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Delayed Cancer Diagnosis in Thyroid Nodules Initially Treated as Benign With Radiofrequency Ablation: Ultrasound Characteristics and Predictors for Cancer

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Objective: Regrowth after radiofrequency ablation (RFA) of symptomatic large thyroid nodules, initially treated as benign, sometimes turns out to be malignancies. This study aimed to assess the ultrasound (US) characteristics of thyroid nodules initially treated as benign with RFA and later diagnosed as cancers, predictive factors for cancers masquerading as benign, and methods to avoid RFA in these cancers.

Materials and Methods: We reviewed the medical records of 134 consecutive patients with 148 nodules who underwent RFA between February 2008 and November 2016 for the debulking of symptomatic thyroid nodules diagnosed as benign using US-guided biopsy. We investigated the pre-RFA characteristics of the thyroid nodules, changes at follow-up after RFA, and the final surgical pathology.

Results: Nodule regrowth after RFA was observed in 36 (24.3%) of the 148 benign nodules. Twenty-two of the 36 nodules were surgically removed, and malignancies were confirmed in seven (19.4% of 36). Of the 22 nodules removed surgically, pre-RFA median volume (range) was significantly larger for malignant nodules than for benign nodules: 22.4 (13.9–84.5) vs. 13.4 (7.3–16.8) mL (P = 0.04). There was no significant difference in the regrowth interval between benign and malignant nodules (P = 0.49). The median volume reduction rate (range) at 12 months was significantly lower for malignant nodules than for benign nodules (51.4% [0–57.8] vs. 83.8% [47.9–89.6]) (P = 0.01). The pre-RFA benignity of all seven malignant nodules was confirmed using two US-guided fine-needle aspirations (FNAs), except for one nodule, which was confirmed using US-guided core-needle biopsy (CNB). Regrown malignant nodules were diagnosed as suspicious follicular neoplasms by CNB. Histological examination of the malignant nodules revealed follicular thyroid carcinomas, except for one follicular variant, a papillary thyroid carcinoma.

Conclusion: Symptomatic large benign thyroid nodules showing regrowth or suboptimal reduction after RFA may have malignant potential. The confirmation of these nodules is better with CNB than with FNA.

Keywords: Thyroid nodule; Radiofrequency ablation; Ultrasonography; Follicular thyroid carcinoma

INTRODUCTION

Radiofrequency ablation (RFA) is a minimally invasive technique for the treatment of various tumors that has been demonstrated to be effective in patients with symptomatic benign thyroid nodules [1-4] and recurrent thyroid cancers [5-7]. Since 2001, many studies, including randomized controlled trials and meta-analyses, have reported the effectiveness and safety of this approach, resulting in its widespread application in patients with benign thyroid nodules [8-12].

Prior to RFA, thyroid nodules should be confirmed as benign based on at least two ultrasound (US)-guided fine-needle aspirations (FNAs) or core-needle biopsy (CNB)

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[13-18]. According to the Korean Society of Thyroid Radiology (KSThR) guidelines, a single diagnosis of benignity is sufficient to confirm thyroid nodules with typical US features highly suggestive of benign nodules (iso/hyperechoic spongiform or partially cystic nodules with an intracystic comet tail artifact) and autonomously functioning thyroid nodules [8-12].

Nodule regrowth after RFA of symptomatic large benign nodules is sometimes diagnosed as malignancy during surgery [19,20]. This implies a malignant transformation of the nodule or an error in the initial diagnosis. However, there is limited information regarding the imaging features, clinical course, and risk factors associated with the diagnosis of nodule malignancy after RFA. Therefore, this study evaluated the US characteristics of thyroid nodules initially treated as benign with RFA and later diagnosed as cancer, predictive factors for cancers masquerading as benign, and methods to avoid RFA in these cancers.

MATERIALS AND METHODS

Study Patients

This retrospective study was approved by the institutional review board of Samsung Medical Center (IRB No. 2022-11-096), and the requirement for informed consent was waived owing to the retrospective nature of the study. Between February 2008 and November 2016, 148 consecutive patients with 162 thyroid nodules underwent US-guided RFA for the debulking of symptomatic benign thyroid nodules at our institution. All the patients had nodule compression or cosmetic problems. Among them, 14 patients with 14 nodules were excluded because of the absence of follow-up US findings after RFA. In total, 134 patients with 148 nodules were included in our study. By reviewing the patients' medical records, we evaluated patients' age and sex, pre-RFA diagnostic method (FNA or CNB) for thyroid nodules, final histological type of thyroid nodules, regrowth interval, volume reduction rate (VRR), and follow-up information.

