performed using high-frequency linear probes with real-time US machines (Accuvix XG or Accuvix V10, Samsung Medison, Seoul, Korea; E-cube 12, Alpinion Medical Systems, Seoul, Korea). The width and height of the nodule were measured on axial images. The length was measured on sagittal images. The volume of each nodule was calculated using the following equation: $V (mL) = \pi abc/6$ (V, volume; a, the largest diameter; b and c, the other two perpendicular diameters in centimeters) [16,17]. All nodules were confirmed to be benign by at least two instances of FNAC or CNB [13,18]. A scoring system was used to measure symptomatic or cosmetic problems. The patients reported a self-measured symptom score using a 10-cm visual analog scale (grade: 0–10) [4,19,20]. The cosmetic score was measured by a physician (1, no palpable mass; 2, no cosmetic problem but a palpable mass; 3, a cosmetic problem on swallowing only; and 4, a readily detected cosmetic problem) [1,4,19,20].

Procedure

The same operator performed RFA using RF generators (RF150 and RF 300, Apro-Korea, Gunpo, Korea) and straight-type modified internally cooled electrodes with active tip lengths of 5, 7, 10, and 15 mm (Well-Point RF Electrode, STARmed, Goyang, Korea; CoAtherm electrode, Apro-Korea). The techniques were performed as suggested by the Korean Society of Thyroid Radiology [13]. Patients were placed in the supine position with their necks fully extended. Under local anesthesia with 2% lidocaine, the trans-isthmus approach was used with the moving-shot technique. The hydrodissection technique was used to protect areas vulnerable to thermal injury, such as the danger triangle and around the carotid sheath. The venous ablation technique was used to fill the draining

vein with bubbles generated by ablation, which was mainly located at the margin of the nodule [21]. When the dominant feeding artery was found, the artery-first ablation technique was used [21]. Complications during and immediately after the procedure were checked to ensure proper management [22]. After RFA, patients were observed for 4–6 hours in the hospital [23]. Each nodule received one to six sessions of treatment. The same techniques were used for additional treatments.

Follow-up

The same operator assessed volume changes and symptoms or cosmetic problems at 1, 3 or 6, and 12 months and additionally at 1-year intervals. Three types of nodule volume (total volume [Vt], ablated volume [Va], and Vv) were defined, measured, and calculated using US images. Vt was defined as the total nodule volume. Va was defined as the ablated nodule volume presenting as a hypoechoic area on US. Vv was defined as the incompletely treated viable nodule volume, which was calculated using the following equation: $Vv=Vt-Va$. The operator then assessed the IAR and volume reduction ratio (VRR) to evaluate the efficacy of the treatment. The IAR is the ratio of the Va to the Vt of the nodule immediately after RFA, which was calculated using the following equation [24]:

$$IAR(\%) = \frac{Vt_{initial} - Vv_{first\ f/u}}{Vt_{initial}} \times 100 (\%)$$

$Vt_{initial}$ is the total nodule volume immediately after RFA. It is practically interchangeable with the nodule volume before RFA. $Vv_{first\ f/u}$ can be calculated by the following formula; $Vv_{first\ f/u} = Vt_{first\ f/u} - Va_{first\ f/u}$. Regrowth

was defined as an increase in the Vt by more than 50% compared to the smallest Vt reported previously [6,25]. A Vv increase was defined as growth of the Vv by more than 50% compared to the smallest Vv reported previously [7].

Statistical Analysis

The statistical analysis was performed using SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Data for continuous variables such as the patient’s age and nodule diameter and volume are presented as the mean and standard deviation. One-way analysis of variance and the Scheffé *post-hoc* test were used to determine the difference between the three groups classified according to whether they underwent additional treatment or showed regrowth. Values such as the initial volume and follow-up period were compared between groups. The IAR, VRR, and final Vt were compared to evaluate the results of RFA in each group. A P-value <0.05 was considered to indicate statistical significance.

