

Radiofrequency Ablation to Treat Loco-Regional Recurrence of Well-Differentiated Thyroid Carcinoma

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Objective: To evaluate the efficacy of radiofrequency ablation (RFA) in the treatment of loco-regional, recurrent, and well-differentiated thyroid carcinoma.

Materials and Methods: Thirty-five recurrent well-differentiated thyroid carcinomas (RTC) in 32 patients were treated with RFA, between March 2008 and October 2011. RTCs were detected by regular follow-up ultrasound and confirmed by biopsy. All patients had fewer than 3 RTCs in the neck and were at high surgical risk or refused to undergo repeated surgery. Average number of RFA sessions were 1.3 (range 1–3). Post-RFA biopsy and ultrasound were performed. The mean follow-up period was 30 months. Pre- and post-RFA serum thyroglobulin values were evaluated.

Results: Thirty-one patients with 33 RTCs were treated with RFA only, whereas 1 patient with 2 RTCs was treated with RFA followed by surgery. At the last follow-up ultrasound, 31 (94%) of the 33 RTCs treated with RFA alone completely disappeared and the remaining 2 (6%) RTCs showed decreased volume. The largest diameter and volume of the 33 RTCs were markedly decreased by 93.2% (from 8.1 ± 3.4 mm to 0.6 ± 1.8 mm, $p < 0.001$) and 96.4% (from 173.9 ± 198.7 mm³ to 6.2 ± 27.9 mm³, $p < 0.001$), respectively. Twenty of the 21 RTCs evaluated with post-RFA biopsies (95%) were negative for malignancy. One (5%) showed remaining tumor that was removed surgically. The serum thyroglobulin was decreased in 19 of 26 patients (73%). Voice change developed immediately after RFA in 6 patients (19%) and was spontaneously recovered in 5 patients (83%).

Conclusion: Radiofrequency ablation can be effective in treating loco-regional, recurrent, and well-differentiated thyroid carcinoma in patients at high surgical risk.

Index terms: Radiofrequency ablation; Recurrent thyroid cancer; Efficacy; Thyroid; Ultrasound

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INTRODUCTION

Well differentiated thyroid carcinoma is the most common thyroid cancer and has a relatively good prognosis (1-3). However, well-differentiated thyroid carcinoma has frequent metastases and recurs at the local cervical lymph nodes or remote organs. The overall recurrence and mortality rates for well-differentiated thyroid carcinoma are 20.5% and 8.5%, respectively, at a mean follow-up period of 11.3 years (4). Surgical removal with radioactive iodine therapy is recommended for recurrent thyroid cancer. However,

repeated neck dissection is difficult for surgeons due to distortion in the normal tissue plane, postsurgical fibrosis, and severe adhesion, and is associated with complications such as nerve injury (recurrent laryngeal and accessory spinal nerves), hypoparathyroidism and cosmetic concerns related to re-incision (5-7). Some recurrent tumor cannot be detected in the surgical field without pre-surgical wire guidance or ultrasound guidance. Non-surgical, minimally invasive, local therapy that could eradicate these nodal recurrences in patients who have high surgical risk or who refuse repeat surgery would eliminate the need for repeat operation with associated difficulties and morbidity. Recently, there have been several reports that ethanol ablation and radiofrequency ablation (RFA) can be effective and valuable treatment options with good local control for recurrent disease (8-12). Both methods have advantages and disadvantages (9, 13). Ethanol ablation is a cheaper and less painful procedure than RFA, and is a good procedure to monitor ethanol diffusion. RFA produces a larger tumor destruction zone and finely adjustable energy, and requires fewer treatment sessions than ethanol ablation.

Several investigators have reported good local control results following RFA of the recurrent thyroid cancer (8-10, 12). However, small number of cases was a limitation of the studies. According to Korean Society of Thyroid Radiology (KSThR) guideline, RFA can be used to treat both benign thyroid nodules and inoperable, recurrent thyroid cancers in the operation bed and lymph nodes, in patients at high surgical risk and in those who refuse to undergo repeated surgery (14).

We intended to evaluate the efficacy of RFA in the treatment of loco-regional, recurrent, and well-differentiated thyroid carcinoma through our experience with a larger number of cases.

MATERIALS AND METHODS

Patients

This retrospective study was approved by our Institutional Review Board, which waived the requirement for informed patient consent. Written informed consent was obtained from each patient before each procedure was performed. From March 2008 to October 2011, 35 recurrent thyroid carcinomas (2 in level III, 7 in level IV, 26 in level VI) in 32 patients (25 women, 7 men; mean age, 53 years; age range, 22–85 years) were treated with ultrasonography

(US)-guided RFA. All cases were detected by US follow-up and were confirmed by fine-needle aspiration (FNA) or core biopsy. Histologic types of recurrent thyroid carcinomas included 34 papillary thyroid carcinomas and one medullary thyroid carcinoma. Seventeen patients and 6 patients previously underwent a lateral neck dissection and central neck dissection, respectively, whereas no neck dissection was performed in 8 patients. Surgical neck dissection history was not available in 1 patient with 2 recurrent tumors. The mean number of surgical procedures performed before RFA was 1.2 (range, 1–3), and the mean radioactive iodine ablation number was 1.5 (range, 0–4). The mean tumor volume and the mean largest diameter were 173.9 mm³ (range, 18.9–4792.0 mm³) and 8.1 mm (range, 4.0–26.0 mm), respectively. The serum thyroglobulin level was evaluated in 26 patients before and after RFA.