Pre-Procedural Evaluation

Thyroid US examinations were conducted using a 5–12 MHz linear array LOGIQ E9 US transducer with an XDclear scanner (General Electric [GE] Healthcare) or an IU22 scanner (Philips Medical Systems). Each nodule was measured in three orthogonal diameters (the two diameters perpendicular to the largest diameter); we calculated the volume using the equation $V = \pi abc/6$ (where V is volume, a is the largest diameter, and b and c are the two perpendicular diameters). Based on the US guidelines, the following features of the thyroid nodules were assessed [21-23]: composition (solid, predominantly solid [cystic portion ≤ 50%], predominantly cystic [cystic portion > 50%], cystic, spongiform), echogenicity (marked hypoechogenicity, mild hypoechogenicity, isoechogenicity, and hyperechogenicity), orientation, margin, presence of a sonographic halo, predominant echotexture, presence of vascularity on Doppler imaging, and calcifications. A halo is defined as a thin rim of decreased echogenicity surrounding the nodule, and is thought to represent the capsule surrounding the follicular neoplasm in resected specimens [24]. Vascularity consists of pattern types 1–4 [25] (type 1, no vascularity; type 2, perinodular vascularity only [circumferential vascularity at the nodule margin]; type 3, mild intranodular vascularity with or without perinodular vascularity [vascularity < 50%]; type 4, marked intranodular vascularity with or without perinodular vascularity [vascularity ≥ 50%]). All patients underwent thyroid function tests, bleeding tendency tests, and clinical examinations prior to RFA.

Procedures

US-guided RFA was performed by one of two radiologists with 14 and 18 years of experience. All ablations were performed using radiofrequency (RF) generators (Cool-Tip RF system, Covidien; SSP-2000, Taewoong Medical; and M-1004, RF Medical) and an 18-gauge internally cooled adjustable RF electrode with a variable-sized active tip and a total length of 8 or 10 cm (Well-point RF electrodes or Proteus RF electrodes, STARmed). Local anesthesia was induced with a 1% lidocaine injection into the puncture site and perithyroidal area [26]. The fluid was aspirated before RFA of the thyroid nodules with cystic components. The RF power used was approximately 30–50 W. RF ablation was terminated when the nodule exhibited hyperechoic changes.

Follow-Up

The patients underwent follow-up US at 6 and 12 months after treatment and annually thereafter. Similar to the evaluations performed before ablation, thyroid nodule volume, largest diameter, symptoms, and cosmetic scores were assessed. The VRR was calculated as follows:
VRR = ([initial volume − final volume] x 100)/initial volume.
Regrowth was defined as an increase in the nodule volume measured on US relative to the initial nodule volume. If

radiological findings of incomplete ablation, such as the presence of viable tissue or vascularity of the ablated thyroid nodules were detected for < 12 months, RFA was repeated at the discretion of a radiologist. Further evaluation with CNB was performed for nodules with an increase in the initial volume or a suboptimal reduction (generally < 50%) after RFA at any follow-up. Surgery was required for patients with unresolved clinical problems (foreign body sensation) or refusal of repeat RFAs because of the higher cost and suspicion of follicular neoplasm on CNB.

Statistical Analyses

We used the χ^2 or Fisher's exact test to compare categorical variables, such as clinicopathological and US features, and the Mann–Whitney U test to compare continuous variables. Continuous variables are expressed as medians and interquartile ranges (25th–75th). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS software (PASW Statistics, version 27; SPSS).

RESULTS

Among 134 patients with 148 nodules who underwent RFA for symptomatic benign thyroid nodules at our institution, 35 patients with 36 (24.3%) presented with regrowth after RFA. Among these, 18 patients with 22 thyroid nodules underwent surgery for unresolved symptoms. Six nodules were treated with additional RFA and eight nodules remained untreated; however, further follow-up with US was performed for the untreated nodules. Ultimately, malignancies were confirmed in seven (19.4%) of the 36 regrown nodules.

The baseline characteristics of the seven patients diagnosed with malignancy after RFA, including two males and five females (mean age, 24 years; age range, 21–62 years), are presented in Table 1. All seven patients with malignancy were treated with a single session of RFA, except for one who underwent a second session 70 months after the first session.

Table 2 shows the US imaging characteristics of benign and malignant nodules surgically confirmed after RFA. In

Table 2. US characteristics of benign and malignant nodules in surgery after RFA

	Benign (n = 15)	Malignant (n = 7)	*P*
Composition			0.73
Predominantly cystic	5 (27.3)	1 (14.3)	
Predominantly solid	6 (40.9)	3 (42.9)	
Solid	4 (31.8)	3 (42.9)	
Echogenicity			1.00
Isoechogenicity	15 (100)	7 (100)	
Hypoechogenicity	0	0	
Margin			0.63
Smooth	15 (100)	6 (85.7)	
Irregular	0	1 (14.3)	
Halo			0.12
Presence	2 (13.3)	3 (42.9)	
Absence	13 (86.7)	4 (57.1)	
Calcification			0.08
No	14 (93.3)	4 (57.1)	
Macrocalcification	1 (6.7)	3 (42.9)	
Vascularity			0.67
No	0	0	
Perinodular	10 (66.7)	4 (57.1)	
Intranodular	5 (33.3)	3 (42.9)	
K-TIRADS			0.63
3 (Low suspicion)	15 (100)	6 (85.7)	
4 (Intermediate suspicion)	0	1 (14.3)	

