

# Factors Associated with the Efficacy of Radiofrequency Ablation in the Treatment of Benign Thyroid Nodules

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## ABSTRACT

**Background:** Minimally thermal treatments, including radiofrequency ablation (RFA), have been widely used for benign thyroid nodules (BTNs). However, factors related to the efficacy are not consistent among studies. Therefore, this study aimed to investigate factors associated with the efficacy and the risk of having multiple RFA sessions in the treatment of BTNs.

**Materials and methods:** We performed a retrospective study of 83 patients with 96 BTNs undergoing RFA from 2018 to 2019. Clinical and ultrasound evaluations were performed before and after RFA 1, 4, 10, and every 6 months afterward. Efficacy outcomes were volume reduction ratio (VRR), symptom and cosmetic scores, and the requirement of multiple RFA sessions.

**Results:** Female was predominant (86%) and the median age was 45 years. Most nodules were solid (64%) with a median volume of 3 mL. Two (2%) minor complications occurred and median time of follow-up was 17 months. The VRR reached to 56.7, 77, 89.4, and 92.8% at 4, 10, 16, and 22 months after the RFA, respectively. The symptom and cosmetic scores also significantly reduced. Multiple RFA sessions were required in 14 nodules (15%). Male had lower VRR of 5.59% than female, while mixed and cystic nodules had higher VRR of 4.88 and 12.7% compared with solid nodule. Larger nodule increased the risk of multiple RFA sessions.

**Conclusion:** Radiofrequency ablation is a safe and effective treatment for BTNs. Gender and solidity associate with VRR, but the large nodule is the risk factor of multiple sessions. More studies are required to reduce the risk of multiple RFA sessions.

**Keywords:** Goiter, Radiofrequency ablation, Thyroid nodule, Volume reduction ratio.

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## INTRODUCTION

Thyroid nodules are common all over the world. The prevalence of a palpable thyroid nodule is estimated as 3–7%, but base on ultrasonography (US), it is estimated that 20–76% of the general population could be detected as an incidental thyroid nodule.<sup>1</sup> Although >90% of thyroid nodules are benign,<sup>2</sup> they may pose several issues such as subjective symptoms, jugular oppression, cosmetic problems, and anxiety of malignant transformation, which affect patients' quality of life.<sup>1,3</sup> Therefore, many benign thyroid nodules (BTNs) require treatment. Previously, there were mostly two choices of treatments for BTNs: surgery and levothyroxine therapy. Currently, levothyroxine is no longer recommended as a single therapy as its modest efficacy but causing iatrogenic hyperthyroidism,<sup>4</sup> while surgery is limited because of its drawbacks such as a permanent scar, hypothyroidism, and the risk of injury to the recurrent laryngeal nerve.<sup>5</sup> In recent years, minimally thermal ablation therapies using radiofrequency, laser, and microwave energies have been widely used and have shown good results in the treatment of thyroid nodules.<sup>6–11</sup>

Among several thermal ablation techniques, radiofrequency ablation (RFA) is the most common use for BTNs in many countries. The advantages of RFA are the reduction of complications and hospital stay, preservation of thyroid function, and improvement of the quality of life, in the comparison with surgery.<sup>12,13</sup> Although the efficacy and safety of RFA have been reported quite consistently in the literature,<sup>7–9,11,14</sup> one of its disadvantages is the requirement of multiple RFA sessions. Some factors related to the efficacy of RFA in the treatment of thyroid nodules have been reported, including initial volume, US structure, and vascularity of the nodules,<sup>15–24</sup> but the data are limited and not consistent among studies. Therefore, we performed this study to investigate factors associated with the

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efficacy of RFA and the requirement of multiple RFA sessions to treat BTNs.

## MATERIALS AND METHODS

This is a retrospective study of all patients who underwent RFA for BTNs from July 2018 to August 2019 at the Thoracic Surgery Department of a tertiary medical center in Ho Chi Minh City, Vietnam.

The study was approved by the institutional ethics committee. The inclusion criteria were (1) evidence of BTN(s) by cytology using two separate US-guided fine-needle aspiration (US-FNA) biopsies and (2) undergoing RFA therapy to treat the nodule(s). We excluded all patients with (1) nodule that was suspicious of malignancy on US findings such as noticeable microcalcifications, marked hypoechoic, or ill-defined margins, and (2) previously undergoing other ablation therapy for thyroid nodule (e.g., microwave ablation).