The inclusion criteria for RFA were fewer than 3 recurrent tumors (2 in 3 patients; 1 in 29 patients) proven by US-guided biopsy before RFA and no recurrent tumor beyond the neck at the time of RFA in patients who had high surgical risk or who refused to undergo repeat surgery.

Radiofrequency Ablation

Under US-guidance, all RFA procedures were performed on an outpatient basis by 1 radiologist with 4 years of RFA experience. All patients received intravenous fentanyl citrate (2 µg/mL) before or during the procedure. The patient's blood pressure, blood O₂ saturation, heartbeat and electrocardiography were monitored.

We performed the several methods to prevent unnecessary complications (Figs. 1, 2). Firstly, continuous and cautious US-guided tracing of the electrode tip was done during the RFA (14). Secondly, we carefully injected lidocaine (0.2%, up to 10 mL) between the tumor and the expected location of the nerves (recurrent laryngeal nerve, vagus nerve, and spinal accessory nerves) and other critical structures (carotid artery, jugular vein, trachea, esophagus) for local anesthesia and to create a protective barrier to radiofrequency (RF) energy (i.e., the hydrodissection technique) (9, 10, 15). Thirdly, the recurrent tumor was pulled away from the adjacent nerves and critical structures by tilting the electrode during ablation. For example, during the treatment of recurrent tumor at level 6, the tumor was elevated to the anterior surface of the common carotid artery. Fourthly, ablation was started with low power (5 W in a 0.5-cm or 0.7-cm active tip and 20 W in a 1.0-cm active tip). RF power was gradually and carefully increased