Values are expressed as frequencies (%).
US = ultrasound, RFA = radiofrequency ablation, K-TIRADS = Korean Thyroid Imaging Reporting and Data System

Table 1. Baseline characteristics of malignant nodules treated with RFA

No. of patients	Age, yr	Sex	Size, cm	Volume, mL	Pre-ablation diagnosis (frequency)	Regrowth duration	Post-ablation diagnosis	Pathology
1	21	F	4.1 x 2.3 x 4.6	22.6	FNA (two)	6 months	ND	FTC
2	30	F	2.4 x 3.0 x 3.7	13.9	FNA (two)	6 years	CNB	FTC
3	62	M	6.3 x 4.5 x 7.5	110.6	FNA (two)	5 years	ND	FTC
4	29	M	4.0 x 3.1 x 5.5	14.2	FNA (two), CNB (one)	2 years	CNB	FTC
5	47	F	2.9 x 2.3 x 3.7	12.8	FNA (two)	8 years	CNB	FTC
6	56	F	5.4 x 4.3 x 7.0	84.5	FNA (two)	5 years	CNB	FTC
7	27	F	3.9 x 2.4 x 4.6	22.4	FNA (two)	1 year	ND	FVPTC

RFA = radiofrequency ablation, F = female, M = male, FNA = fine-needle aspiration, ND = not done, FTC = follicular thyroid carcinoma, CNB = core needle biopsy, FVPTC = follicular variant of papillary thyroid carcinoma both groups, all nodules were isoechoic. Solid composition, halo, irregular margins, and macrocalcifications were more frequently observed in malignant nodules than in benign nodules, but the differences were not statistically significant (42.9% vs. 31.8%, $P = 0.73$; 42.9% vs. 13.3%, $P = 0.12$; 14.3% vs. 0%, $P = 0.63$, 42.9% vs. 6.7%, $P = 0.08$). The subtypes of vascularity in malignant thyroid nodules included perinodular vascularity (57.1%, 4 of 7) and mild intranodular vascularity (42.9%, 3 of 7). All benign thyroid nodules and six of the seven malignant thyroid nodules were classified as K-TIRADS 3 (Low suspicion), whereas one malignant thyroid nodule was classified as K-TIRADS 4 (Intermediate suspicion).

The clinical data of the benign and malignant nodules confirmed during surgery are summarized in Table 3. The cosmetic score was significantly different between the two groups, with a median score of 3 (interquartile range: 2–4) for benign nodules and 4 (interquartile range: 3–4) for malignant nodules ($P = 0.03$). Although not statistically significant, the pre-RFA maximum diameter was slightly higher in malignant nodules, with a median of 4.6 cm (interquartile range: 3.7–7.0), compared to 3.9 cm (interquartile range: 3.0–4.7) in benign nodules ($P = 0.07$). Additionally, the pre-RFA volume was significantly larger in malignant nodules compared to benign nodules, with a median volume of 22.4 mL (interquartile range: 13.9–84.5) and 13.4 mL (interquartile range: 7.3–16.8), respectively ($P = 0.04$). There was no significant difference in the regrowth interval between the two groups ($P = 0.49$). Furthermore, the VRR at 12 months showed a significant difference, with a median VRR of 83.8% (interquartile range: 47.9–89.6) for benign nodules and 51.4% (interquartile range: 0–57.8) for malignant nodules ($P = 0.01$). Five (71.4%) of the seven malignant nodules showed a VRR > 50% at 12 months but regrowth progressed thereafter. Two (28.6%) thyroid nodules increased in volume 6–12 months after RFA. Histological examination of the nodules diagnosed as malignant revealed follicular thyroid carcinoma (FTC), except for one follicular variant of papillary thyroid carcinoma (FVPTC) (Figs. 1, 2).

In contrast, 15 thyroid nodules were confirmed as benign during surgery after RFA. Nine benign nodules were subjected to CNB in seven (77.8%) patients and FNA in two (22.2%) patients before surgery. The CNB results indicated follicular neoplasms in five nodules and benignity in two nodules. The final surgical results included follicular adenoma in two nodules and nodular hyperplasia in 13 nodules.

CNB was used for the preoperative confirmation of 11 of the 22 ablated nodules. Malignant nodules were correctly diagnosed as follicular neoplasms when using CNB. Total thyroidectomy was performed in seven (31.8%) of the 22 ablated thyroid nodules, which comprised three (42.9%) malignant nodules and four (26.7%) benign nodules.

The T stages of the 7 malignant nodules were classified as T2 in three and T3a in four nodules. No evidence of lymph node or distant metastases was observed. No telomerase reverse transcriptase (TERT) mutations were detected.

DISCUSSION

Nodule regrowth was observed after RFA for the debulking of symptomatic large benign nodules in 36 (24.3%) of the 148 nodules. The malignancy rate of regrown nodules was 19.4% (7/36). Of the seven malignant lesions, the final pathologies were FTC (85.7%, 6/7) and FVPTC (14.3%, 1/7). In these malignant cases, the VRR was approximately 50% or even increased at 12 months after RFA.

