International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: http://www.tandfonline.com/loi/ihyt20

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To cite this article: Jung Suk Sim, Jung Hwan Baek, Joongyub Lee, Woojin Cho & Sung Il Jung (2017): Radiofrequency ablation of benign thyroid nodules: depicting early sign of regrowth by calculating vital volume, International Journal of Hyperthermia, DOI: 10.1080/02656736.2017.1309083

To link to this article: http://dx.doi.org/10.1080/02656736.2017.1309083

Accepted author version posted online: 21 Mar 2017.
Published online: 10 Apr 2017.

INTERNATIONAL JOURNAL OF HYPERTHERMIA, 2017
http://dx.doi.org/10.1080/02656736.2017.1309083

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Radiofrequency ablation of benign thyroid nodules: depicting early sign of regrowth by calculating vital volume

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ABSTRACT

Objective: We evaluated long-term follow-up results of radiofrequency ablation of benign thyroid nodules to analyse the role of marginal vital tissue on nodule regrowth.

Materials and methods: We reviewed the medical records of 54 patients who underwent radiofrequency ablation between June 2008 and November 2013 with pressure symptoms, and/or cosmetic problems. All patients were followed up at least 12 months on three occasions. To evaluate an early sign of regrowth, three types of nodule volumes (total volume, ablated volume and vital volume) were measured and calculated using ultrasonography. Regrowth was defined as a more than a 50% increase in the total volume and vital volume increase was defined as a more than 50% increase compared to the previously reported smallest volume on ultrasonography.

Results: The mean follow-up period was 39.4 ± 21.7 (range, 13–87) months. Vital volume increases occurred in 31 nodules (57.4%) and there was regrowth in 13 nodules (24.1%). The mean timing of the vital volume increase was 27.5 ± 18.5 months, and for regrowth it was 39.9 ± 17.5 months. Vital volume increase tended to precede regrowth.

Conclusion: Vital volume increase tended to occur earlier than regrowth and might be an early sign of regrowth in following-up after the radiofrequency ablation of benign thyroid nodules.

ARTICLE HISTORY
Received 8 December 2016
Revised 14 March 2017
Accepted 15 March 2017
Published online 5 April 2017

KEYWORDS
Radiofrequency/microwave; thermal ablation; ultrasound; benign thyroid nodule

Introduction

Thermal ablations for benign thyroid nodules have been reported to be an effective and safe treatment [1–4]. Particularly for radiofrequency ablation (RFA), the recommendations of the Korean Society of Thyroid Radiology suggested a trans-isthmic approach and a moving-shot technique [5]. These techniques have been reported to have a high efficacy with a low complication rate [1,6]. Recently, thermal ablation for recurrent thyroid cancers and primary thyroid cancers has been reported [4,7–12].

Regarding the efficacy of thyroid RFA, short-term results have reported a 50–80% volume reduction at 6 months [1,13], 79–90% volume reduction at 2 years [14,15], and 93% volume reduction at 4 years [14]. Although thyroid RFA can achieves excellent volume reduction and may improve symptoms and/or cosmetic problems, several studies have reported recurrence after RFA. Recurrence rates of 5.6% and 9% have been reported after RFA [14] and laser ablation [16], respectively. All recurrent cases showed regrowth of the incompletely treated nodule margin. Baek et al. [17] also proposed marginal regrowth as an important cause of recurrence after RFA of autonomously functional nodules.

Because of recurrence induced by marginal regrowth [17,18], it is important to completely treat the nodule margin. In cases of incompletely treated nodule margins, repeat treatment is necessary to prevent recurrence. Although there was no widely-accepted consensus on the optimal timing of additional ablation we usually did it when symptom resolution was not achieved, regrowth of the residual vital tissue was evident or growing vascularity was observed. However, there has been no research to determine the proper timing of additional treatment for the remaining undertreated nodule margin. We therefore evaluated long-term follow-up results of RFA of benign thyroid nodules to analyse the role of marginal vital tissue on nodule regrowth.

Materials and methods

Patients

The national public IRB designated by the Korean Ministry of Health and Welfare approved this retrospective study (P01–201606-21–002) and it waived the requirement for written informed consent for use of these data. However, all patients provided written informed consent for RFA.

From June 2008 to November 2013, among the patients who were treated by ultrasonography (US)-guided RFA in Withsim clinic for symptomatic benign thyroid nodules, 52 patients (54 nodules) were included in this study. Eligibility

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Table 1. Patients' demographic data and information of nodules.