Results

After the exclusion of one nodule, 90 nodules in 88 patients were included in this study (male:female ratio=6:82; mean age, 39.2 years). One nodule was excluded because it was too large (extending under the clavicle), and the measurement was not accurate on the first US examination. Table 1 shows the demographics of the

Table 1. Patients’ demographic data and characteristics of the nodules

Variable	Value
No. of patients	88
Sex (male:female)	6:82
Age (year)	39.2±11.4
No. of nodules	90
Nodule diameter, longest (cm)	3.7±1.2 (0.9–7.7)
Nodule volume (mL)	14.3±16.2 (1.5–90.1)
Solidity ^{a)}	
Solid or predominantly solid	80
Cystic or predominantly cystic	10
No. of RFA sessions (range)	1.5±0.9 (1–6)
F/U period (month) (range)	66.6±23.2 (33–122)

Values are presented as mean±SD (range).

RFA, radiofrequency ablation; F/U, follow-up.

^{a)}Solid: no obvious cystic component; predominantly solid: cystic portion ≤50%; predominantly cystic: cystic portion >50%; cystic: no obvious solid component.

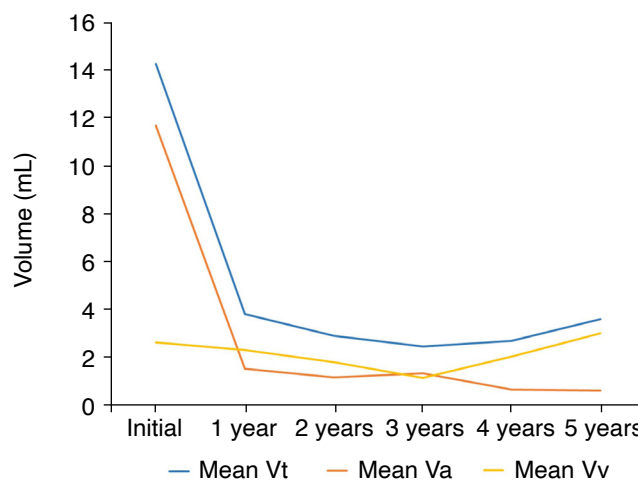


Fig. 1. Diagram showing changes in the Vt, Va, and Vv. Here, initial means the status immediately after RFA. Va shows a decreasing pattern during the follow-up period, and the slope is steep during the first year and there is little change in the slope thereafter. Vt shows a decreasing pattern until about 3 years and shows a slight increase afterward. Vv is relatively stable up to 3 years. However, it increases slightly thereafter. Vt, total volume; Va, ablated volume; Vv, viable volume; RFA, radiofrequency ablation.

Table 2. Nodule volume changes according to the follow-up period

Variable	Index	1 year	2 years	3 years	4 years	5 years	Final
No. of nodules	90	64	55	47	40	38	90
Vt	14.3	3.8	2.9	2.4	2.7	3.6	2.6
Va	–	1.5	1.2	1.3	0.7	0.6	0.6
Vv	–	2.3	1.8	1.1	2.0	3.0	2.6
VRR (%)	–	76.6	84.1	85.4	87.4	74.5	81.2
No. of cases with Vv increase (%)	–	11 (17.2)	8 (14.5)	5 (10.6)	4 (10.0)	8 (21.1)	40 (44.4) ^{a)}
No. of cases with regrowth (%)	–	1 (1.6)	4 (7.3)	4 (8.5)	2 (5.0)	8 (21.1)	25 (27.8) ^{b)}
No. of RFA sessions	–	1.1	1.2	1.2	1.3	1.4	1.5 ^{c)}

Vt, total volume; Va, ablated volume; Vv, viable volume; VRR, volume reduction rate; RFA, radiofrequency ablation.

^{a)}The cumulative number of nodules that showed more than a 50% increase in viable volume. ^{b)}The cumulative number of nodules that showed more than a 50% increase in total volume. ^{c)}The cumulative number of RFA sessions during follow-up.

