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ORIGINAL ARTICLE

Outcomes of Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules: A Mayo Clinic Case Series

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Abstract

Objective: To assess the effectiveness, tolerability, and complications of radiofrequency ablation (RFA) in patients with benign large thyroid nodules (TNs).

Patients and Methods: This is a retrospective review of 14 patients with predominantly solid TNs treated with RFA at Mayo Clinic in Rochester, Minnesota, from December 1, 2013, through October 30, 2016. All the patients declined surgery or were poor surgical candidates. The TNs were benign on fine-needle aspiration, enlarging or causing compressive symptoms, and 3 cm or larger in largest diameter. We evaluated TN volume, compressive symptoms, cosmetic concerns, and thyroid function.

Results: Median TN volume reduction induced by RFA was 44.6% (interquartile range [IQR], 42.1%-59.3%), from 24.2 mL (IQR, 17.7-42.5 mL) to 14.4 mL (IQR, 7.1-19.2 mL) ($P<.001$). Median follow-up was 8.6 months (IQR, 3.9-13.9 months). Maximum results were achieved by 6 months. Radiofrequency ablation did not affect thyroid function. In 1 patient with subclinical hyperthyroidism due to toxic adenoma, thyroid function normalized 4 months after ablation of the toxic nodule. Compressive symptoms resolved in 8 of 12 patients (67%) and improved in the other 4 (33%). Cosmetic concerns improved in all 8 patients. The procedure had no sustained complications.

Conclusion: In this population, RFA of benign large TNs performed similarly to the reports from Europe and Asia. It induces a substantial volume reduction of predominantly solid TNs, improves compressive symptoms and cosmetic concerns, and does not affect normal thyroid function. Radiofrequency ablation has an acceptable safety profile and should be considered as a low-risk alternative to conventional treatment of symptomatic benign TNs.

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Thyroid nodules (TNs) are common in clinical practice, affecting 19% to 68% of randomly selected individuals.[1,2] Although most TNs are benign and require only serial observation, a minority display progressive growth that can lead to compressive symptoms and cosmetic concerns that might require intervention. Thyroid surgery is the main therapeutic approach for large nodules that result in compressive symptoms.[3,4] However, the operative risk, although limited, may not be acceptable to some patients.

During the past few years, radiofrequency ablation (RFA) has been shown to be a promising and well-tolerated new approach to benign TNs by inducing tissue necrosis and fibrosis through heat.[5] Randomized trials in Italy and South Korea reported a 50% to 80% volume reduction in treated TNs, with sustained results 3 years after the intervention.[5-8] In the United States, RFA is commonly used for percutaneous treatment of tumors in the lung, liver, kidney, and bone.[9] Yet, this intervention has not been validated for treating TNs in the North American population.

The first aim of this retrospective review was to assess the effectiveness of RFA on volume reduction of benign TNs and improvement in the nodule-related compressive and cosmetic concerns in a US population. The second aim was to assess tolerability and the

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adverse effect profile of this procedure in the present population. We also sought to determine the factors associated with volumetric response to RFA and the correlation between the reduction in TN volume and improvement in patient-reported symptoms.

PATIENTS AND METHODS

Study Population

On December 1, 2013, RFA was implemented at Mayo Clinic in Rochester, Minnesota, as a treatment technique for select benign TNs. Radiofrequency ablation was offered only to patients with large (≥3 cm in at least 1 diameter), predominantly solid TNs that were increasing in size or causing compressive symptoms and cosmetic concerns. Except in 1 patient with toxic adenoma, ultrasound-guided fine-needle aspiration (FNA) biopsy was performed on all the nodules before RFA on at least 2 occasions, with the most recent benign FNA biopsy performed no more than 6 months before the procedure. The patients were retrospectively evaluated through medical record review to assess the efficacy and safety profile of RFA. The protocol for this study was reviewed and approved by Mayo Clinic Institutional Review Board.

We extracted data from the clinical records of 14 consecutive patients who underwent RFA of TNs from December 1, 2013, through October 30, 2016. The following pretreatment ultrasound features were evaluated: nodule echogenicity (hyperechoic, isoechoic, or hypoechoic); solid (≥70% solid component) or mixed (>50% but <70% solid component)[5]; intranodular vascularity on color flow Doppler (grade 1, no flow; grade 2, peripheral flow only; grade 3, low intranodular flow; grade 4, high intranodular flow)[10]; and presence of calcifications (coarse calcifications or microcalcifications). The ultrasound and color flow Doppler examinations were performed and registered by skilled sonographers according to a standard procedure.