Variables	Characteristics
Gender (male:female)	5:49
Age (years)	44.1 ± 13.2 (20–78)
Nodule diameter, largest (cm)	3.8 ± 1.1 (1.9–7.7)
Volume (mL)	14.0 ± 12.7 (3.1–56.6)
Volume <10 mL	29
Volume 10–20 mL	13
Volume >20 mL	12
Solidity	
Predominantly solid	38
Mixed solid and cystic	11
Predominantly cystic	5

Ranges are in parentheses.

criteria for inclusion in the study were patients with nodules and cosmetic or symptomatic problems [5], a follow-up period of at least 12 months and at least three follow-ups. The demographic characteristics of patients and thyroid nodules are summarised in Table 1. All the nodules treated were cold nodules. The mean follow-up period was 39.4 ± 21.7 (range, 13–87) months.

Pre-ablation assessment

One radiologist (J.S.S.) with 13 years of experience with thyroid imaging and US-guided procedures performed careful US examinations [19,20] and US-guided cytology/biopsy [21,22]. RFA was performed using high-frequency linear probes on real-time US machines (Accuvix XG or Accuvix V10, Samsung Medison, Seoul, Korea). Three orthogonal diameters were measured between the outer margins of the nodule [1]. The width and height of the nodule were measured on an axial image. The length was measured on a sagittal image [23]. The volume of each nodule was calculated using the following equation: $V = \pi abc/6$ (V: volume, a: the largest diameter, b and c: the other two perpendicular diameters) [24–26]. All nodules were confirmed to be benign by at least two instances of fine needle aspiration cytology and/or core needle biopsy [5,27]. Serum levels of calcitonin were checked to rule out the possibility of medullary carcinoma, and these proved to be within normal limits in all patients [5].

Procedure

The same operator (J.S.S.) performed RFA using RF generators (RF150 and RF 300, Apro-Korea, Gyeonggi, Korea) and straight-type modified internally cooled electrodes with active tip lengths of 5, 7, 10 and 15 mm (Well-Point RF Electrode, STARmed, Gyeonggi, Korea; CoATherm electrode, Apro-Korea, Gyeonggi, Korea). We used the following basic techniques suggested by the Korean Society of Thyroid Radiology [5]. Patients were in a supine position with their necks fully extended. Under local anaesthesia with 2% lidocaine, we used a trans-isthmic approach and a moving-shot technique. If the nodule had cystic portion, we aspirated the fluid first as much as possible, and then RFA was done for the remaining solid portion [28]. Complications during and immediately after the procedure were checked for proper management [6]. After RFA, the patients were observed for 4–6 hours in the hospital [1].

Follow-up

The same operator (J.S.S.) assessed volume changes at 1, 3 or 6, and 12 months and additionally at 1-year intervals. Three types of nodule volumes (total volume [*V*t], ablated volume [*V*a] and vital volume [*V*v]) were defined, measured and calculated using US images (Figure 1). *V*t was defined as the total nodule volume, *V*a was defined as an ablated nodule volume that presents as a hypoechoic area without vascularity on US. *V*v was defined as an incompletely treated vital nodule volume, which was calculated by the following equation, Vv = Vt - Va. When a *V*t increased by more than 50% compared to the previously reported smallest volume, we defined it as regrowth [14]. When *V*v increased by more than 50% compared to the previously reported smallest volume, we defined it as a *V*v increase [29].

Additional treatment was recommended when patient's symptom or cosmetic problem had not been resolved or recurred. When regrowth was observed without symptom recurrence, we considered additional treatment and decision was made after share discussion with patients. When *V*v increase was observed but regrowth was not observed, we considered additional treatment and decision was made after share discussion with patients. When colour Doppler signal was observed to be more abundant than previous ultrasonogram, we also considered additional treatment and decision was made after share discussion with patients. Additional RFA was done seldom by the patient's need only, such as anxiety. Data collection was done until the retreatment.

Data analysis

The endpoint of this study was to find early sign of regrowth by evaluating the total volume, ablated volume and vital volume of treated nodules. During the follow-up periods, we compared the frequency and timing of *V*v increase and regrowth of treated nodules.

Results

A total of 54 nodules met the eligibility criteria. The mean volume reduction ratio (VRR) after the first RFA was 77.0%. Central well-ablated areas showed hypoechogenicity, and incompletely ablated nodule margins showed isoechogenicity (Figure 1(A)). During the follow-up period (Figure 1(B–D)), central well-ablated areas gradually decreased and nearly disappeared; however, marginal vital areas showed continuous regrowth with increased vascularity.