Table 3. Final volume reduction rate according to group

	Group		
	1	2	3
No.	29	15	46
Initial volume, mean±SD (range) (mL)	23.3±21.5 (1.5–90.1)	14.1±13.4 (1.7–56.0)	8.7±9.5 ^{a)} (1.6–61.8)
IAR (%)	81.1	82.8	94.5 ^{a)}
Session	2.6 ^{a)} (2–6)	1	1
F/U (month)	68.5	64.9	65.9
Final Vt	2.5±2.9	8.1±8.1 ^{a)}	0.9±2.6
VRR	84.6±19.0	39.8±43.5 ^{a)}	92.8±10.0
No. of cases with Vv increase ^{b)}	25	15	0
No. of cases with regrowth ^{c)}	15	10	0

SD, standard deviation; IAR, initial ablation ratio; F/U, follow-up period; Vt, total volume; VRR, volume reduction rate; Vv, viable volume.

^{a)}Significantly different between the indicated group and the other two groups.

^{b)}The number of nodules that showed a Vv increase by more than 50% compared to the previously reported smallest Vv. ^{c)}The number of nodules that showed a Vt increase by more than 50% compared to the previously reported smallest Vt.

included patients and the characteristics of the nodules in this study. The mean follow-up period was 66.6 months after RFA (range, 33 to 122 months).

Overall, Vt and Vv began to increase after 3 years, and the increase was greater in Vv than in Vt. In contrast, Va showed a declining curve during the follow-up period, with the steepest decrease during the first year after RFA (Fig. 1). The mean VRR at the final follow-up was 81.2% (Table 2). The number of nodules with regrowth gradually increased during the follow-up period, whereas the highest number of nodules with Vv increase was in the first year. In the first 2 years, all three groups showed continuous volume reduction, but in group 2, regrowth occurred thereafter. In groups

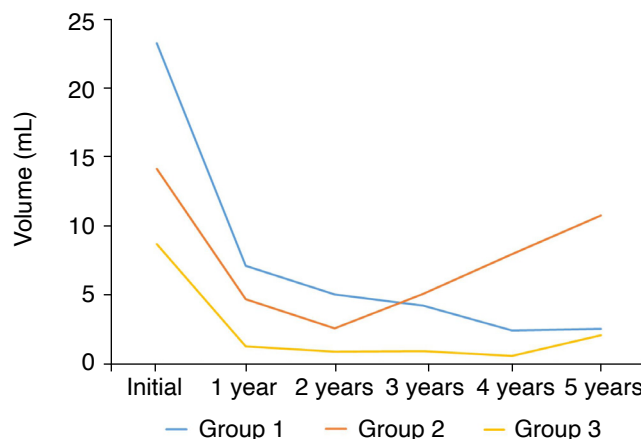


Fig. 2. Diagram showing changes in Vt according to the groups. Group 1 show declining curve during follow-up period, while group 2 show a volume increase 2 years after RFA. Group 3 show a declining curve during 4 years, but its volume increased slightly at 5 years. Vt, total volume; RFA, radiofrequency ablation.

1 and 3, volume reduction occurred until 4 years, but in group 3, there was slight regrowth. The final Vt of groups 1 and 3 was much smaller than that of group 2 (Fig. 2).

The initial volume of the nodules was significantly larger in group 1 (23.3 mL) than in group 3 (8.7 mL, $P<0.001$), while there was not a significant difference between groups 1 and 2 (14.1 mL, $P=0.569$) (Table 3, Fig. 2). The IAR was significantly higher in group 3 (94.5%) than in group 1 (81.1%, $P<0.001$) and group 2 (82.8%, $P=0.003$). At the last follow-up, group 1 showed significantly smaller mean nodule volume and higher VRR (2.5 mL and 84.6%, respectively) than group 2 (8.1 mL and 39.8%, respectively, $P<0.001$), but it did not show a significant difference from group 3 (0.9 mL, $P=0.347$ and 92.8%, $P=0.238$). The mean interval until the first additional treatment in group 1 was 37.6 months after the first RFA. The mean

VRR at the time of first additional treatment was 52.2%, which was significantly lower than the mean VRR at the last follow-up (81.2%, $P < 0.001$).

