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ORIGINAL ARTICLE

Successful radiofrequency ablation strategies for benign thyroid nodules

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Abstract

Purpose This study aimed to evaluate the effectiveness of ultrasound (US)-guided radiofrequency ablation (RFA) treatment of benign thyroid nodules in consecutive large number series. To find out whether there is any difference according to the nature of the nodules, nodules were subdivided into two groups of predominantly solid vs. predominantly cystic lesions.

Methods We retrospectively analyzed clinical data of thyroid nodules receiving percutaneous RFA treatment in our institution. We subdivided data into two groups according to the nodule's sonographic characteristics. We defined therapeutic success as a volume reduction rate >50% at 6 months post-RFA. The second ablation was performed in case where <50% VRR was achieved at 6 months. The primary endpoint was to identify factors prognosticating response to RFA treatment.

Results A total of 1000 patients with 1619 thyroid nodules received US-guided RFA treatment. A volume reduction of >50% (therapeutic success) after the first ablation was 78.9% vs. 78.2% ($p = 0.439$) and 91.4% vs. 93.4% ($p = 0.148$) after the final ablation for predominantly cystic vs. predominantly solid lesions, respectively, with comparable post-interventional morbidity. RFA sessions were more frequent in the solid group than in the cystic group. Small volume of thyroid nodule (<4 mL) was the only factor significantly associated with therapeutic success in the multivariate analysis (OR 1.848; 95% CI 1.537–2.789, $p = 0.030$).

Conclusion RFA was effective in reducing the volume of benign thyroid nodules volume with non-inferior result in PS group comparing to PC group and can be considered a principal treatment method for treating benign thyroid nodules, including cystic nodules.

Keywords Radiofrequency ablation · Benign thyroid nodule · Volume reduction · Therapeutic success · Nature of thyroid nodule

Introduction

Thyroid nodules (TNs) are detected frequently and are commonly known to be present in 20–76% of the general population [1]. TNs are often detected as a palpable neck mass or as an incidental finding during imaging of other organs, such as the chest or the brain. The development of computed tomography, magnetic resonance imaging, high-resolution ultrasound (US), isotope scanning, and other medical imaging technologies have made it possible to detect many hidden TNs [2, 3].

Most nodules are asymptomatic and benign and require only follow-up for management. The Revised American Thyroid Association guidelines do not recommend thyroid-stimulating hormone-suppressive therapy with levothyroxine for benign TNs [4]. However, some nodules require treatment for symptomatic growth, cosmetic problems, or a

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possibility of malignant transformation [5, 6]. In such cases, surgery is considered as an acceptable therapy [7]. Although thyroid surgery is widely practiced and is typically a safe procedure, it carries a risk of complications and may not be appropriate for surgical high-risk patients or for those who refuse surgical management [8].

In the past decade, several non-surgical minimally invasive ultrasonography-guided techniques have been proposed to reduce the volume of TNs in situations where a patient declines consent for a surgical approach or when surgery is contraindicated [9]. Recently, image-guided tumor ablation treatments, such as radiofrequency ablation (RFA), ethanol ablation, and laser ablation (LA) have been clinically useful and effective [10–13].

RFA has been used to treat various tumors [14] and has been reported to be effective in the treatment of TNs [15], which are either predominantly cystic (PC) or predominantly solid (PS) [16]. However, few studies have examined whether the nature (e.g., cystic or solid) of the nodules affects the therapeutic success rate, and the reported studies are very small in number. The only systematic review in this area comprised a total of 306 treatments pooled from 9 original articles [17].

This study aimed to evaluate the effectiveness of RFA treatment of benign TNs in consecutive large number series. To find out whether there is any difference according to the nature of the nodules, nodules were subdivided into two groups of PS vs. PC lesions.