Table 2 and Figure 2 shows the changes in *V*t, *V*a and *V*v during the follow-up period. *V*t and *V*a showed a declining curve. Table 2 compares the amount of *V*v increase and regrowth. *V*v increase occurred in 31 nodules (57.4%) and there was regrowth in 13 nodules (24.1%). The mean timing of *V*v increase was 27.5 ± 18.5 months after RFA and that

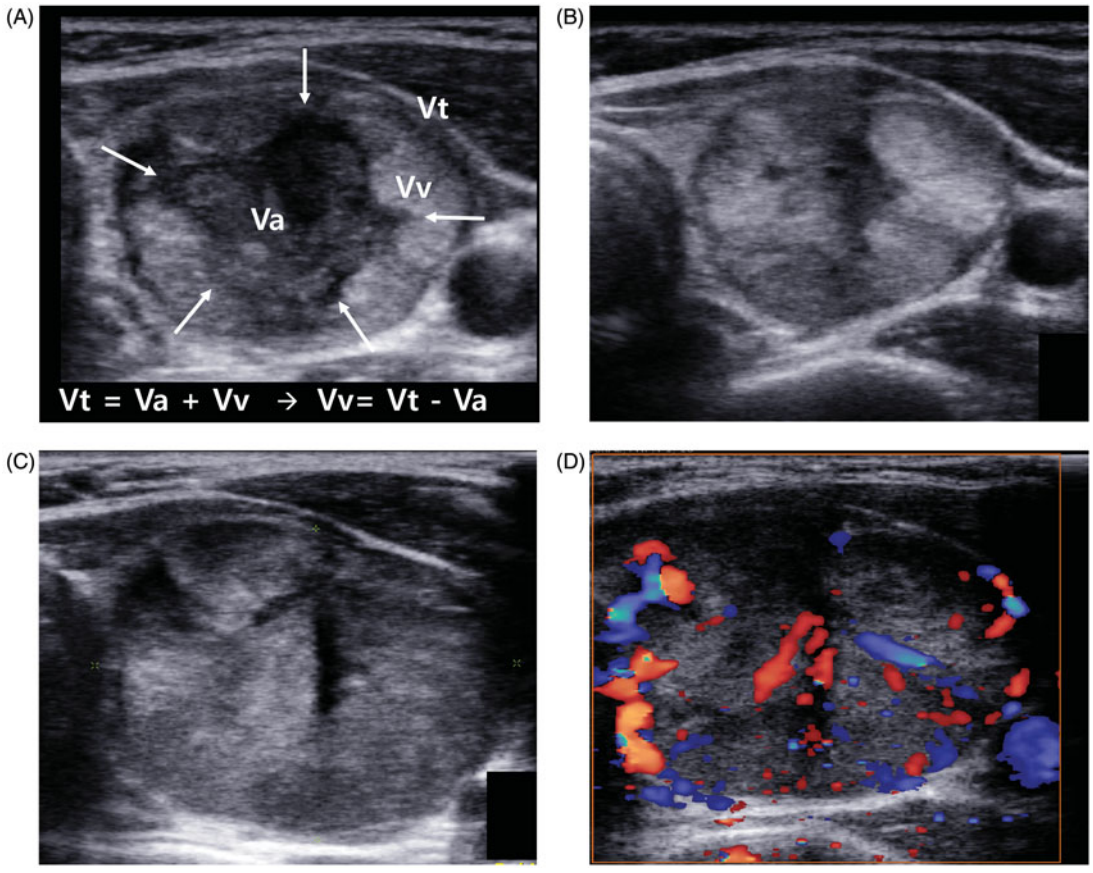

Figure 1. (A) Transverse image from a 29-year-old woman who received RFA for a benign thyroid nodule 4 months previously. The index nodule volume was 21.1 mL. At the centre of the nodule, the ablated area was seen as a hypoechoic area (*Va*, arrows). At the margin of the nodule, the incompletely treated viable portion showed an isoechoic area (*Vv*). The volumes at 4 months were *Vt* = 7.4 mL, *Va* = 2.1 mL and *Vv* = 5.3 mL. (B) Transverse image at the 7-month follow-up. The *Vt* decreased to 5.3 mL whereas the *Vv* increased to 5.2 mL. (C) Transverse image at the 21-month follow-up. The *Va* decreased and nearly disappeared. The *Vt* increased to 12.4 mL through an increase in the *Vv* (12.3 mL). (D) Colour Doppler US image showing increased vascularity in the viable area of the nodule.