To quantify the improvement in nodule-related symptoms, we used a previously validated symptom score (SYS)[11] to assess pressure symptoms in the neck, difficulty swallowing (dysphagia), and aesthetic concerns. Symptoms were scored separately as follows: 0 (absent), 1 (moderate), and 2 (severe). The sum of the individual scores generated a final score ranging from 0 to 6.

Procedure

Each patient underwent RFA in a single session and was then evaluated for immediate, short-term, and long-term complications. When multiple nodules were present (13 of 14 patients), the dominant and growing TN, thought to be responsible for symptoms, was selected for treatment. The TN volume, TN-related compressive symptoms, cosmetic concerns, and thyroid function were evaluated at baseline and during follow-up.

Ultrasonography was performed using a 6- to 15-MHz probe with the GE Logiq E9 ultrasound system. Nodule volume and the percentage of volume reduction were calculated using the following equations: volume = length × width × depth × 0.525; volume reduction percentage = [(initial volume − final volume) × 100%]/initial volume.

All the patients were sedated with general anesthesia during the procedure. General anesthesia was used in light of the length of the procedure, the improved pain control, and the desire to avoid any motion interference that could compromise the accuracy of the technique. A radiofrequency generator (Cool-tip; Covidien) and an 18-gauge, 15-cm electrode with a 1- or 2-cm active tip were used. All radiofrequency procedures were performed by 1 of 3 operators under ultrasonographic control with the same scanner model as was used for the initial diagnostic evaluation. We used an in-plane oblique approach for electrode placement as opposed to directly entering the TN using the shortest pathway. The longer oblique pathway was chosen to lengthen the distance between the skin and the active tip of the RF electrode to reduce the chance of skin burns. We initially positioned the electrode in the deepest portion of the nodule, followed by more superficial placement. This approach was usually transisthmic, but to treat certain nodules in the upper portion of the thyroid, alternative oblique needle placements were used to reach the nodule and to protect extrathyroidal structures from generated thermal energy. To minimize the risk of complications, the outer approximately 5 mm of the nodule was not treated, and the active tip of the electrode

was kept at a safe distance to prevent a skin burn. The nodules were ablated with the moving-shot technique as described elsewhere.[12,13]

The number of ablation cycles (number of times the RF generator was turned off to reposition the electrode to a new location in the nodule), total energy delivered, and total ablation times were different according to target size. Patients were intensively monitored during RFA and then were observed for approximately 3 hours after the procedure and released home thereafter, unless adverse effects developed.

Statistical Analyses

Descriptive statistics were computed on thyroid volume and other clinical variables. Continuous variables are expressed as medians with interquartile ranges (IQRs). Categorical variables are expressed as percentages. We used the Wilcoxon signed rank test to evaluate the difference between TN volumes. The statistical software JMP version c10.0.0 (SAS Institute Inc) was used for all the analyses.

RESULTS

Baseline Characteristics

Fourteen patients (11 women and 3 men) underwent RFA for the treatment of benign, predominantly solid TNs. The median age of patients was 60 years (IQR, 47-65 years). The nodules had a median volume of 24.2 mL (IQR, 17.7-42.5 mL) before RFA. One patient had a single TN, and 13 patients had multinodular goiter. The median duration of follow-up before treatment was 38 months (IQR, 4-95 months). The baseline characteristics of the series are summarized in Table 1.

Before intervention, TNs were enlarging from their clinical reference size in 10 of 14 patients (71%), with a median increase of 114% (IQR, 49%-148%) over a median of 51 months (IQR, 29-107 months). Twelve nodules (85.7%) were causing compressive symptoms and 8 nodules (57.1%) were causing cosmetic concerns. Further details about the ultrasonographic features of TNs are described in the Supplemental Table (available online at http://www.mayoclinicproceedings.org). None of the patients had previous radioiodine therapy, thermal ablation, or neck or trunk external beam radiotherapy.