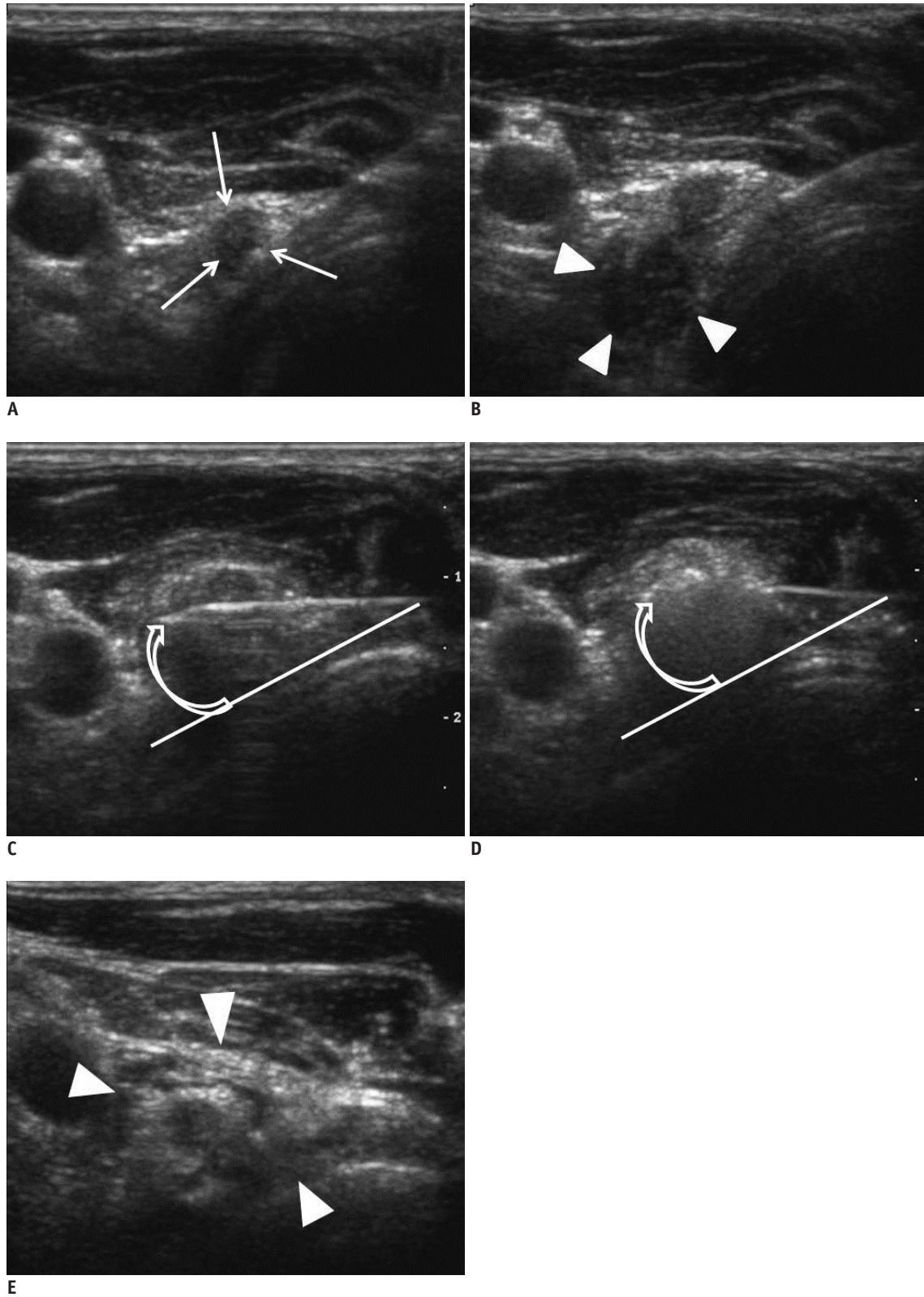


Fig. 1. Three procedures to prevent major organ injuries near tumors in level 6.

Metastatic tumor is detected in right level 6 on ultrasound (A, straight arrows). First, lidocaine is injected around tumor to separate invisible recurrent laryngeal nerve, trachea, and carotid artery from tumor and to provide pain control before ablation (B, arrowheads). Second, tumor is pulled away from three organs by tilting electrode during ablation (C, D, curved arrows). Third, cold fluid is injected around ablated tumor after ablation (E, arrowheads).

(up to 10 W in a 0.5-cm or 0.7-cm active tip and 60 W in a 1.0-cm active tip) (10, 11). Fifth, cold fluid was injected around the ablated tumor after ablation to lower heat generated by RFA. We performed all 5 steps in 7 tumors (2 tumors in the level IV and 5 tumors in the level VI) in 7 patients.

We used a RF generator (Cool-Tip RF system, Covidien, Boulder, Co, USA; SSP-2000, Taewoong Medical, Gimpo, Korea) and a thyroid-dedicated, internally cooled electrode (Well-Point RF electrode, Taewoong Medical, Gimpo, Korea). A 7-cm long, 18-gauge electrode with a 0.5-, 0.7-, or 1.0-cm active tip, was chosen according to the tumor size.

Initially, the electrode tip was positioned in the deepest, most remote portion of the lesion. Then, we treated the recurrent tumors gradually and anteriorly with the moving shot technique (14). Ablation was started with lower power,

and if a transient hyperechogenicity was not formed at the electrode tip within 5 seconds, RF power was gradually and carefully increased. The power was reduced or turned off for several seconds if a patient could not tolerate pain during ablation. Ablation was terminated when the recurrent tumor changed to a transient hyperechoic zone or hoarseness developed. During the ablation, we frequently checked the patient's voice and pain. After the procedure, all patients were observed for 1 or 2 hours in the hospital while we assessed any discomfort or complications associated with RFA.

Follow-Up

Patients were followed-up by US or biopsy at 1 or 2 months after RFA. The presence or absence of the RFA-treated recurrent tumor was first evaluated with US.