Materials and methods

Patients

From July 2012 through September 2014, 1000 patients were identified from a prospectively collected institutional database ($n = 1098$) who had been diagnosed with benign TNs and who had been treated by a single endocrine surgeon (G.M.L) using US-guided RFA. The indications for RFA were: (a) benign nodules diagnosed by fine-needle aspiration cytology (FNAC) according to Bethesda classification; (b) presence of subjective symptoms (i.e., compressive symptoms and neck discomfort); (c) refusal to undergo surgery; and (d) severe accompanying comorbidities being a contraindication for surgery. We explained three strategies to the RFA-indicated patients: observation, surgery, and RFA. Those who were willing to go on RFA were included. The exclusion criteria were: (a) indeterminate or malignant FNAC; (b) US criteria suggestive for malignancy (i.e., a taller-than-wide shape, ill-defined margin, marked hypoechoic pattern), even in cases of benign FNAC results; (c) history of radiation to the neck; and (d) loss to follow-up after the RFA. We used US criteria in accordance with the consensus statement and recommendations established by the Korean Society of Thyroid Radiology [18]. The primary endpoint was the therapeutic success of RFA, which was defined as a thyroid lesion volume reduction rate (VRR) of >50% [19]. This retrospective study was conducted with institutional review board approval and the informed consent was obtained from all individual participants included in the study for the storage and use of their data (IRB No. KS 2016-0001).

RFA preparation

US results, laboratory data, and FNAC results of all patients were examined prior to the RFA. The nodules were divided into a PC group and a PS group according to the sonographic character of the nodules. A PC nodule was defined as a nodule with a cystic portion >50%, as determined in the sonographically measured surface area. A PS nodule was defined as a nodule with a solid portion >50%, as measured in the sonographically measured surface area. There was no nodule in our database exactly having both 50% of solid and 50% of cystic portion, which could not be allocated to either the PC or the PS group. The volume of the tumor was calculated using the following equation for an ellipsoid: $V = \frac{4}{3} \times \pi \times a \times b^2$, where a is defined as half of the axial lesion spread and b is defined as half of the radial lesion spread.

RFA procedures and follow-up

The patients were positioned supine with the neck extended, in a small operating room, and vital signs were monitored. The patients were administered 2% lidocaine for local anesthesia at the puncture site. An RF generator (Cool-tip RF system: Covidien, Bolder, USA/VIVA RF system: STARmed, Goyang, Korea) and an 18-gauge, 1–1.5 cm active-tip internally cooled electrode (Well-Point RF Electrode: STARmed, Goyang, Korea) were used, and the ablation power was set at 30–50 W. A continuous US-tracing trans-isthmic approach was used to insert an electrode along the short axis of the nodule (from the isthmus to the TN), and then ablation of the nodules was performed using the "moving shot technique" [20].

US follow-up was performed 1 month after the first RFA session. An additional RFA was performed, as required, during the 6-month follow-up period, in cases of failure to achieve a VRR of >50% or when the residual lesion size remained >4 cm at the largest diameter.

Statistical analysis

Results were analyzed using SPSS, version 22 (SPSS, Inc. Chicago, IL, USA). Chi-square test was used to compare

Table 1 Characteristics of the predominantly cystic (PC) vs. predominantly solid (PS) thyroid nodule groups

Characteristics	Predominantly cystic group ($n = 374$)	Predominantly solid group ($n = 626$)	p Value
Age (years)	48.75 ± 12.29	49.41 ± 11.87	0.401
Sex			0.185
Female	282 (75.4%)	489 (78.1%)	
Male	92 (24.6%)	137 (21.9%)	
Location			0.395
Left	77 (20.6%)	152 (24.3%)	
Right	107 (28.6%)	167 (26.7%)	
Both	190 (50.8%)	307 (49.0%)	
Multiplicity			0.501
Single	137 (36.6%)	243 (38.9%)	
Multiple	237 (63.4%)	383 (61.1%)	
Nodule size (cm)	1.88 ± 1.32	1.95 ± 1.46	0.400
Nodule volume (mL)	10.17 ± 22.68	12.85 ± 29.66	0.109
Number of RFA sessions	1.74 ± 1.40	2.05 ± 1.77	0.003

RFA radiofrequency ablation

categorical variables, and independent two-sample t tests were used to compare the values of continuous variables between the PC and PS groups. Variables with statistically significant predictors in univariate analysis were assessed in multivariate analysis, using a binary logistic regression model. Multivariate analysis was performed to identify factors prognosticating the therapeutic success of RFA. The results are presented as odds ratios (ORs) with a 95% confidence interval (CI). The differences were considered significant when the p value was <0.05.