TABLE 1. Main Characteristics and Baseline Clinical Data of the 14 Study Patients

Characteristic	Value
Sex, F/M (No.)	11/3
BMI, median (IQR)	25.8 (22.9-31.3)
Age at treatment (y), median (IQR)	60 (47-65)
TN volume at initial diagnosis (mL), median (IQR)	14.5 (7.9-26.7)
Follow-up of TN before treatment (mo), median (IQR)	37.9 (3.8-95.3)
TN volume at treatment (mL), median (IQR)	24.2 (17.7-42.5)
Multinodular goiter/single nodule (No.)	13/1
Thyroid disorder—related therapy: levothyroxine/no treatment (No.)	2/12
TN features (No. [%])	
Isoechoic/hypoechoic	8 (57.1)/6 (42.9)
CFD, grade 2/grade 3/grade 4	7 (50.0)/5 (35.7)/2 (12.3)
Coarse calcifications/microcalcifications/no calcifications	10 (71.4)/1 (7.1)/3 (21.4)

BMI = body mass index; CFD = color flow Doppler; IQR = interquartile range; TN = thyroid nodule.

Nodule Volume

Median TN volume reduction in response to RFA was 44.6% (IQR, 42.1%-59.3%) during follow-up (median, 8.6 months [IQR, 3.9-13.9 months]) (Table 2). Each nodule was ablated with a median of 8 ablation cycles (IQR, 6-13). The median final volume was 14.4 mL (IQR, 7.1-19.2 mL), and the median absolute change in volume was 11.1 mL (IQR, 8.3-19.7 mL) ($P<.001$). The median volume decreased by 36.8% (IQR, 15.3%-58.3%; n=2) at 0 to 3 months; 43.9% (IQR, 41.0%-59.2%; n=9) at 3 to 6 months; 44.2% (IQR, 40.7%-59.0%; n=7) at 6 to 12 months; 54.3% (IQR, 29.2%-57.9%; n=3) at 12 to 24 months, and 52.8% (IQR, 45.3%-60.2%; n=2) by more than 24 months (Figures 1, 2, and 3).

TABLE 2. Response to Radiofrequency Ablation in the 14 Study Patients[a]

Variable	Pretreatment	Posttreatment	*P* value
Thyroid function status: hypothyroid/euthyroid/hyperthyroid (No.)	0/13/1	0/14/0	
SYS, median (IQR)[b]	3.5 (1-4)	1 (0-1)	<.001
Volume (mL), median (IQR)	24.2 (17.7-42.5)	14.4 (7.1-19.2)	<.001
Volume change (%), median (IQR)	NA	44.6 (42.1-59.3)	

[a]IQR = interquartile range; NA, not applicable; SYS = symptom score.
[b]The SYS was calculated based on the following variables: (1) pressure symptoms in the neck, (2) difficulty swallowing (dysphagia), and (3) aesthetic concerns (0 = absent, 1 = moderate, and 2 = severe).

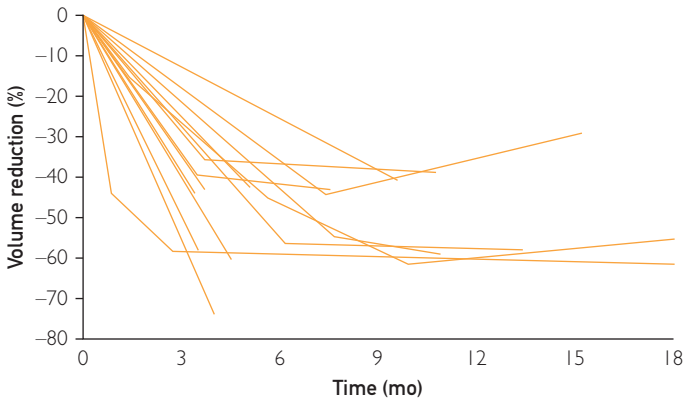

FIGURE 1. Changes in thyroid nodule volume after radiofrequency ablation. Each line represents individual patient data during follow-up.

Hormonal Evaluation

Thirteen of 14 patients had normal thyroid function before RFA. Two of these patients were taking levothyroxine replacement for primary hypothyroidism. Thyroid function test parameters and the dose of levothyroxine did not change during follow-up.