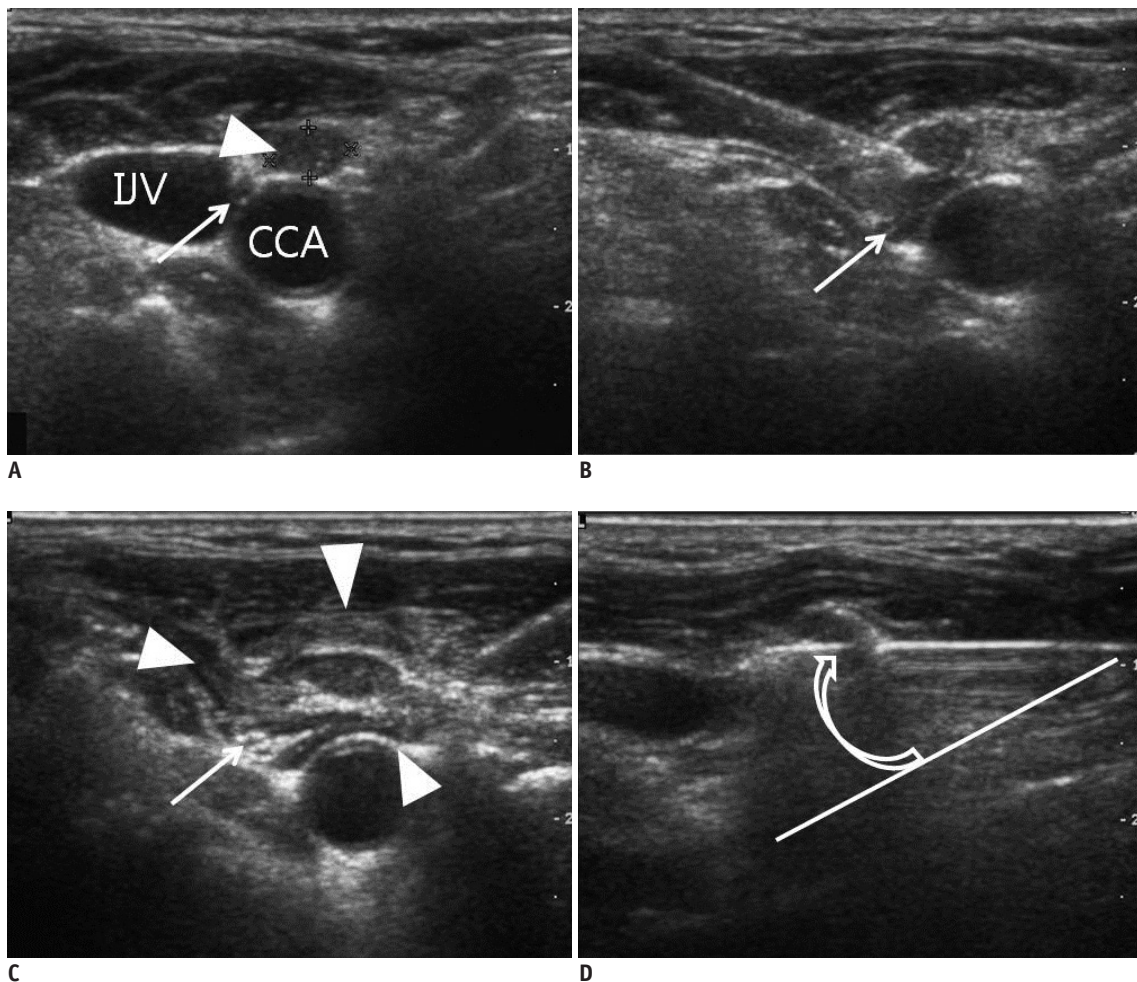


Fig. 2. Three procedures to prevent major organ injuries near tumor in level 3.

Metastatic tumor (arrowhead) in right level 3 is detected near vagus nerve (straight arrow), common carotid artery (CCA) and internal jugular vein (IJV) on ultrasound (A). First, lidocaine is injected around tumor to separate visible vagus nerve (short arrow), CCA, IJV, and sternocleidomastoid muscle from tumor and to provide pain control before ablation (B, C, arrowheads). Second, tumor is pulled away from three major organs by tilting electrode during ablation (D, curved arrow). Third, cold fluid is injected around ablated tumor after ablation (not shown).

Biopsy was performed under US-guidance if a lesion was detected at the site of the RFA-treated recurrent tumor. We also calculated the tumor volume as “V (volume) = a (anteroposterior) x b (transverse) x c (craniocaudal) x $\pi/6$ ”; volume reduction rate was calculated as “VRR (volume reduction rate) = [initial volume - final volume] x 100 / initial volume; the largest tumor diameter; and intratumoral vascularity of some detected lesions before biopsy. We performed additional RFA even though the tumor volume had been reduced, if residual tumor cells were diagnosed. Cases with no residual tumor cells or a disappeared tumor, were recommended for regular follow-up US (every 6 months for 1 year, and subsequent annual follow-up US with serum thyroglobulin [Tg]) for newly recurrent tumors. The therapeutic success was a negative FNAB result or disappearance of the recurrent well differentiated thyroid carcinoma on follow-up US examination after RFA treatment. Complications during follow-up were assessed using the reporting standards of the Society of Interventional Radiology (16, 17). The serum Tg level was also evaluated during the follow-up period.

RESULTS

The patient and RFA treatment characteristics were summarized in Table 1. A total of 45 RFA sessions (average, 1.3; range, 1–3) were performed for 35 recurrent tumors. The mean active ablation time was 4.4 minutes (range, 40 seconds–15 minutes), and the mean maximum power output of the RFA procedure was 14.2 W (range, 5–60 W).

At the first follow-up visit after RFA, biopsy was performed in 21 tumors, while 14 tumors were followed only with US without biopsy. The reasons for not obtaining a biopsy were as follows: disappearance (n = 8) and reduced volume with change of the tumor shape, increased

echogenicity, or disappeared vascular signals (n = 6) on the first follow-up ultrasound. Of the 21 tumor biopsied after RFA, 12 were negative for residual tumor and 9 revealed recurrent tumors, for which a follow-up second RFA (n = 8) or surgery (n = 1) was performed. Of the 8 recurrent tumors that were treated with a second RFA, 7 tumors were shown to be negative for residual tumor at a biopsy after the second RFA. One remaining tumor at level VI required a third RFA treatment without a post-second RFA biopsy, because the tumor volume was not reduced after the second RFA. This tumor was ultimately negative for malignancy on two of the post-third RFA biopsies and was reduced in volume (volume reduction rate, 53%) by 38 months after the first RFA.