### Radiofrequency Ablation Procedure

All patients underwent the RFA procedure in a supine position with mild extended neck in aseptic conditions, under US guidance. First, we performed local anesthesia at the puncture site and then dissected the thyroid gland and subcutaneous tissues using 10 mL of 1% lidocaine. Then, we inserted an 18-gauge internally cooled monopolar RFA electrode with 7-mm active tip into the thyroid nodule using the “trans-isthmus” approach to minimize the risk of injury to the recurrent laryngeal nerve.<sup>25,26</sup> The electrode was connected to a radiofrequency generator (Mygen V-1000, RF Medical Inc.) which could deliver up to 140-Watt power. In case of mixed or cystic nodule, we aspirated the whole internal fluid before ablation. We then performed the ablation using the “moving-shot” technique<sup>25,26</sup> with a 30–50-Watt power until the whole nodule became a transient hyperechoic zone. During the ablation, we paid attention to preventing the injury to the surrounding important structures, such as the laryngeal nerve, carotid vessels, esophagus, and trachea. After the procedure, patients were under observation for 1–2 hours and were discharged if having no severe pain or complications. Oral analgesic with acetaminophen was prescribed for three days.

### Assessment of Patients and Definition of Outcomes

Clinical and US evaluations were performed before and after the RFA 1, 4, 10, and every 6 months afterward. Clinical examinations included the evaluation of the symptom and cosmetic scores.<sup>26</sup> The symptom score was obtained from patients using a visual analog scale of 0 to 10 by asking the question “To what degree did the thyroid nodule(s) affect you in terms of cosmetic, functional, or psychological problem?”. Higher scores represent greater distress of patients by symptoms. The cosmetic score was evaluated by the doctor and had four grades: grade 0 was no palpable mass, grade I was a palpable but invisible mass, grade II was a visible mass when extending the neck or swallowing, and grade III was an easily visible mass. In the US examination, we evaluated the diameters, volume, echogenicity, solidity, number, location, and the signs of suspicious malignancy of the thyroid nodule(s). The volume of a nodule was calculated from the three orthogonal diameters using the equation  $V = \pi abc/6$  ( $V$  is the volume in mL;  $a$ ,  $b$ , and  $c$  are the three diameters in cm; and  $\pi$  is 3.14). The solidity of the nodules was classified into three categories: solid when the solid component was >75%; cystic when the solid component was <25%; and mixed was in-between.

Complications and side effects were assessed during and after the procedure and classified into minor and major complications as recommended by the international working group on image-guided tumor ablation.<sup>27</sup> A complication was classified as major if it led to increasing the level of care, caused substantial disability, or was fatal. Other complications were minor.

The efficacy of the RFA was mainly evaluated using the volume reduction ratio (VRR) of the treated thyroid nodule, which is the percentage of volume reduction during the follow-up period compared to the initial volume before ablation:

$VRR (\%) = 100\% \times (V_0 - V_x) / V_0$  (VRR: VRR in %;  $V_0$ : initial volume before ablation in mL;  $V_x$ : volume at follow-up in mL). Other parameters to evaluate the efficacy were the symptom and cosmetic scores, and the requirement of multiple RFA sessions. The indication of an additional RFA after the first ablation was a low VRR during the follow-up period (VRR was <25% at 1 month, or <50% at 6 months, or <75% at 12 months) in combination with an evidence of a viable portion inside the nodule on the US examination (same echogenicity with that nodule before any ablation, or the presence of vascularity inside the nodule).

### Statistical Analysis

Characteristics of the patients and all treated thyroid nodules were summarized by count and percentage for categorical variables, and median and interquartile range (IQR) for continuous variables. The efficacy outcomes (VRR and symptom and cosmetic scores) were reported before the RFA and at each time-point of follow-up using median and IQR. To find factors associated with the VRR, uni- and multivariable linear mixed-effects models were used to account for the correlated data from multiple nodules of a patient and repeated measurements of VRR for a nodule. We performed the univariable model for each factor of gender, age, time from diagnosis to the first RFA, comorbidities, initial volume and solidity of the nodule, and the requirement of multiple RFA sessions. A multivariable model including all of these co-variables was then performed. Results of the models were expressed by the mean difference (MD) of the VRR, 95% confidence interval (CI), and  $p$  value. In addition, we compared the characteristics of patients and nodules before ablation of the two groups (group required only one RFA session and group required multiple RFA sessions) using Fisher’s exact test for categorical variables and Mann–Whitney  $U$  test for continuous variables. Finally, a multivariable logistic regression model was used to find factors associated with the requirement of multiple RFA sessions. All  $p$  values were two-sided and  $p$  values of <0.05 defined statistical significance. All analyses were performed using the statistical software R version 3.6.3.

## RESULTS

### Patient’s Characteristics

A total of 83 patients with 96 BTNs were included in the study. Female was predominant (86%) and the median age was 45 years. The median time from thyroid nodule diagnosis to the first RFA was eight months. Seventeen patients (20%) had comorbidities with most were hypertension. Patients had high distress with a median symptom score of seven (IQR: 5–8). Regarding the cosmetic score, 59% of all patients had a visible mass: 21 cases (25%) with grade II and 28 cases (34%) with grade III. There were 13 patients (16%) with two treated nodules. All patients underwent a safe RFA procedure with only two (2%) minor complications occurred: one with small hematoma at the puncture site and the other with temporary voice change. Both recovered in 1 week after the procedure. The median time of follow-up was 17 months (Table 1).