One patient was diagnosed as having subclinical hyperthyroidism due to toxic adenoma (thyrotropin level, 0.03 mIU/L; free thyroxine level, 1.0 ng/dL [to convert to pmol/L, multiply by 12.871]), confirmed by focal I-123 radiotracer uptake in the dominant TN that became the RFA target. The uptake of radiotracer was relatively suppressed in the remaining thyroid gland. The location of the adenoma corresponded with a large nodule (3.2 cm) seen on thyroid ultrasound; FNA biopsy was not performed on this nodule. The patient received no other treatments before RFA given the mild degree of subclinical hyperthyroidism. After RFA of this lesion, thyroid function normalized at a 4-month follow-up visit (the thryotropin level increased to 2.7 mIU/L, and the free thyroxine level remained within the reference range).

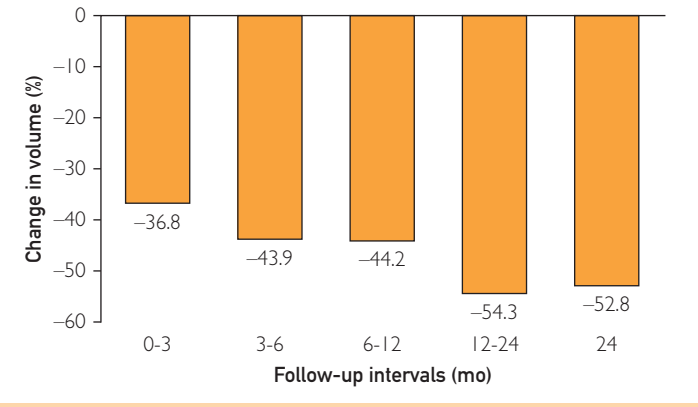

FIGURE 2. Percentage volume reduction of thyroid nodules at each follow-up point. To assess incremental changes in the volume of treated thyroid nodules, available follow-up imaging data are grouped by specified intervals.

Symptom Evaluation

Twelve of 14 patients noted TN-related compressive symptoms or cosmetic concerns. The SYS improved by at least 1 point in all symptomatic patients (12 of 12) during follow-up. The SYS improved from a median of 3.5 (IQR, 1-4) before treatment to 1 (IQR, 0-1) during follow-up ($P<.001$). Compressive symptoms (pressure in the neck or dysphagia) resolved in 8 of 12 patients (67%) and improved in the other 4 (33%). Cosmetic concerns improved in all 8 patients.

Complications and Safety

One of 14 patients (7%) developed hypotension after the procedure, attributed to a vasovagal response due to the deep, posterior location of the nodule, in proximity to the vagal nerve. The patient was monitored overnight and dismissed the following day without any residual hemodynamic changes. Three patients (21%) developed mild neck discomfort, swelling, bruising, and dysphagia shortly after RFA. These symptoms completely resolved within 2 to 5 days of the procedure. The procedure was tolerated well by all the patients. During follow-up, all the patients expressed overall satisfaction with the decision to undergo the procedure. No patient has had thyroidectomy performed subsequent to the procedure to date.

DISCUSSION

The use of RFA to treat TNs is not currently endorsed in the United States. According to the 2015 American Thyroid Association guidelines for Differentiated Thyroid Cancer and Thyroid Nodules, most asymptomatic nodules demonstrating modest growth should be followed without intervention.[4] Surgery may be considered for growing benign nodules if they are large (>4 cm), causing compressive