The mean follow-up period was 30 months (range, 6–49 months). At the last follow-up US examination, 31 recurrent tumors had completely disappeared (93.9%) (Fig. 3). The remaining 2 tumors in the level IV and level VI, decreased in volume (volume reduction rate, 84% and 53%, respectively) (Fig. 4): the first remained as a tiny calcified nodule, and the second remained as a hypoechoic nodule with an internal hyperechoic dot. The other 2 tumors in one patient were not eligible for US follow-up, as they had been removed by surgical resection.

When the 2 surgically treated recurrent tumors were excluded from the analysis, the mean \pm standard deviation (SD) of the largest diameter of the 33 treated tumors decreased from 8.1 \pm 3.4 mm to 0.6 \pm 1.8 mm ($p < 0.001$), representing a 93.2% decrease; and the mean \pm SD of the tumor volume decreased from 173.9 \pm 198.7 mm³ to 6.2 \pm 27.9 mm³ ($p < 0.001$), representing a 96.4% decrease. There was no recurrence in the treatment site until the last follow-up visit. The serum Tg concentration was evaluated in 26 patients and decreased in 19 patients (73%) from 16.7 \pm 32.3 ng/mL to 10.5 \pm 26.3 ng/mL ($p = 0.004$, 37.3%

Table 1. Results of RFA for Loco-Regional, Recurrent, Well-Differentiated Thyroid Carcinomas According to Location

Location of Recurrence (Levels)		III	IV	VI
Number of cases (tumors)		2	7	26
Mean number of RFA sessions		1	1.4	1.2
Mean largest diameter (mm)	Pre-RFA	11	12.1	7.6
	The last FU	0 (100%)	4.7 (61%)	0.5 (94%)
Mean volume (mm ³)	Pre-RFA	191	1367.4	148.2
	The last FU	0 (100%)	227.1 (83%)	5.9 (96%)
Tg (ng/mL)	Pre-RFA	1.47	8.5	13.4
	The last FU	0.12 (92%)	1.5 (82%)	8.1 (40%)

Note.— Values given in parentheses are reduction rates of mean largest diameter or mean volume. III, IV, VI: levels of lymph node in neck. FU = follow-up, RFA = radiofrequency ablation, Tg = thyroglobulin

decrease) after RFA (Table 2).

One patient with 2 recurrent nodes had surgical treatment after the first RFA session. The post-surgical pathologic result of both nodes showed the same results (one, total necrosis; one, remaining recurrent papillary thyroid carcinoma) with those of the post-first RFA biopsy (Fig. 5). In other words, 1 of the 2 recurrent PTCs was completely treated after 1 RFA session.

Six patients experienced voice change immediately after RFA. Voice change was recovered in 5 patients. One patient without recovery was treated with vocal cord medialization. All 6 patients with voice change had tumors in the level VI. There were no other significant complications, and most of the patients tolerated the RFA procedure well. Although some patients reported a burning sensation, pain, or both, the symptoms were relieved by reducing the RF power or stopping the ablation for several seconds.

DISCUSSION

In this retrospective study of 35 locally recurrent, well-differentiated thyroid cancers treated with RFA, we showed that US-guided RFA was an effective and safe treatment method.

The efficacy observed in our study was similar or somewhat superior to the results reported in previous RFA studies (Table 3) (11). According to previous RFA studies (Table 3), researchers reported a therapeutic success rates of 75–91.6%, a mean volume reduction of 51% to 93%, complete disappearance of 25% to 50% of tumors, improvement of symptoms in 64% of patients (12), and a drop of serum Tg level in the majority of patients. However, we observed disappearance of lesions in 93.9% of our cases. The strength of our study was that we actively controlled the recurrent tumors with post-RFA biopsy and additional RFA. Local tumor recurrence has been reported as 0–25% following RFA (Table 4), whereas there was no cervical recurrence in the present study during the follow-up period.