All three groups showed improvements in symptoms and cosmetic problems at the final follow-up compared to the initial score. However, aggravation of symptoms and cosmetic scores was observed in group 2 at 5 years after RFA, although there was no significant difference in the scores between the groups (Fig. 3).

Discussion

This study demonstrated that the VRR was high when additional treatment was performed for nodules with regrowth, increased Vv, or symptom recurrence, while a single session of RFA was effective for initially small nodules without regrowth or symptom recurrence. The VRR was significantly lower in group 2 than in groups 1 and

3. The average initial nodule volume of group 2 was smaller than that of group 1 and the IAR was similar; however, the final Vt was significantly larger and the final VRR was lower than in group 1. These results demonstrated that additional treatment may be effective in achieving a high VRR in nodules with regrowth or increased Vv.

Additional treatment was also effective for the treatment of large nodules. Group 1 showed a high VRR at the final follow-up despite the large initial volume and lower IAR of those nodules, potentially reflecting the effect of additional RFA. However, considering that group 3 achieved a high VRR without additional RFA, unnecessary additional treatment should be avoided in nodules with a small initial volume and high IAR. Additional RFA should be limited to patients with large nodules, unresolved clinical problems, or nodules showing regrowth or increased Vv after the first RFA.

In the present study, a single treatment was sufficiently effective