### Nodule’s Characteristics

The median largest diameter and median volume of all treated thyroid nodules were 26 mm and 3 mL, respectively. The majority were isoechoic (61%) or spongiform (25%). There were 61 nodules (64%) classified as solid, 26 nodules (27%) as mixed, and 9 nodules (9%) as cystic. Most of the nodules required one RFA session, but 14 nodules (15%) required multiple sessions (Table 2).

**Table 1:** Clinical features of patients

	Summary statistic (N = 83)
Gender female	71 (86)
Age (years)	45 (36–54)
Time from diagnosis to first RFA (months)	8 (6–10)
Comorbidities	17 (20)
• Hypertension	16 (19)
• Diabetes	3 (4)
Symptom score	7 (5–8)
Cosmetic score	
• Grade 0	2 (2)
• Grade I	32 (39)
• Grade II	21 (25)
• Grade III	28 (34)
Number of treated nodules	
• 1 Nodule	70 (84)
• 2 Nodules	13 (16)
Complication	
• Major complications	0 (0)
• Minor complications	2 (2)
Follow-up period (months)	17 (15–22)

Summary statistic is the number of patients and percentage for categorical variables and median (interquartile range) for continuous variables RFA, radiofrequency ablation

**Table 2:** Characteristics of the treated thyroid nodules

	Summary statistic (N = 96)
Largest diameter (mm)	26 (18–36)
Volume (mL)	3 (1–10)
Echogenicity	
• Isoechoic	59 (61)
• Spongiform or partially cystic	24 (25)
• Hyperechoic	13 (14)
Solidity	
• Solid	61 (64)
• Mixed	26 (27)
• Cystic	9 (9)
Location	
• Right lobe	51 (53)
• Left lobe	45 (47)
Number of RFA sessions	
• 1 Session	82 (85)
• 2 Sessions	12 (13)
• 3 Sessions	2 (2)

Summary statistic is a number of patients and percentage for categorical variables and median (interquartile range) for continuous variables RFA, radiofrequency ablation

**Table 3:** Efficacy outcomes during the follow-up period

Outcome	Before RFA	1 Month	4 Months	10 Months	16 Months	22 Months
VRR (%)	–	37.1 (31.0; 43.5)	56.7 (50.1; 63.4)	77.0 (74.9; 78.9)	89.4 (84.2; 93.9)	92.8 (86.5; 96.7)
Symptom score	7 (5; 8)	4 (4; 5)	3 (2; 3)	2 (0; 2)	0 (0; 2)	0 (0; 0)
Cosmetic score	2 (1; 3)	1 (1; 2)	1 (1; 2)	1 (0; 1)	0 (0; 1)	0 (0; 0)

Summary statistic is median (interquartile range) RFA, radiofrequency ablation; VRR, volume reduction ratio

### Factors Related to the Efficacy Outcomes

Table 3 shows the efficacy of RFA in our study. The VRR increased during the follow-up period, reached to 37.1% (IQR: 31.0–43.5%) at 1 month, 56.7% (IQR: 50.1–63.4%) at 4 months, 77% (IQR: 74.9–78.9%) at 10 months, and approximately 90% at 16 and 22 months after the ablation. The symptom and cosmetic scores also significantly reduced and were nearly zero after 1 year.

In the univariable analyses, significant factors associated with the VRR were gender, comorbidities, initial volume and solidity of the nodules, and multiple RFA sessions. However, in the multivariable analysis, only gender and solidity of the nodules were associated with the VRR: male had lower VRR of 5.59% (95% CI: 0.64–10.54%) compared to female, and mixed and cystic nodules had higher VRR than solid nodule of 4.88 (1.02–8.75) and 12.7 (6.66–18.75) %, respectively (Table 4).

Compared to the group with one RFA session, the multiple RFA sessions group had a significantly longer time from diagnosis to the first RFA (median: 12 vs 8 months), higher symptom and cosmetic scores, significantly larger thyroid nodules with higher diameter (median: 48 vs 20 mm) and volume (median: 28 vs 2 mL) (Table 5). In the multivariable model, after correcting for time of diagnosis and solidity, initial volume of the treated nodules significantly increased the risk of requiring multiple RFA sessions [OR (95% CI): 1.23 (1.12–1.42)] (Table 6).

### DISCUSSION

This study shows the safety and efficacy of RFA in the treatment of BTNs. Only two minor complications occurred and no major complication was found. The volume of the nodules reduced by 37.1, 56.7, 77, and around 90% at 1, 4, 10, and ≥16 months after the ablation. We also found that gender male had lower VRR than female and more cystic of the nodules associated with the higher VRR during following up. There were 15% of cases requiring multiple RFA sessions and the initial volume of the nodules was the significantly associated factor: larger nodule leads to a higher risk of the requirement of multiple RFA sessions.