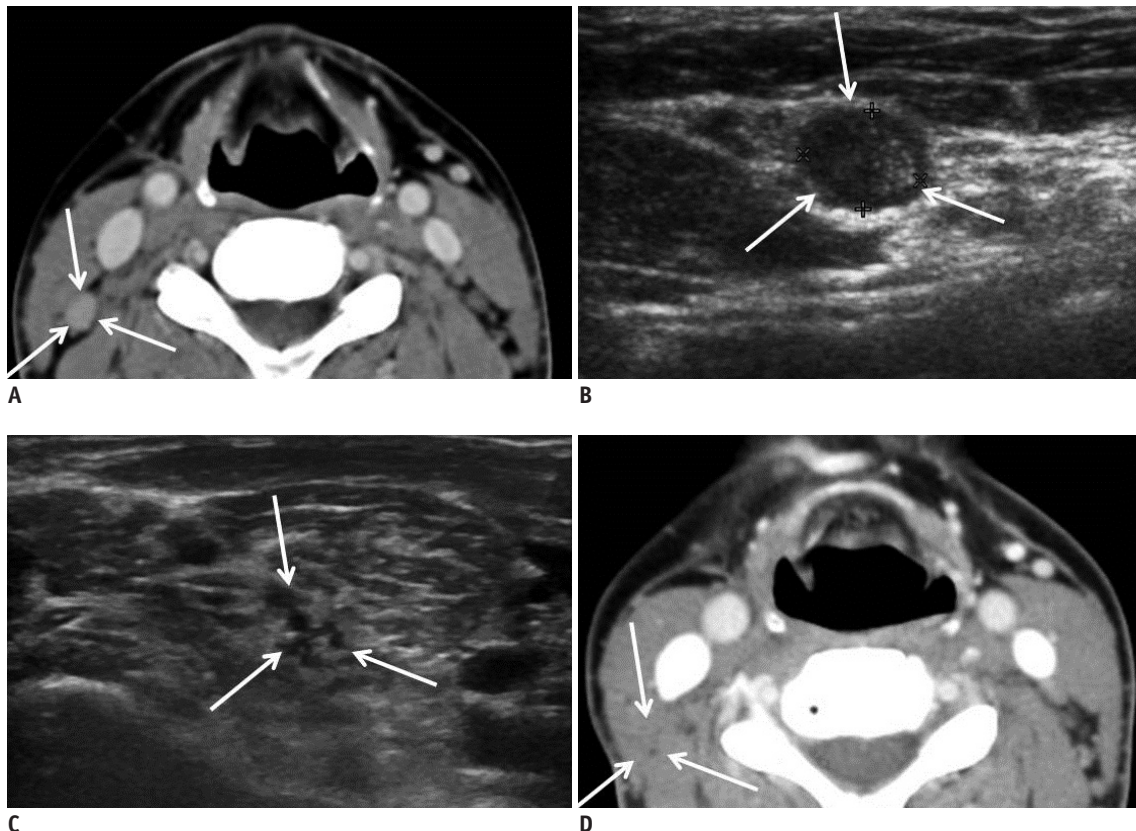


Fig. 3. 39-year-old man with recurrent thyroid cancer in right level 3.

Initial CT (A) and ultrasound (B) demonstrate recurrent nodule in right level 3 (arrows, 13 mm). One session of radiofrequency ablation (RFA) (1.0-cm electrode, 10–20 W, one minutes 20 seconds) is performed. Nodule shows decreased size with 76.9% volume reduction rate on post-RFA one-month follow-up ultrasound (not shown) and is invisible on 19-month follow-up ultrasound (C, arrows) and 22-month follow-up CT (D, arrows).

Among 6 patients with voice change, only 1 patient showed permanent voice change and was improved after vocal cord medialization. Multicenter study of KSThR reported that voice change occurred after RFA in 1% (15 patients) (14). Several studies have reported voice change as a complication of RFA (Table 4), in which all patients with voice change including our patients have had tumors in the level VI or the surgical bed. More patients (6/31, 19%) had voice change after RFA in our study as compared with the previous studies. This was probably due to more tumors with central location included in our study.

Frequency of voice change in centrally located tumors in our study was 24% (6/25), while that of the previous studies was 33–100% (Table 4). Contrarily, Park et al. (12) reported no voice change, probably due to conservative treatment for centrally located tumors. All patients with immediate voice changes in our study had received RFA without prevention procedures. However, after prevention procedures, there were no cases with voice change.

Ethanol ablation, RFA, and laser ablation may be mainly considered as non-surgical treatment of recurrent thyroid carcinoma in patients with high surgical risk. Comparison