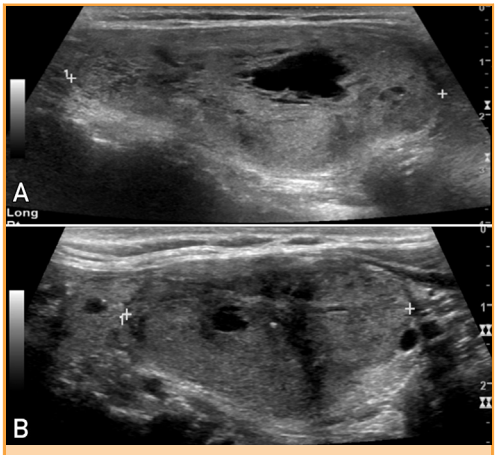

FIGURE 3. Longitudinal view ultrasound images show response to radiofrequency ablation (RFA). A, A predominantly solid thyroid nodule before RFA. At initial diagnosis, the nodule was 7.3 mL. During observation for 11 years, it demonstrated continuous growth to the pre-RFA volume of 27.2 mL (275% growth) and started to cause compressive symptoms and cosmetic concerns. Thyroid function was normal before RFA (thyrotropin level, 3.7 mIU/L; free thyroxine level, 0.9 ng/dL [to convert to pmol/L, multiply by 12.871]). B, The ablated nodule shows a final volume of 12.4 mL (a 54% decrease from the pre-RFA value) after 19 months of follow-up. Thyroid function remained normal.

symptoms or cosmetic concerns, or based on clinical concern. However, these data indicate that RFA is beneficial for patients with benign, large, predominantly solid TNs from the perspective of decreasing nodule volume, preserving existing thyroid function, improving compressive symptoms, and alleviating cosmetic concerns without any major long-term adverse effects. These results are consistent with data from multiple studies performed outside North America.[6,7,14,15]

The median reduction in nodule volume in this series was 45%. Most of the effect was achieved within 6 months. In other studies, the maximum benefit was reported to be 69% to 90% and was found at 6 to 9 months.[6,7,14,15] The volume reduction noted in the present study is smaller compared with the available literature. Possible explanations for this discrepancy are likely to relate to the number of RFA procedures per nodule and the total energy delivered per procedure.

We did not find any factors correlating with volumetric reduction. In a study evaluating factors predictive of response to RFA, greater efficacy was present in smaller nodules ($\leq$12 mL).[6] There was no correlation between initial baseline sonographic characteristics of the nodule and the degree of final volume reduction.[6,13] However, in another study, factors related to superior response to RFA were initial solid component of 50% or less (compared with >50%) and smaller initial volume (0–10 mL compared with >10 mL).[15]

In the present series, we observed a substantial improvement in compressive symptoms and cosmetic concerns in all the patients during follow-up. Similarly, other studies reported progressive improvement in compressive symptoms (pressure in the neck, difficulty swallowing, and aesthetic concerns) 12 months after RFA.[7,8]

All patients treated with RFA maintained previously stable thyroid function, and for the patient with toxic adenoma, thyroid function normalized after RFA. By comparison, surgical therapy for nodular thyroid disease imposes a substantial risk of hypothyroidism. After thyroid lobectomy for benign thyroid disease, thyroid hormone replacement is required in approximately 15% to 20%.[16,17]

Regarding the safety of the procedure, RFA had a relatively benign adverse effect profile, also documented by others.[5,7,8,13-15] The only major adverse event was an episode of vasovagal reaction, as described earlier.

Surgical resection, the standard approach for nodules that are growing or causing symptoms, also has few undesirable effects to be considered. Lobectomy can pose a 1% to 2% risk of recurrent laryngeal nerve injury.[18-20] In addition, postsurgical scarring can be a cosmetic concern for some individuals. A variety of studies, all outside of North America, have compared surgery with RFA for treatment of TNs. One such study targeted patients with benign nodular goiters with cosmetic concerns, TN-related compressive symptoms, and thyrotoxicosis related to hyperfunctional nodules and showed that both procedures were effective in TN volume reduction (84.8%) at 12-month follow-up.[21] However, posttreatment hypothyroidism was completely avoided in the RFA group, and the incidence of complications (hoarseness, transient

hypoparathyroidism, hematoma, and nodule rupture) was significantly lower after RFA than after surgery (1.0% vs 6.0%).

We used general anesthesia, whereas other authors have described conscious sedation for dealing with the discomfort generated by the procedure. We targeted only large TNs, which takes a substantial amount of time in a sensitive location with critically important neurovascular structures within a few centimeters. Any patient movement could cause a major complication. The patient movement could be triggered by pain, anxiety, or other causes related to the procedure. We believe that for patient safety and comfort, general anesthesia has served us best. This might not apply to every center. We think this decision is best made by the physician performing the procedure based on experience, nodule location, size, intended therapeutic outcome, type of patient, and other local factors.

From a technical perspective, we also think that it is important to explore alternative electrodes, such as the 7-cm needle with a variety of active tip sizes (down to 5 mm), which could be more convenient for TN RFA.