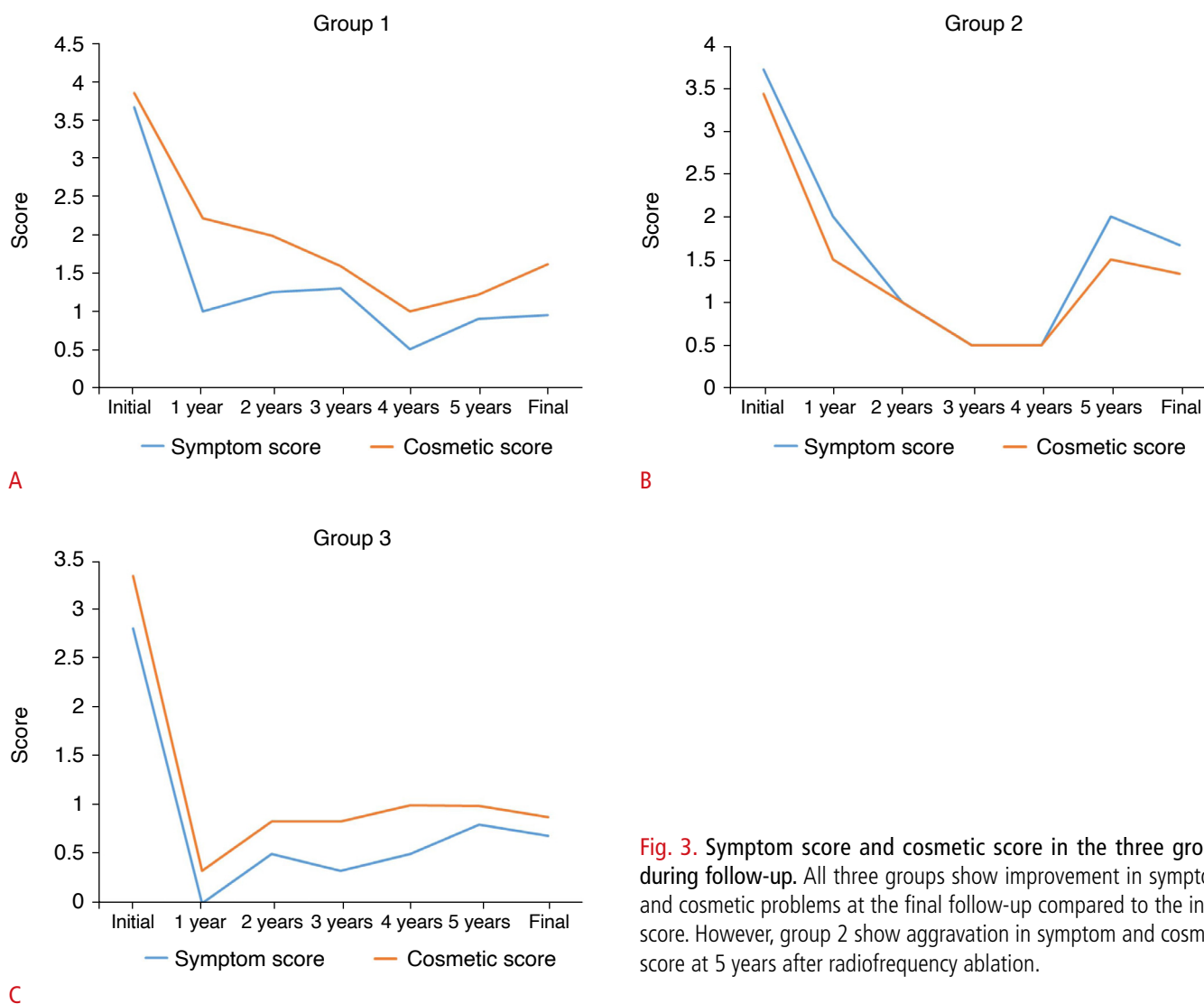


Fig. 3. Symptom score and cosmetic score in the three groups during follow-up. All three groups show improvement in symptoms and cosmetic problems at the final follow-up compared to the initial score. However, group 2 show aggravation in symptom and cosmetic score at 5 years after radiofrequency ablation.

for small nodules without recurrence. Group 3 had a significantly higher IAR than the other two groups. As the IAR is correlated to the VRR at 1 year, the higher IAR may be one of the reasons for the absence of regrowth in group 3 [24,26].

The IAR is a value indicating how much nodule tissue was ablated during the RFA procedure, and it can be obtained using the simple formula: $IAR (\%) = Va_{initial} / Vt_{initial} \times 100 (\%)$. Here, "initial" denoted as a subscript means the time immediately after the RFA procedure (Fig. 4A). However, unfortunately, $Vt_{initial}$ and $Va_{initial}$ are practically difficult

to measure on US immediately after the RFA because the images are not clear due to hemorrhage and edema (Fig. 4B). The exact value of $Vt_{initial}$ is known, because it is the same value as the nodule volume before RFA. Therefore, in practice, $Vt_{initial}$ and $Vt_{before\ RFA}$ can be used interchangeably. It is now only necessary to know $Va_{initial}$ to calculate the IAR, for which an indirect method was used with the images from the first follow-up, usually conducted within 1 to 3 months (Fig. 4C). Since the images are clear at this time, measurements can be performed accurately (Fig. 4D). As shown by Fig. 4A and 4C, $Vv_{initial}$