To date, no consecutive studies have addressed the long-term effects and diagnosis of malignancy after RFA treatment of symptomatic large benign thyroid nodules in a large series. FNA or CNB for these nodules cannot completely represent the surgical pathology; therefore, a warning about the malignancy rate is necessary before RFA for benign nodules that are too large. Therefore, the findings of this study provide important insights that may be used to revise the RFA guidelines.

Table 3. Characteristics of benign and malignant thyroid nodules before and after RFA

	Benign (n = 15)	Malignant (n = 17)	*P*
Cosmetic score	3 (2–4)	4 (3–4)	0.03
Pre-RFA maximum diameter, cm	3.9 (3.0–4.7)	4.6 (3.7–7.0)	0.07
Pre-RFA volume, mL	13.4 (7.3–16.8)	22.4 (13.9–84.5)	0.04
Regrowth interval, month	24.0 (0–72.0)	60.0 (12.0–72.0)	0.49
VRR at 12 months, %	83.8 (47.9–89.6)	51.4 (0–57.8)	0.01

Values are presented as median (interquartile ranges).
RFA = radiofrequency ablation, VRR = volume reduction rate

Korean Journal of Radiology
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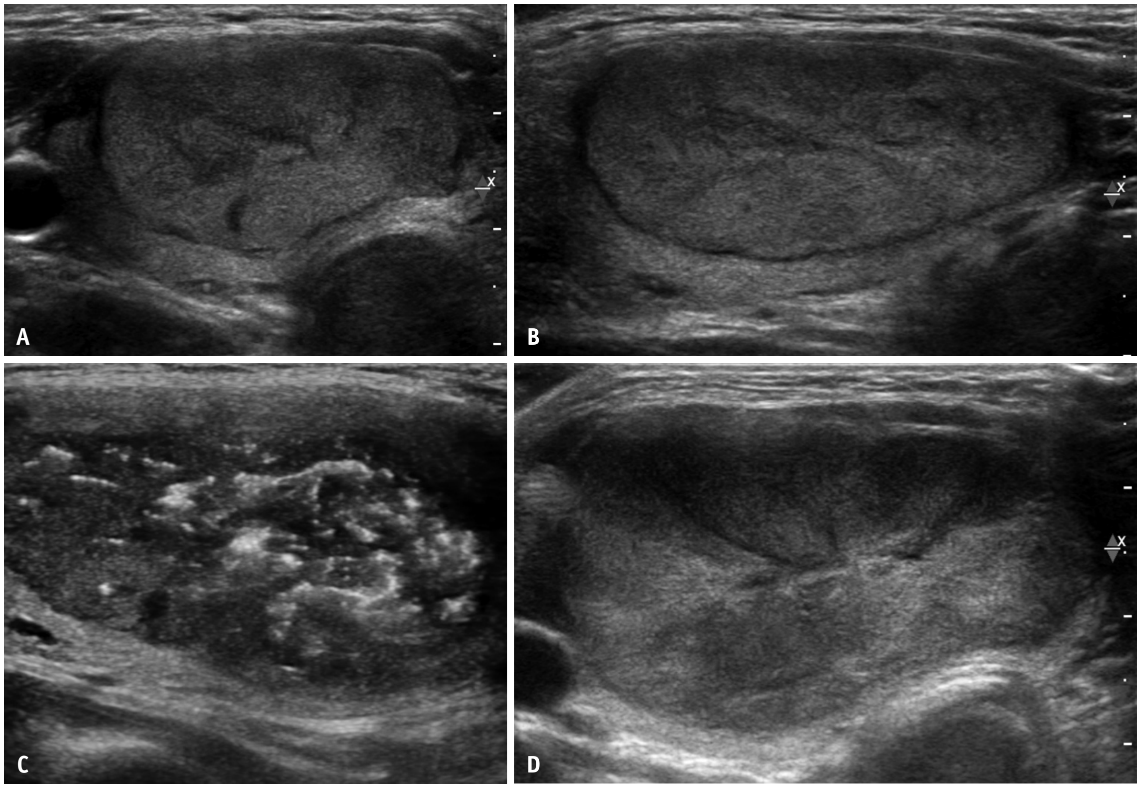

Fig. 1. A 21-year-old female patient with minimally invasive follicular thyroid carcinoma (FTC) in surgery after radiofrequency ablation (RFA). The patient had a 4.6-cm sized symptomatic large thyroid nodule (**A:** transverse ultrasound [US] image, **B:** longitudinal US image) located in the right thyroid gland, classified as low suspicion on US and confirmed as benign using two fine-needle aspirations and treated with RFA **(C)**. One year after RFA, the nodule size increased to 5.0 cm, appeared hypoechoic, and revealed hypervascularity **(D)**. Pathology report after right lobectomy revealed minimally invasive FTC.