Results

The study group involved 1619 benign TNs in 1000 patients comprising 771 females and 229 males. The mean age of the study population was 49.2 ± 12.0 years. The follow-up periods were 1.8 ± 2.8 months for the first ablation and 9.9 ± 8.9 months for the last ablation.

Analysis of the two groups according to the nature of the TN

The characteristics of the PC vs. PS groups are shown in Table 1. The PC group comprised 374 patients (37.4%), and the PS group comprised 626 patients (62.6%). 100% cystic or solid pure nodules did not exist. Baseline characteristics such as age, sex, location of nodule, and multiplicity were similar between the two groups. Initial nodule size and volume showed no significant difference between the two groups. The number of RFA sessions was more frequent in the PS group (2.1 ± 1.8) than in the PC group (1.8 ± 1.4) ($p = 0.003$).

Treatment outcomes

The RFA treatment outcomes comparing the PC and PS groups at each treatment session post first follow-up and last follow-up are demonstrated in Table 2. Follow-up periods, nodule size, and nodule volume showed similar outcomes in both groups. The therapeutic success rate of the PC group was not significantly different than that of the PS group, after the first and after the final ablations. Post-interventional complications were comparable between the groups (Table 3). There was no hematoma, hypoparathyroidism and skin burn in two groups. Voice change, localized edema and infections were shown no statistical difference in two groups. Voice change was transient and it recovered in 6 months. No patients required surgery for post-RFA complications in this series.

Factors associated with therapeutic success

TNs with a small volume (volume <4 mL) had a higher final therapeutic success rate than nodules with a large volume. The OR was 1.821, 95% CI: 1.504–2.771 ($p = 0.032$) in univariate analysis and was significant in multivariate analysis (OR 1.848, 95% CI: 1.537–2.789, $p = 0.030$). (Table 4). However, other factors including age, sex, location of the nodule, multiplicity, and nature of the nodule did not show any statistically significant differences.

Discussion

This retrospective study demonstrated that one single RFA treatment was effective in reducing benign non-functional TN volume with non-inferior result in the PS group comparing to the PC group. This large study involving 1000 patients is likely to have had greater statistical significance. Multi-fractioned RFAs (minimum 3 sessions) are required for successful ablation of benign TNs. In particular, the smaller the TN volume, the higher the therapeutic success rate. Cesareo et al. also found better success rates in small nodules [21]. PC nodules exhibited as high a therapeutic success rate as PS nodules. Thus our results show that RFA could be applied to a wide variety of nodule configurations. Post-interventional complications were shown to be rare.

Previously held opinions related to LA considered this technique superior to RFA in managing cystic benign TNs. However, many researchers have recently reported contrasting results. Mauri et al. compared LA and RFA technique efficacy and safety in the treatment of benign TNs and reported that LA and RFA showed very similar outcomes [22]. The only essential influencing factor was the skill of the operating surgeon in determining the extent of nodule volume reduction, regardless of the technique used.

Table 2 Treatment results in the predominantly cystic and predominantly solid nodule groups

	First follow-up		*p* Value	Last follow-up		*p* Value
	Cystic	Solid		Cystic	Solid	
Period (months)	1.82 ± 2.58	1.76 ± 2.89	0.743	9.94 ± 8.85	9.80 ± 8.93	0.817
Size (cm)	1.88 ± 1.32	1.96 ± 1.46	0.037	0.82 ± 0.79	0.89 ± 0.91	0.160
Volume (mL)	3.83 ± 11.95	6.06 ± 15.30	0.011	1.65 ± 6.21	2.23 ± 7.13	0.180
VRR (%)	68.33 ± 32.27	66.85 ± 28.80	0.454	83.68 ± 5.62	84.01 ± 24.37	0.917
Therapeutic success[a] (%)	295 (78.9%)	489 (78.2%)	0.439	342 (91.4%)	584 (93.4%)	0.148

Cystic predominantly cystic group ($n = 374$), *Solid* predominantly solid group ($n = 626$), *VRR* volume reduction ratio