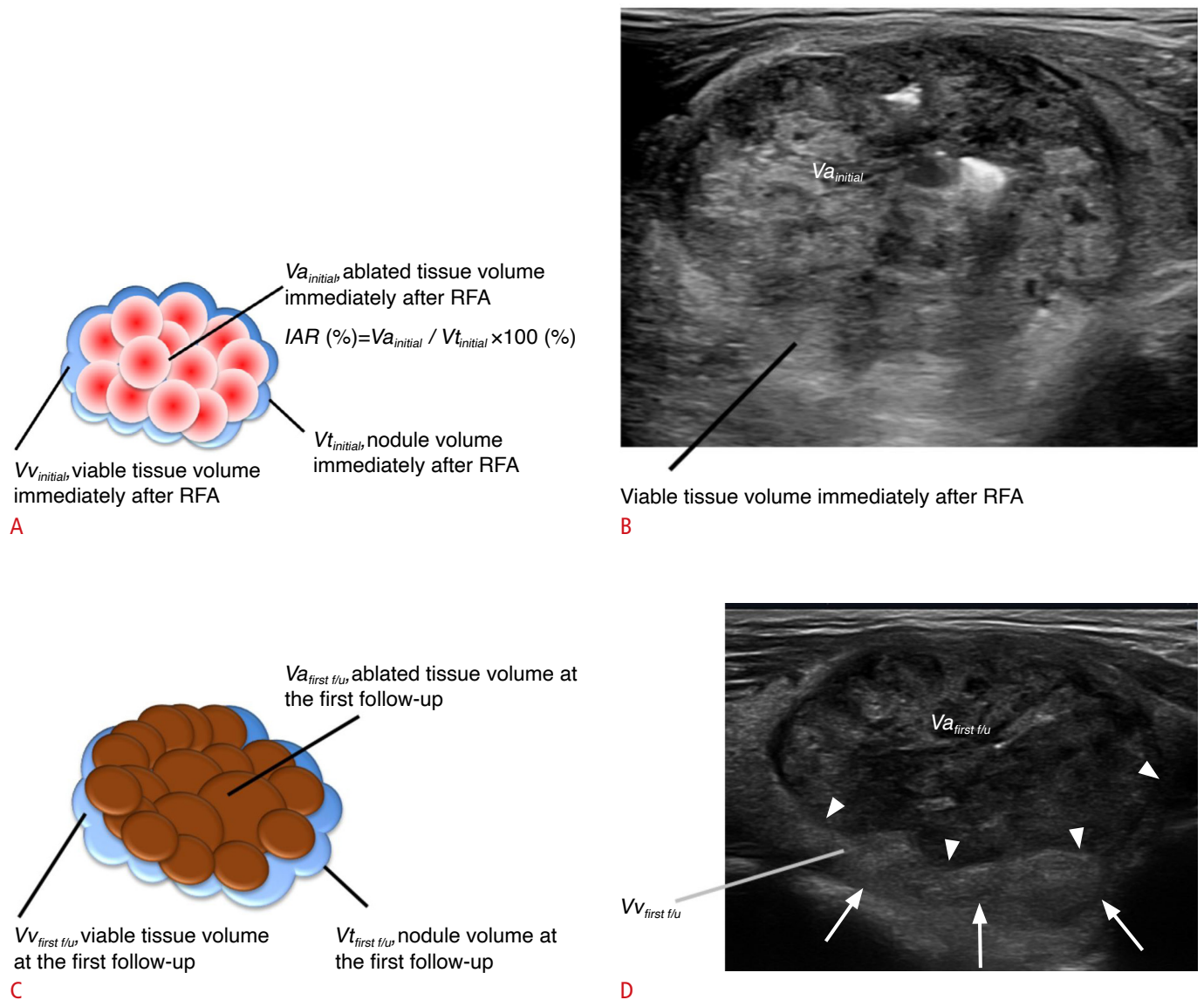


Fig. 4. Diagram and US images immediately after RFA and at the first follow-up. Diagram (A) and US image (B) show a nodule immediately after RFA. As there is marked swelling due to the hemorrhage and edema, an accurate measurement of both $Vt_{initial}$ and $Va_{initial}$ is not possible. Diagram (C) and US image (D) show the nodule at the first follow-up. The swelling has been absorbed and measurements can be made accurately. The arrows and arrowheads in D indicate the deeper margins of Vt and Va , respectively. IAR, initial ablation ratio; RFA, radiofrequency ablation; US, ultrasonography; Va , ablated volume; Vt , total volume; Vv , viable volume.