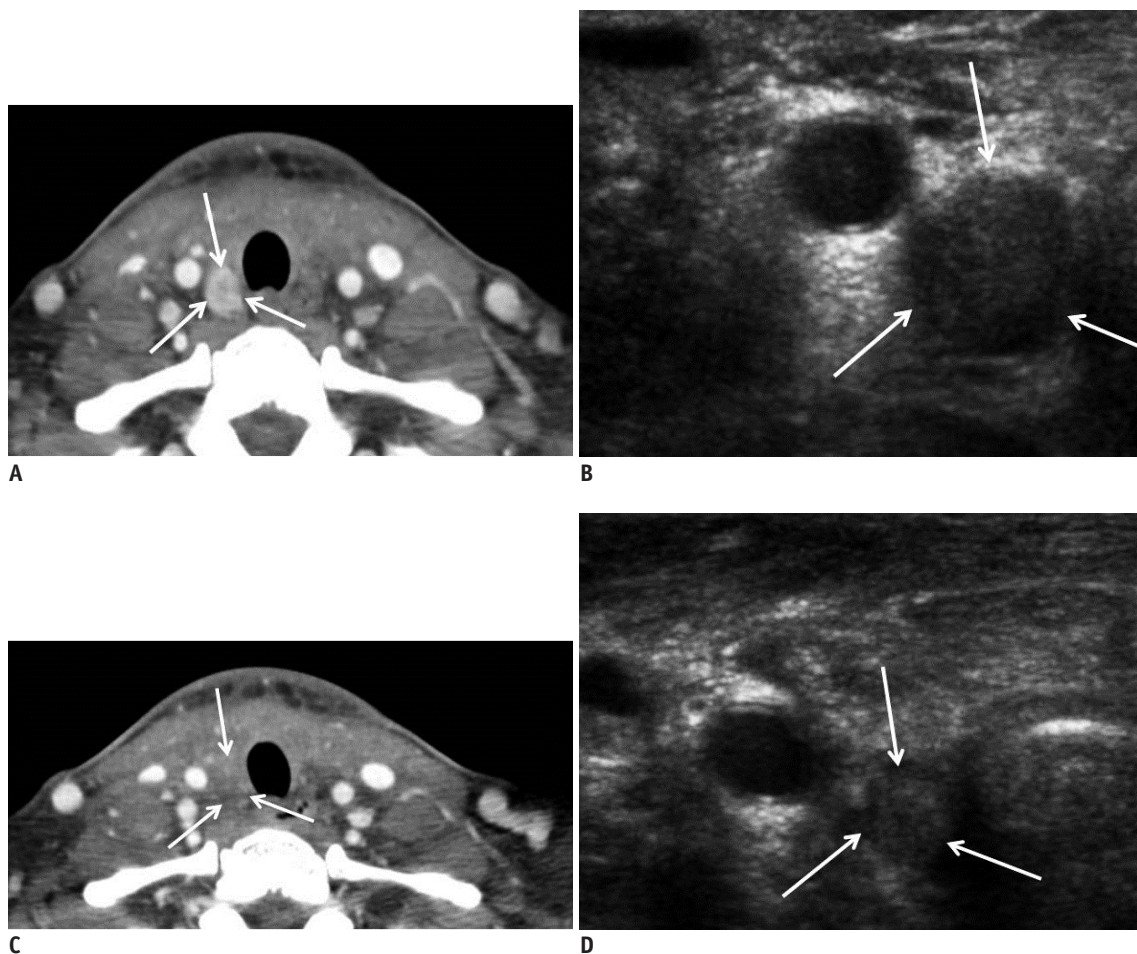


Fig. 4. 38-year-old woman with recurrent thyroid cancer in right level 6. Initial CT (A) and ultrasound (B) show enhancing nodule in right level 6 (arrows, 18 mm). There is no enhancing nodule (arrows) on 2-month follow-up CT after radiofrequency ablation (RFA) (C). On ultrasound for post-RFA fine-needle aspiration (D), volume of this nodule was markedly reduced (87.0% volume reduction rate) and biopsy result was negative for malignancy.

Table 2. Outcomes of Radiofrequency Ablation

Measurement	Before	After (Last Months)	P
Largest diameter (mm)	8.1 ± 3.4	0.6 ± 1.8	< 0.001
Volume (mm ³)	173.9 ± 198.7	6.2 ± 27.9	< 0.001
Serum Tg (ng/mL)	16.7 ± 32.3	10.5 ± 26.3	0.004

Note.— Values are presented as mean ± standard deviation (%). Tg = thyroglobulin

of their efficacy and complications were listed in Table 5. Studies using ethanol ablation were reported in the first, followed by the RFA and laser ablation recently (18, 19).

RFA is similar or somewhat superior to ethanol ablation in treatment efficacy and fewer number of treatment sessions is the advantage of RFA, as compared to that of the