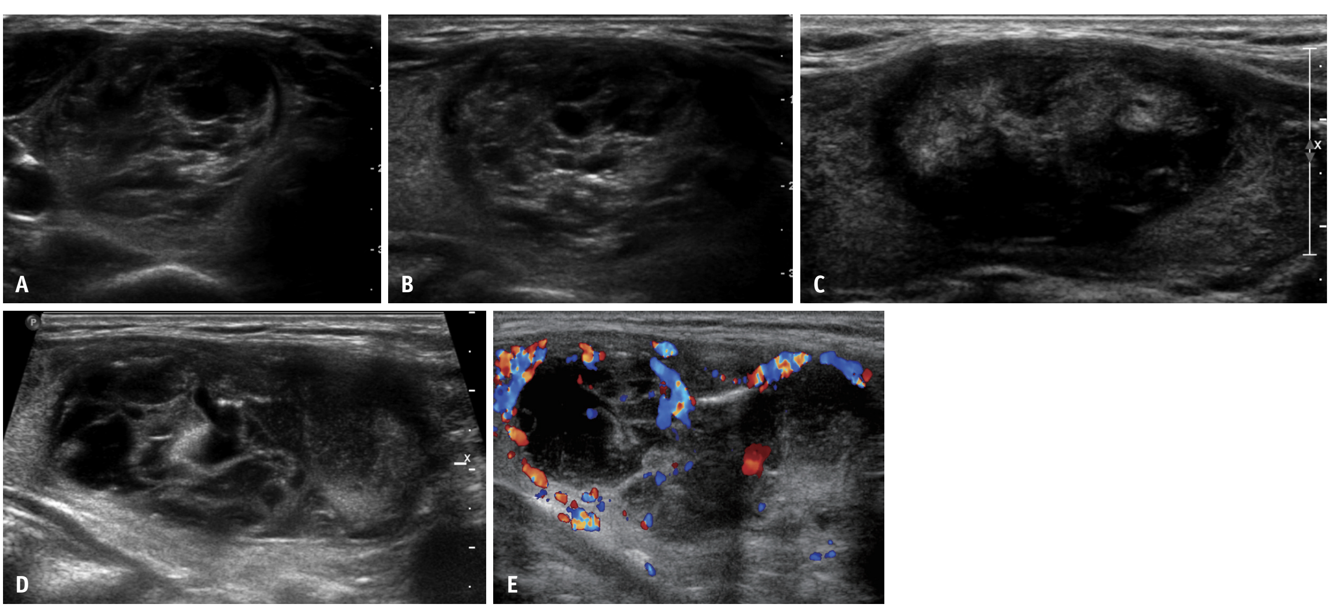

Fig. 2. A 47-year-old female patient with encapsulated angioinvasive follicular thyroid carcinoma (FTC) in surgery after radiofrequency ablation (RFA). Ultrasonography shows a 3.7 cm-sized predominantly solid isoechoic nodule with an initial volume of 12.8 mL (**A:** transverse, **B:** longitudinal ultrasound [US] images). This nodule was classified as low suspicion at US and confirmed as benign by two fine-needle aspirations. Six months after RFA, the mass reduced to 3.2 cm. **C:** Eight years after RFA, the nodule increased to a 4.9-cm predominantly solid hypervascular nodule (**D, E:** Doppler US image) with a volume of 26.5 mL. The core-needle biopsy results suggested follicular neoplasm, and a final pathology report after right lobectomy confirmed encapsulated angioinvasive FTC.

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Our study revealed a relatively higher malignancy rate than expected at long-term follow-up. The reason for the relatively high risk of malignancy after RFA was that the RFA candidates in our institution were patients who complained of symptoms due to large nodule size but were reluctant to undergo surgery. Therefore, the thyroid nodules diagnosed as malignancies after RFA in our series were large nodules > 3.7 cm in diameter, which are considered a risk factor for false-negative FNAs [27-34]. A previous study reported that thyroid nodules measuring ≥ 3 cm with subsequent benign cytology had a relatively high (3.6%) false-negative risk; therefore, additional work-ups, such as surgery should be recommended [35].

However, the malignancy rate of thyroid nodules after confirmation of benignity is very low; therefore, nodules without suspicious US features may be considered benign [36]. In our study, thyroid malignancies after RFA, including FTC and FVPTC, exhibited follicular morphological features on cytopathological examination. FTCs [37] with a macrofollicular pattern and abundant background colloids and FVPTCs [28,38] presenting with only focally pathognomonic nuclear features are frequently mistaken for benign adenomatoid colloid nodules on cytological examination. Therefore, it seems that these two FNAs methods are not sufficient for the diagnosis of benignity before RFA in terms of diagnosing follicular neoplasms. In contrast, CNB is more accurate for the diagnosis of follicular neoplasms in terms of obtaining follicular patterns and capsules [39,40].