and $Vv_{\text{first f/u}}$ can be assumed to be equal. Because the period until the first follow-up is short, it is rare for the remaining viable tissue to grow after RFA. With the values of Vt_{initial} and Vv_{initial} in Fig. 4A, it is possible to calculate Va_{initial} and then the IAR, using the following equations:

$$IAR (\%) = Va_{\text{initial}} / Vt_{\text{initial}} \times 100 (\%) \text{ and then } IAR (\%) = (Vt_{\text{initial}} - Vv_{\text{first f/u}}) / Vt_{\text{initial}} \times 100 (\%).$$

Some authors have used other formulas ignoring the importance of the time point of measurement, such as $Vv_{\text{first f/u}} / Vt_{\text{first f/u}}$. However, it would be better to use Vt_{initial} instead of $Vt_{\text{first f/u}}$ because, the volume reduction between the initial measurements and the first follow-up could result in an error in the calculation [24,27].

There have been debates on the necessity of multiple treatments. Papini et al. [9] reported that a single session of laser ablation (LA) was effective and safe for solid nodules, achieving $\geq 50\%$ VRR in 67% of patients. Huh et al. [28] reported that single-session RFA was effective in improving symptomatic and cosmetic problems in most patients, as it achieved a high VRR of 70.2%. However, based on the reported follow-up results over 3 years, regrowth issues have become evident in both RFA and LA [7,8,28–30]. As regrowth is the cause of recurrence of symptoms and cosmetic problems, researchers who regard TA as an alternative to surgery have attempted multiple treatments to obtain complete or near-complete ablation and minimize regrowth, with the ultimate aim of avoiding surgical intervention after TA. Although some researchers believe that multiple treatments have an unfavorable outcome [31], others have adopted a multiple-session treatment approach to achieve the maximum ablation effect [6]. Several well-known international guidelines have indicated that additional treatment is necessary [13,32,33].

Since short-term results do not guarantee long-lasting effects due to marginal regrowth, it is important to control regrowth to relieve compressive symptoms and cosmetic problems without recurrence. From this perspective, Sim and Baek [12] proposed that the ultimate clinical goal of the TA of benign thyroid nodules should be the "permanent avoidance of surgery." Additional treatment can help attain this goal by preventing regrowth and achieving a higher VRR.

The appropriate timing for additional treatment remains unclear to date. Predicting regrowth is important for determining the timing of additional treatment. Several studies have attempted to predict the regrowth of benign thyroid nodules after RFA. Sim et al. [7] and Yan et al. [34] found that Vv increase can be a predictive factor of regrowth. Vv increase occurred earlier and was greater than Vt increase in the present study. These results are consistent with those of the previous study by Sim et al. [7]. In the early period after RFA,

Vv increase is masked by Va decrease. Vt increase, which indicates regrowth, occurs when the Vv increase exceeds the Va decrease. Therefore, regrowth may be detected earlier by monitoring Vv rather than Vt, which can help determine the appropriate timing of additional treatment.

In addition to the retrospective nature of this study, it has several limitations. First, this study was conducted with a relatively small number of patients from a single institution. These results should be validated in further prospective studies with a larger number of patients. Second, the characteristics of the nodules included in the study were not identical. As the vascularity and composition of nodules can affect the results of RFA [21,35–37], further well-designed studies are needed.

In conclusion, a greater VRR may be achieved by multiple-session RFA in large nodules. Therefore, additional treatment could be considered in the treatment of patients with unresolved clinical problems or nodules showing regrowth or increased Vv during follow-up after the first RFA.

ORCID: Hyun Jin Kim: <https://orcid.org/0000-0002-3411-3690>; Jung Hwan Baek: <https://orcid.org/0000-0003-0480-4754>; Woojin Cho: <https://orcid.org/0000-0002-9059-648X>; Jung Suk Sim: <https://orcid.org/0000-0001-6803-3544>

Author Contributions

Conceptualization: Baek JH. Data acquisition: Sim JS, Cho W. Data analysis or interpretation: Kim HJ. Drafting of the manuscript: Kim HJ, Sim JS. Critical revision of the manuscript: Baek JH, Sim JS, Kim HJ. Approval of the final version of the manuscript: all authors.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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