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

Variables	Index	1 year	3 years	5 years	7 years
No. nodules	54	52	37	16	5
Vt (mL)	14.0	3.7	4.2	3.7	0.3
Va (mL)		1.8	1.0	1.2	0.1
Vv (mL)		1.9	3.2	2.6	0.2
VRR (%)		73.6	69.6	73.5	97.9
No. *Vv* increase		16	10	4	1
No. regrowth		2	7	4	0
Disappearance		7	2	1	0

No.: Numbers; *Vt*: total volume; *Va*: ablated volume; *Vv*: vital volume; VRR: volume reduction ratio.

of regrowth was 39.9 ± 17.5 months. As shown in Figure 3, *Vv* increase occurred about 1 year prior to the regrowth.

The overall complication rate was 3.6% (2/56), with one major and one minor complication. One patient complained of a change in voice during the procedure but had completely recovered at 3-month follow-up. The side-effect rate was 3.6% (2/56). There were no life-threatening complications and all patients with complications recovered without sequelae (Table 3).

Discussion

Our current study has demonstrated that *Vv* increase preceded regrowth. Therefore, monitoring *Vv* increase is important to predict regrowth and symptom recurrence. To the best of our knowledge, there has been no previous investigation of, and there is no consensus on, the proper timing of additional treatment. We found that changes in *Vt* consist of two parts, namely, a *Va* decrease and a *Vv* increase. When the *Va* decrease is greater than the *Vv* increase, *Vt* becomes smaller. This kind of change in volume usually occurs in the earlier period after RFA. When the *Vv* increase exceeds the *Va* decrease, *Vt* becomes larger, which means regrowth. This kind of change in volume usually occurs late. If we trace only *Vt*, the *Vv* increase can be masked by the *Va* decrease. Therefore, we suggest that tracing *Vv* can indicate regrowth earlier than tracing *Vt*. If a *Vv* increase is detected, we should be ready to do additional sessions of ablation. In this aspect, tracing *Vv* rather than *Vt* may provide earlier signs of regrowth.

Several studies have suggested marginal recurrence of ablated thyroid nodules. Baek et al. [17] first described the clinical significance of marginal recurrence after treating autonomously functioning thyroid nodules by RFA. Deandrea et al. [13] also reported an improvement in thyroid function after RFA of autonomous nodules, but a complete normalisation was obtained in only a few patients (approximately 24%). Although their case number was too small to draw a conclusion and the meaning of the terminologies of recurrence and regrowth might be different, we could agree to their concept of marginal recurrence. These authors explained that it was difficult to ablate the entire

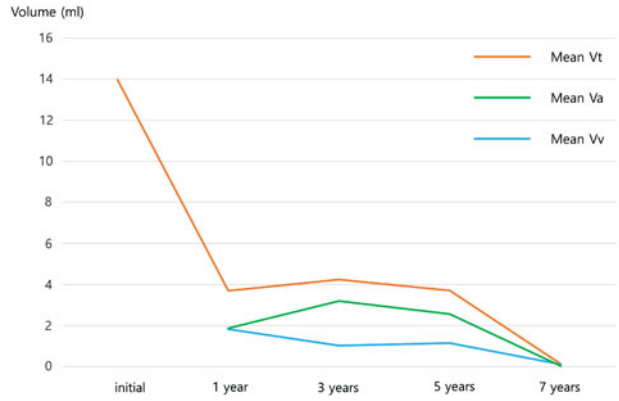

Figure 2. Changes in the *Vt*, *Va* and *Vv*. The *Vt* and *Va* showed a declining slope during follow-up, whilst the *Vv* showed relatively still.

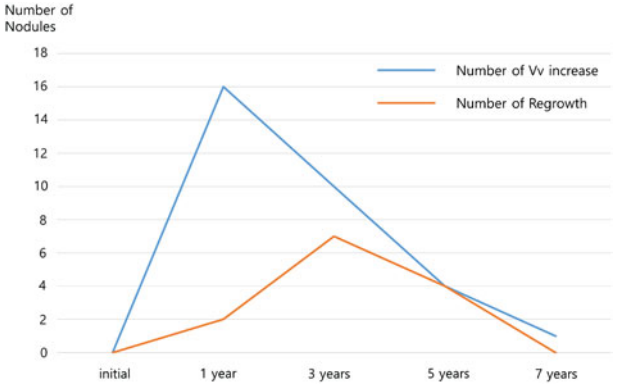

Figure 3. Comparison of the amount of *Vv* increase and *Vt* increase. The peak timing of *Vv* increase was 1 year after RFA. Regrowth started to occur after 1 year and occurred most frequently at 2–4 years after RFA. The mean timing of regrowth was 39.9 ± 17.5 months after RFA.