In our study, the K-TIRADS categories did not contribute to the differentiation between post-RFA benign and malignant nodules. FTC and FVPTC exhibit benign US features, such as regular iso- or mildly hypoechoic nodules, instead of suspicious US features, such as markedly hypoechoic nodules or microcalcifications [41,42]. On average, the majority of these lesions are large and have a solid composition, as observed in our cases. In particular, a previous study conducted by Park et al. [39] indicated that when radiological findings are suspicious for a follicular neoplasm with a circumscribed solid or peripheral halo or nodule-in-nodule appearance and a growing solid tumor on US, it is feasible to obtain pathological specimens through CNB rather than FNA. If US features, such as K-TIRADS 3 or 4 are suggestive of a follicular neoplasm, it is necessary to confirm the diagnosis using at least one CNB before RFA. Therefore, further modifications and standardization are recommended to establish international RFA guidelines.

Current RFA guidelines by the American Thyroid Association and KSThR do not recommend RFA for the treatment of follicular neoplasms because there is no evidence of a treatment benefit [14,43]. Furthermore, clinical research on the application of RFA for follicular neoplasms remains limited. A few studies have reported conflicting results regarding the role of RFA in the treatment of indeterminate lesions. Ha et al. [44] reported that 10 patients with follicular neoplasms of < 2 cm treated with RFA showed no recurrence during a 5-year follow-up period and an average VRR of 99.5% was achieved. In contrast, Dobrinja et al. [45] reported RFA in six follicular neoplasms, two of which regrew and ultimately required surgery. The final surgical pathology revealed one minimally invasive FTC and one follicular neoplasm with indeterminate malignant behavior. If a follicular neoplasm is suspected, especially for nodules measuring > 2 cm that are symptomatic, a warning about the malignancy risk after RFA is required.

The goal of RFAs for benign thyroid nodules is to achieve > 50% volume reduction over a 1-year period and relieve symptoms. However, in our study, the median VRR at 12 months was significantly lower for malignant nodules than for benign nodules (51.4 [0–57.8] vs. 83.8 [47.9–89.6] mL, $P = 0.01$). In addition, the volume increased at 12 months in two malignant nodules. Therefore, CNB should be considered for RFA-treated thyroid nodules if the VRR at 12 month is < 50%. In addition, there was no difference in the regrowth period between benign and malignant nodules ($P = 0.49$). Subsequently, several studies with longer follow-up periods have shown a tendency for treated thyroid nodules to increase in size after 2–3 years [46-48]. Therefore, a long-term follow-up period of > 1 year is required.

This study has a few limitations. First, the retrospective data collection may have resulted in case selection bias, and our sample size was small, which may not reflect a representative population. Malignancy may be a rare post-RFA event in the treatment of symptomatic thyroid nodules of average size. Second, although the overall indications for RFA of benign thyroid nodules were similar, the detailed criteria for the inclusion of large nodules may not be identical to those of other institutions. Finally, the actual malignancy rate may differ from the suggested rate. One group of patients was followed-up without surgery.

In conclusion, large symptomatic benign thyroid nodules that show regrowth or suboptimal reduction after RFA may have malignant potential. The confirmation of these nodules is better with CNB than with FNA.

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Availability of Data and Material

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

Jung Hee Shin, a contributing editor of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Myoung Kyoung Kim, Soo Yeon Hahn, Jung Hee Shin. Data curation: Myoung Kyoung Kim, Soo Yeon Hahn, Jung Hee Shin. Formal analysis: Myoung Kyoung Kim, Jung Hee Shin. Investigation: all authors. Methodology: Myoung Kyoung Kim, Jung Hee Shin. Project administration: Myoung Kyoung Kim, Jung Hee Shin. Resources: all authors. Software: all authors. Supervision: Jung Hee Shin. Validation: Soo Yeon Hahn, Jung Hee Shin. Visualization: Myoung Kyoung Kim, Jung Hee Shin. Writing—original draft: Myoung Kyoung Kim, Jung Hee Shin. Writing—review & editing: Myoung Kyoung Kim, Jung Hee Shin.