[a]Therapeutic success is defined as a volume reduction of >50%

Table 3 Complications in the predominantly cystic and predominantly solid nodule groups

Complications	Predominantly cystic group ($n = 374$)	Predominantly solid group ($n = 626$)	*p* Value
Hematoma ($n = 0$)	0	0	NA
Transient voice change ($n = 4$)	2 (0.5%)	2 (0.3%)	0.976
Hypoparathyroidism ($n = 0$)	0	0	NA
Skin burn ($n = 0$)	0	0	NA
Localized edema[a] ($n = 15$)	7 (1.9%)	8 (1.3%)	0.938
Infection ($n = 3$)	1 (0.3%)	2 (0.3%)	0.996

[a]Localized edema: minimal soft tissue swelling without hematoma

Table 4 Univariate and multivariate regression analysis of the factors affecting therapeutic success

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age >45 years	1.571 (0.968–2.549)	0.068		
Male (vs. female)	1.274 (0.698–2.327)	0.430		
Right lobe (vs. left lobe)	0.820 (0.422–1.592)	0.557		
Multiple (vs. single)	1.148 (0.707–1.864)	0.576		
Predominantly solid (vs. cystic)	1.333 (0.824–2.156)	0.242		
Initial volume <4 mL	1.821 (1.504–2.771)	0.032	1.848 (1.537–2.789)	0.030

OR odds ratio, *CI* confidence interval

Although still disputed, RFA has not only been used for benign nodules but also for recurrent thyroid cancer in patients with relative contraindications for surgical treatment. Radzina et al. reviewed the literature to evaluate indications, techniques, complications, and limitations and assessed outcomes for both benign, solid and partially cystic nodules and recurrent malignant nodules [23]. They concluded that RFA was proven to be effective and safe in cases of benign TNs and was a promising alternative treatment method to surgery for recurrent papillary thyroid cancer patients.

RFA has disadvantages that include its high cost and technical operating challenges. Moreover, multiple ablations may be necessary to achieve the desired result. In the current guideline for recurrent cystic TNs, ethanol ablation is recommended as the treatment of choice because it is a less expensive option [24]. If RFA costs were to be lower in future, the non-surgical treatment of choice for benign cystic TN may change to RFA, because RFA requires a shorter treatment time than ethanol ablation and has a greater effect on repeated treatment. Lee et al. [25] reported that additional RFA treatment was needed more frequently in PC nodules than in PS nodules. However, in this study, only 27 patients (20%) in the 137 patients of PC group required additional ablation. The reasons for additional RFA were as follows: VRR < 50% (45 patients in the PC group; 79 patients in the PS group) and the presence of a large TN volume (>4 cm at the largest diameter) even after VRR > 50% (32 patients in the PC; 73 in the PS group). The patients with persisting nodules had detected these either visually or via palpation, otherwise these nodules were asymptomatic.

The total number of patients enrolled in many other similar studies, including those mentioned above, approximated between 400 and 500 patients. Our study enrolled the 1000 patients with 1619 nodules, and such a large number of patients increases confidence in the statistically significant results.

However, this study has some limitations. First, the follow-up period for this retrospective study was not long. Second, the lack of detailed tracing of patients' cosmetic satisfaction or checking for minor complications are further limitations of this study. However, we collected the data consecutively, and only one surgeon treated the nodules using the same protocol with serial follow-up, to avoid some confounding factors.

In conclusion, our study demonstrates that RFA of benign TNs may be feasible and safe with low complication rates when performed by an experienced thyroid surgeon. Therapeutic success was achieved more frequently with smaller volume nodules. Most patients who undergo RFA were those who have cosmetic concerns of minifying palpable nodules and those with even smaller nodules who noticed their having TN were willing to undergo RFA. Moreover, even cystic nodules could often be successfully ablated with radiofrequency. Further studies with larger numbers of patients on a follow-up duration >6 months are needed to confirm the long-term efficacy of RFA in patients with benign TNs.

Conclusion

Our study showed that RFA was effective in reducing benign TN volume. RFA can be recommended as a safe tool in the non-surgical management of high-risk groups with benign TNs, regardless of whether the nodules are PC or PS in nature.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study, formal consent is not required.

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