From an economic perspective, the cost of RFA at Mayo Clinic is approximately 30% to 50% that of a lobectomy. None of the present patients underwent repeated RFA sessions, which would change the cost equation. By comparison, the cost of both procedures in the Chinese health care system was not significantly different.[21]

We recognize that the present study cohort is small. Additional data are needed to fully assess the utility of RFA in the US population because most published studies come from a handful of expert centers, mainly in Italy and South Korea. We know from the development of other thyroid procedures, eg, robotic thyroid surgery,[22] that the dissemination of these procedures in other populations has to be done carefully, studying the response of both patients and physicians to these new techniques. Although RFA has been studied in populations from Asia and Europe, there are variations in cultural norms regarding nonsurgical vs surgical procedures, medical support logistics, and potential differences in the pathogenesis of multinodular goiter related to the iodine status between those areas and the US population. These differences mandate that RFA be evaluated in the United States before deciding on its broad utilization in this country. To our knowledge, this is the first study to test the effectiveness and feasibility of RFA in the treatment of TNs in the United States. The population targeted herein was a select one: thyroid surgery either was contraindicated due to comorbidities or unacceptable perioperative risks or was refused by the patients; the patient with toxic adenoma declined treatment with radioactive iodine or surgery to avoid the risk of hypothyroidism and to avoid a surgical scar.

This study has several limitations: we treated a small population sample, followed them for relatively short-term to date (<6 months in 6 patients), and collected the data in a retrospective manner. Despite these limitations, the data seemed homogeneous regarding efficacy and safety, and patient satisfaction remained high based on the follow-up evaluation.

We have not studied the impact of multiple treatments on subsequent volume changes in this cohort. The criteria used for repeating RFA (up to 6 procedures in some patients) varied across different studies and included a remaining portion of the nodule on the follow-up ultrasound[13]; a volume-reduction ratio of less than 50%[13]; or if a patient noted incompletely resolved compressive symptoms.[15] In contrast, a prospective evaluation of the efficacy of additional RFA (a single session vs 2 monthly sessions) concluded that single-session RFA showed satisfactory volume reduction and clinical response in most patients.[23] Therefore, the indications for repeated RFA remain unclear.

In addition, we did not study regrowth of the treated nodules beyond this period of follow-up. The overall rate of regrowth and recurrence (defined as a >50% increase in nodule volume compared with previous ultrasound) has been reported to be 5.6% to 24.1%.[15,24] That study concluded that incompletely treated nodules may start to enlarge 1 to 2 years after ablation, an aspect that we plan to study in the coming years.

As discussed in multiple studies, patient selection for RFA is important. The technique requires a substantial amount of experience and expertise with specific training in this procedure. This is essential to replicate the results

in other practices, maintain efficacy of the procedure, while also keeping the adverse effects at an acceptably low rate. Some patients might not be good candidates for this procedure if ultrasonographic visualization of the nodule of interest is poor and access to the nodule cannot be achieved with ease. Combining the efficacy and safety data with patients' medical limitations and cultural preferences will be an ongoing process to understand the potential role of this procedure in US clinical practice as RFA evolves into an attractive approach for the therapy of large compressive or toxic TNs.

CONCLUSION

The present experience confirms that ultrasound-guided RFA is a clinically effective and safe outpatient treatment in patients with symptomatic or steadily growing benign, large, predominantly solid TNs, reproducing the experience generated in European and Asian studies. This procedure induces substantial volume reduction of TNs by approximately 45% at 3 to 6 months, alleviates compressive symptoms, and improves aesthetic appearance while preserving normal thyroid function. In centers with appropriate expertise, this technique could become an alternative for the management of benign large toxic and nontoxic TNs. Additional studies should be conducted in similar populations, with particular focus on factors predicting greater response to RFA, comparing the performance of RFA with other procedures, and timing of the additional RFA sessions.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CFD** = color flow Doppler; **IQR** = interquartile range; **RFA** = radiofrequency ablation; **SYS** = symptom score; **TN** = thyroid nodule

Potential Competing Interests: The authors report no competing interests.

Data Previously Presented: An abstract of this study was presented at the 86th Annual Meeting of the American Thyroid Association in Denver, CO, on September 22, 2016.

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