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REFERENCES

1. Baek JH, Moon WJ, Kim YS, Lee JH, Lee D. Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. *World J Surg* 2009;33:1971-1977
2. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. *Eur Radiol* 2008;18:1244-1250
3. Kim YS, Rhim H, Tae K, Park DW, Kim ST. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. *Thyroid* 2006;16:361-367
4. Baek JH, Kim YS, Lee D, Huh JY, Lee JH. Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. *AJR Am J Roentgenol* 2010;194:1137-1142
5. Baek JH, Kim YS, Sung JY, Choi H, Lee JH. Locoregional control of metastatic well-differentiated thyroid cancer by ultrasound-guided radiofrequency ablation. *AJR Am J Roentgenol* 2011;197:W331-W336
6. Guenette JP, Monchik JM, Dupuy DE. Image-guided ablation of postsurgical locoregional recurrence of biopsy-proven well-differentiated thyroid carcinoma. *J Vasc Interv Radiol* 2013;24:672-679
7. Kim JH, Yoo WS, Park YJ, Park DJ, Yun TJ, Choi SH, et al. Efficacy and safety of radiofrequency ablation for treatment of locally recurrent thyroid cancers smaller than 2 cm. *Radiology* 2015;276:909-918
8. Deandrea M, Sung JY, Limone P, Mormile A, Garino F, Ragazzoni F, et al. Efficacy andsafety of radiofrequency ablation versus observation for nonfunctioning benign thyroid nodules: a randomized controlled international collaborative trial. *Thyroid* 2015;25:890-896
9. Ha EJ, Baek JH, Kim KW, Pyo J, Lee JH, Baek SH, et al. Comparative efficacy of radiofrequency and laser ablation for the treatment of benign thyroid nodules: systematic review including traditional pooling and bayesian network meta-analysis. *J Clin Endocrinol Metab* 2015;100:1903-1911
10. Chung SR, Suh CH, Baek JH, Park HS, Choi YJ, Lee JH. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. *Int J Hyperthermia* 2017;33:920-930
11. Cesareo R, Palermo A, Benvenuto D, Cella E, Pasqualini V, Bernardi S, et al. Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2019;20:37-44
12. Jung SL, Baek JH, Lee JH, Shong YK, Sung JY, Kim KS, et al. Efficacy and safety of radiofrequency ablation for benign thyroid nodules: a prospective multicenter study. *Korean J Radiol* 2018;19:167-174
13. National Institute for Health and Care Excellence. Ultrasound-guided percutaneous radiogrequency ablation for benign thyroid nodules. Interventional procedure guidance [IPT562] [accessed on March 1, 2023]. Available at: https://www.nice.org.uk/guidance/ipg562
14. Kim JH, Baek JH, Lim HK, Ahn HS, Baek SM, Choi YJ, et al. 2017 thyroid radiofrequency ablation guideline: Korean Society of Thyroid Radiology. *Korean J Radiol* 2018;19:632-655
15. Papini E, Pacella CM, Solbiati LA, Achille G, Barbaro D, Bernardi S, et al. Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT)