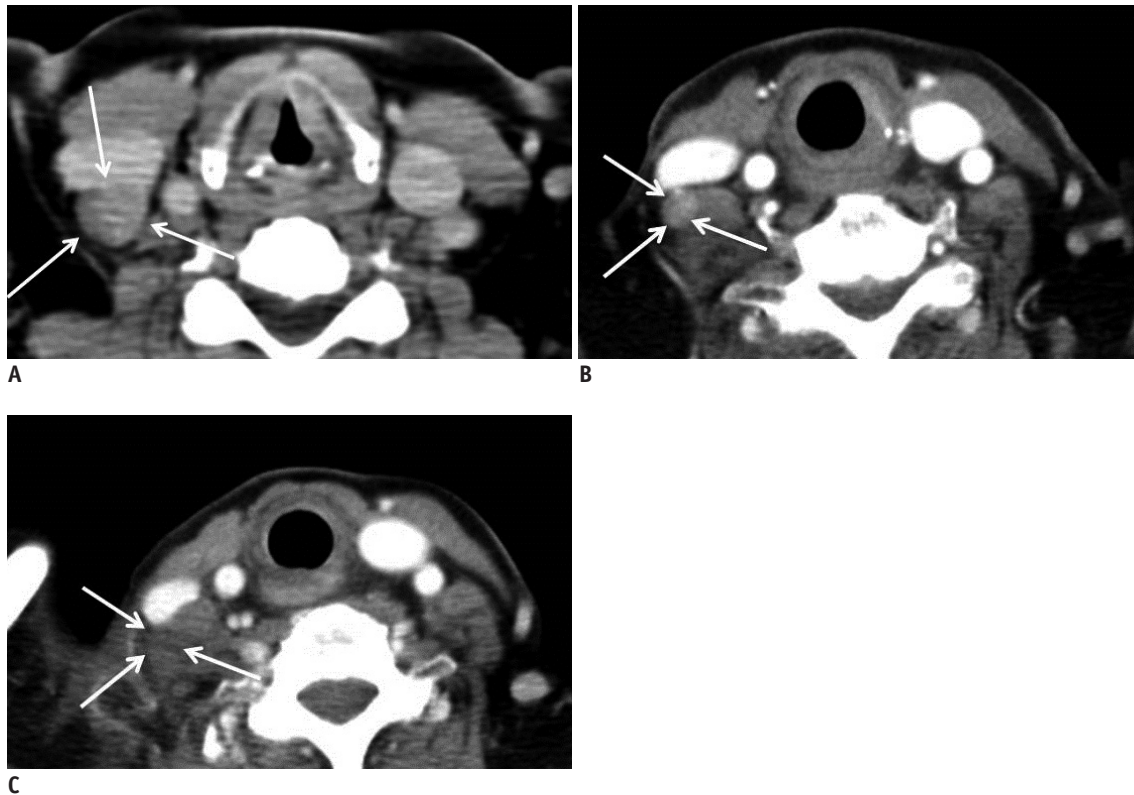


Fig. 5. 85-year-old woman with two recurrent thyroid cancers in right level 4 (23 mm and 26 mm).

Recurrent node (23 mm) is seen on initial CT (A, arrows). Volume of this node is reduced, but it is still enhanced on CT scan after 1st radiofrequency ablation (RFA) (B, arrows). Suspicion of malignancy was demonstrated in this nodule on post-1st RFA biopsy. This nodule was surgically treated (C, arrows). Another recurrent node (26 mm) was completely treated with RFA (not shown).

Table 3. Clinical Findings and Outcomes after Radiofrequency Ablation of Recurrent Thyroid Cancer in Literature

Authors	Number of Tumors	Follow-Up Range (Months)	Largest Diameter (mm)		VRR (%)	Complete Disappearance (%)	Tg	
			Before	After			A Number of Patient	Reduction Rate (%)
Dupuy et al. (8)	11 (8 patients)	6–26 (10.3)	24	18, 3 months-FU	-	25	6	92.4
Monchik et al. (9)	24 (16 patients)	10–68 (40.7)	17	-	-	50	11	95
Baek et al. (10)	12 (10 patients)	16–31 (23.6)	13.7	3.3	93	50	7	73
Park et al. (12)	16 (11 patients)	1–14 (6)	29	21.7	50.9	-	9	58.4
Present study	35 (33 patients)	6–40 (30)	8.1	0.5	96.4	93.3	26	44.9

Note.— Number in parentheses is mean follow-up months. FU = follow-up, Tg = thyroglobulin, VRR = volume reduction rate

Table 4. Clinical Findings and Complications after Radiofrequency Ablation of Recurrent Thyroid Cancer in Literature

Author	Site of Tumors		Voice Change		Skin Burn	Recurrence	Death
	Central	Lateral	Patient Number	Tumor Location			
Dupuy et al. (8)	2	6	1	Central	1	2	1
Monchik et al. (9)	3	21	1	Central	1	1	1
Baek et al. (10)	1	11	1	Central	0	0	0
Park et al. (12)	7	9	0	0	1	2	1
Present study	26	9	6	Central	0	0	0

Table 5. Comparison of Efficacy and Complications of RF Ablation, Ethanol Ablation, and Laser Ablation in Patients with Loco-Regional Recurrent Thyroid Cancer

	VRR (%)	Complete Disappearance (%)	Success Rate (%)	Reduction of Tg Level (%)	Mean Session Number	Recurrence (%)	Voice Change (%)
RF ablation (3, 8-12)	56-93	42-58.2	75-91.6	N/A	1.2	0-25	7 (7/45)
Ethanol ablation (9, 11, 13)	37.5-96	31-65	78-98	N/A	2.0-2.1	3.2-33	2.4 (3/126)
Laser ablation (18-20)	87.7	N/A	N/A	75	1	0 (1 yr FU)	20 (1/5)

Note.— FU = follow-up, N/A = not available, RF = radiofrequency, Tg = thyroglobulin, VRR = volume reduction rate

ethanol ablation (11). Laser ablation (LA) is reported as an effective thermal ablation technique for the treatment of thyroid nodules (20). LA is an easier method compared with the RFA moving-shot technique. However, voice change post-procedure was more frequent in laser ablation (20%, 1/5) than RFA (7%, 7/45) (18, 19).

Our study had some limitations. Although a relatively larger group of patients and tumors were included in the present study compared with previous studies, the modest sample size remains a limitation of this study. Considering the characteristic of slow growing tumors, longer follow-up period is also needed. Finally, because of the retrospective nature of this study, we did not perform RFA using standardized procedures in all patients. Further large, long-term, prospective studies are required to provide further evidence for the efficacy of RFA in controlling local recurrence of well-differentiated thyroid cancer.

In conclusion, RFA can be effective in treating loco-regional, recurrent, and well-differentiated thyroid carcinoma in patients at high surgical risk.

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