Table 3. Complications and side effects.

Complications	Number of complications (%)	Time of detection (days)	Time to recovery (days)
Major complications	1 (1.8)	1	90
Voice change	1 (1.8)	1	90
Minor complications	1 (1.8)	1	<7
Haematoma	1 (1.8)	1	<7
Side effects	2 (3.6)	1	1–2
Pain	2 (3.6)	1	1–2

Numbers in parentheses are the percentage of complications in the total patients.

nodule to minimise complications. There are several critical structures in the perithyroidal area, such as the trachea, oesophagus, recurrent laryngeal nerve [30], vagus nerve [31], sympathetic ganglion [32] and blood vessels [19]. Previous studies have suggested that the primary purpose of RFA for benign thyroid nodules is to perform debulking to reduce symptoms of pressure rather than obtaining complete ablation [13]. However, we previously experienced a regrowth of the incompletely treated nodule margin [33]. In a laser ablation study, Dossing et al. [34] also reported that thyroid-stimulating hormone in serum was normalised in only 50% of patients. Therefore, the margin of the thyroid nodule should be completely treated to minimise marginal recurrence.

Several factors were described to influence the nodule regrowth. Several investigators described that initial solidity and initial nodule volume was the factors affecting treatment response. Larger nodules were known to require more treatment session, because complete ablation of all the periphery of the nodule could not be achieved by single session of treatment [1,14,35]. Post-procedural marginal vascularity was another influencing factor [36]. Moreover, possible other influencing factors of the regrowth are nature of thyroid nodule, the maximum temperature reached during treatment, treatment modalities and the type of energy source. In the future, validation of these factors is necessary.

Regarding minimising marginal recurrence, Ha et al. [37] suggested that a moving-shot technique using a straight-type, internally cooled electrode could minimise marginal recurrence. The small active tip of the electrode could minimise thermal damage to the surrounding critical structures [7]. A hydrodissection technique has also been suggested to minimise thermal damage [38]. Knowledge of critical structures in the perithyroidal area has been suggested [19]. Huh et al. [18] suggested that single-session ablation is effective in most thyroid nodules; however, for nodules larger than 20 mL, additional ablation may be required to achieve sufficient volume reduction.

Our current study has demonstrated that RFA is effective for the volume reduction of a benign thyroid nodule for up to 7-year follow-up. We also found a low complication rate without sequelae or procedure-related deaths during this follow-up period. In the earlier period of follow-up, about 1 year, our data indicated a VRR of 73.6%, which is comparable to previous investigations [1, 14] and recently published RFA and LTA comparing study [39,40]. Our data indicated mean VRR of 77.0%, which is comparable to previous studies, namely, 93% at a 4-year follow-up [14] and 79% at a 2-year follow-up [15]. Our results showed a lower VRR than previous report by Lim et al. [14], especially in larger tumour group. These results may be due to marginal regrowth in our study series. Therefore, additional ablation sessions are necessary to prevent recurrence [18].

Single-session laser-ablation studies have also shown a gradual volume reduction up to 2 years but also reported recurrence after 3–5 years of follow-up [15,16,41]. We found a similar pattern in our current analyses. Regrowth began at 12 months and tended to be prominent at 2–4 years of follow-up. A secondary peak of regrowth appeared later than 5 years. This delayed regrowth suggests that long-term stabilised nodules can show regrowth in a slowly growing, marginal, incompletely treated area; therefore, additional ablation is necessary to prevent long-term regrowth. Lim et al. [14] used multiple treatment sessions (2.2 ± 1.4 sessions) to achieve continuous volume reduction and to prevent marginal recurrence. Their final mean VRR was 93.5% at 4-year follow-up, and the recurrence rate was 5.6%. Single-session laser ablation effectively decreased nodule volume and relieved nodule-related symptoms until 2 years; however, nodule volume increase was detected after 3 years, probably due to marginal regrowth [16,41,42]. In a 3-year follow-up laser ablation study, the final VRR was 58% [42].

Conclusions

In conclusion, *Vv* increase occurred about 1 year earlier than regrowth. Thus, tracing *Vv* can indicate regrowth of marginal vital tissue earlier than tracing *Vt* after RFA of benign symptomatic thyroid nodules.

Disclosure statement

Grant: none.

Jung Hwan Baek. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: patent holder of the unidirectional ablation electrode. Other relationships: none to disclose.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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