group. *Int J Hyperthermia* 2019;36:376-382
16. Garberoglio R, Aliberti C, Appetecchia M, Attard M, Boccuzzi G, Boraso F, et al. Radiofrequency ablation for thyroid nodules: which indications? The first Italian opinion statement. *J Ultrasound* 2015;18:423-430
17. Dobnig H, Zechmann W, Hermann M, Lehner M, Heute D, Mirzaei S, et al. Radiofrequency ablation of thyroid nodules: "Good Clinical Practice Recommendations" for Austria: an interdisciplinary statement from the following professional associations: Austrian Thyroid Association (OSDG), Austrian Society for Nuclear Medicine and Molecular Imaging (OGNMB), Austrian Society for Endocrinology and Metabolism (OGES), Surgical Endocrinology Working Group (ACE) of the Austrian Surgical Society (OEGCH). *Wien Med Wochenschr* 2020;170:6-14
18. Ha EJ, Baek JH, Che Y, Chou YH, Fukunari N, Kim JH, et al. Radiofrequency ablation of benign thyroid nodules: recommendations from the Asian Conference on Tumor Ablation task force. *Ultrasonography* 2021;40:75-82
19. Bernardi S, Dobrinja C, Fabris B, Bazzocchi G, Sabato N, Ulcigrai V, et al. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. *Int J Endocrinol* 2014;2014:934595
20. Oddo S, Spina B, Vellone VG, Giusti M. A case of thyroid cancer on the track of the radiofrequency electrode 30 months after percutaneous ablation. *J Endocrinol Invest* 2017;40:101-102
21. Ha EJ, Chung SR, Na DG, Ahn HS, Chung J, Lee JY, et al. 2021 Korean Thyroid Imaging Reporting and Data System and imaging-based management of thyroid nodules: Korean Society of Thyroid Radiology consensus statement and recommendations. *Korean J Radiol* 2021;22:2094-2123
22. Ha EJ, Shin JH, Na DG, Jung SL, Lee YH, Paik W, et al. Comparison of the diagnostic performance of the modified Korean Thyroid Imaging Reporting and Data System for thyroid malignancy with three international guidelines. *Ultrasonography* 2021;40:594-601
23. Chung SR, Ahn HS, Choi YJ, Lee JY, Yoo RE, Lee YJ, et al. Diagnostic performance of the modified Korean Thyroid Imaging Reporting and Data System for thyroid malignancy: a multicenter validation study. *Korean J Radiol* 2021;22:1579-1586
24. Sillery JC, Reading CC, Charboneau JW, Henrichsen TL, Hay ID, Mandrekar JN. Thyroid follicular carcinoma: sonographic features of 50 cases. *AJR Am J Roentgenol* 2010;194:44-54
25. Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, et al. Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology consensus statement and recommendations. *Korean J Radiol* 2016;17:370-395
26. Park HS, Baek JH, Park AW, Chung SR, Choi YJ, Lee JH. Thyroid radiofrequency ablation: updates on innovative devices and techniques. *Korean J Radiol* 2017;18:615-623
27. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. *Surgery* 2007;142:837-844; discussion 844.e1-e3
28. Mehanna R, Murphy M, McCarthy J, O'Leary G, Tuthill A, Murphy MS, et al. False negatives in thyroid cytology: impact of large nodule size and follicular variant of papillary carcinoma. *Laryngoscope* 2013;123:1305-1309
29. Agcaoglu O, Aksakal N, Ozcinar B, Sarici IS, Ercan G, Kucukyilmaz M, et al. Factors that affect the false-negative outcomes of fine-needle aspiration biopsy in thyroid nodules. *Int J Endocrinol* 2013;2013:126084
30. Giles WH, Maclellan RA, Gawande AA, Ruan DT, Alexander EK, Moore FD Jr, et al. False negative cytology in large thyroid nodules. *Ann Surg Oncol* 2015;22:152-157
31. Shin JJ, Caragacianu D, Randolph GW. Impact of thyroid nodule size on prevalence and post-test probability of malignancy: a systematic review. *Laryngoscope* 2015;125:263-272
32. Koo DH, Song K, Kwon H, Bae DS, Kim JH, Min HS, et al. Does tumor size influence the diagnostic accuracy of ultrasound-guided fine-needle aspiration cytology for thyroid nodules? *Int J Endocrinol* 2016;2016:3803647
33. Cavallo A, Johnson DN, White MG, Siddiqui S, Antic T, Mathew M, et al. Thyroid nodule size at ultrasound as a predictor of malignancy and final pathologic size. *Thyroid* 2017;27:641-650
34. Ahn HS, Na DG, Baek JH, Sung JY, Kim JH. False negative rate of fine-needle aspiration in thyroid nodules: impact of nodule size and ultrasound pattern. *Head Neck* 2019;41:967-973
35. Nam SJ, Kwak JY, Moon HJ, Yoon JH, Kim EK, Koo JS. Large (>/=3cm) thyroid nodules with benign cytology: Can Thyroid Imaging Reporting and Data System (TIRADS) help predict false-negative cytology? *PLoS One* 2017;12:e0186242
36. Orlandi A, Puscar A, Capriata E, Fideleff H. Repeated fine-needle aspiration of the thyroid in benign nodular thyroid disease: critical evaluation of long-term follow-up. *Thyroid* 2005;15:274-278
37. Sclabas GM, Staerkel GA, Shapiro SE, Fornage BD, Sherman SI, Vassillopoulou-Sellin R, et al. Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. *Am J Surg* 2003;186:702-709; discussion 709-710
38. Jean-Gilles J, Fischer AH, Luu MH, Owens CL. Clinical and pathologic features and clinical impact of false negative thyroid fine-needle aspirations. *Cancer Cytopathol* 2012;120:326-333
39. Park KW, Shin JH, Hahn SY, Oh YL, Kim SW, Kim TH, et al. Ultrasound-guided fine-needle aspiration or core needle biopsy for diagnosing follicular thyroid carcinoma? *Clin Endocrinol (Oxf)* 2020;92:468-474
40. Na HY, Moon JH, Choi JY, Yu HW, Jeong WJ, Kim YK, et al. Preoperative diagnostic categories of fine needle aspiration cytology for histologically proven thyroid follicular adenoma and carcinoma, and Hurthle cell adenoma and carcinoma: analysis of cause of under- or misdiagnoses. *PLoS One* 2020;15:e0241597

41. Yoon JH, Kim EK, Hong SW, Kwak JY, Kim MJ. Sonographic features of the follicular variant of papillary thyroid carcinoma. *J Ultrasound Med* 2008;27:1431-1437
42. Russ G. Risk stratification of thyroid nodules on ultrasonography with the French TI-RADS: description and reflections. *Ultrasonography* 2016;35:25-38
43. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1-133
44. Ha SM, Sung JY, Baek JH, Na DG, Kim JH, Yoo H, et al. Radiofrequency ablation of small follicular neoplasms: initial clinical outcomes. *Int J Hyperthermia* 2017;33:931-937
45. Dobrinja C, Bernardi S, Fabris B, Eramo R, Makovac P, Bazzocchi G, et al. Surgical and pathological changes after radiofrequency ablation of thyroid nodules. *Int J Endocrinol* 2015;2015:576576
46. Lim HK, Lee JH, Ha EJ, Sung JY, Kim JK, Baek JH. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. *Eur Radiol* 2013;23:1044-1049
47. Baek JH, Lee JH, Valcavi R, Pacella CM, Rhim H, Na DG. Thermal ablation for benign thyroid nodules: radiofrequency and laser. *Korean J Radiol* 2011;12:525-540
48. Sim JS, Baek JH, Lee J, Cho W, Jung SI. Radiofrequency ablation of benign thyroid nodules: depicting early sign of regrowth by calculating vital volume. *Int J Hyperthermia* 2017;33:905-910