Radiofrequency ablation has been applied in the treatment of BTNs in many countries. Several studies have evaluated its efficacy and have shown that the volume reduction of treated nodules reached approximately >60% at 6 months, >70% at 12 months, and >80% at 24 months after the ablation.<sup>8,9,11,14</sup> The variation of the results between different studies might be due to different types and sizes of the nodules as well as a variety of instruments and techniques used. Our study showed similar results to others, of which the volume reduction increased rapidly within the first 4 months after the procedure and then steadily rose thereafter. The significant reduction of the nodule’s volume within the first 4 months helps to solve the clinical symptoms and cosmetic concerns of patients caused by the nodule(s), which is demonstrated in our study that the symptom and cosmetic scores significantly decreased after the ablation. In addition, RFA is safe as having a very low rate of complications, particularly while comparing with surgery.<sup>13,14</sup>

**Table 4:** Factors associated with volume reduction ratio

Factor	Univariable analysis			Multivariable analysis		
	MD	95% CI	p value	MD	95% CI	p value
Gender male	-5.78	-10.92; -0.65	0.029	-5.59	-10.54; -0.64	0.027
Age (per 1-year increase)	0.12	-0.02; 0.26	0.090	0.04	-0.15; 0.22	0.696
Time from diagnosis to first RFA (per 1-month increase)	-0.26	-0.70; 0.17	0.235	-0.09	-0.62; 0.43	0.724
Comorbidities (yes)	5.30	1.15; 9.44	0.014	4.53	-0.74; 9.80	0.093
Initial volume (per 1-mL increase)	-0.14	-0.26; -0.03	0.017	-0.10	-0.27; 0.07	0.250
Solidity						
• Solid	Ref	Ref	Ref	Ref	Ref	Ref
• Mixed	3.98	0.15; 7.81	0.044	4.88	1.02; 8.75	0.014
• Cystic	12.56	6.77; 18.36	<0.001	12.70	6.66; 18.75	<0.001
Multiple RFA sessions	-7.61	-12.00; -3.22	<0.001	-4.05	-10.41; 2.30	0.212

CI, confidence interval; MD, mean difference; Ref, reference

**Table 5:** Characteristics across groups regarding the number of microwave ablation compared sessions

Characteristic	1 RFA session (N = 82)	>1 RFA sessions (N = 14)	p value
Gender female	72 (88)	12 (86)	0.686
Age (years)	46 (36-56)	43 (40-52)	0.506
Time from diagnosis to first RFA (months)	8 (6-10)	12 (7-12)	0.014
Comorbidities	19 (23)	2 (14)	0.728
Symptom score	6 (5-7)	10 (9-10)	<0.001
Cosmetic score			<0.001
• Grade 0	2 (2)	0 (0)	
• Grade I	34 (41)	0 (0)	
• Grade II	26 (32)	1 (7)	
• Grade III	20 (24)	13 (93)	
Complication (yes)	2 (2)	0 (0)	1.000
Largest diameter (mm)	20 (18-30)	48 (40-54)	<0.001
Volume (mL)	2 (1-5)	28 (12-50)	<0.001
Echogenicity			0.537
• Isoechoic	52 (63)	7 (50)	
• Spongiform or partially cystic	19 (23)	5 (36)	
• Hyperechoic	11 (13)	2 (14)	
Solidity			0.814
• Solid	53 (65)	8 (57)	
• Mixed	21 (26)	5 (36)	
• Cystic	8 (10)	1 (7)	

Summary statistic is a number of nodules and percentage for categorical variables and median (interquartile range) for continuous variables. p values were calculated based on Fisher's exact test (categorical data) and Mann-Whitney U test (continuous data). RFA, radiofrequency ablation

Several potential complications of RFA are bleeding due to nodule rupture while performing the procedure, injury to the recurrent laryngeal nerve, or other important structures (carotid vessels, trachea, and esophagus), skin burn, and infection. Currently, with the support of US guidance and internally cooled technology, RFA can be performed safely. Major complications are infrequent and

**Table 6:** Factors associated with multiple RFA sessions

Factor	OR	95% CI	p value
Time from diagnosis to first RFA (months)	1.13	0.93; 1.37	0.185
Initial volume (per 1-mL increase)	1.23	1.12; 1.42	<0.001
Solidity			
• Solid	Ref	Ref	Ref
• Mixed	0.37	0.03; 2.69	0.371
• Cystic	0.10	0.01; 6.15	0.111

CI, confidence interval; Ref, reference

the rate of minor complications is almost <10%.<sup>8,9,11,14</sup> Currently, RFA and other minimally thermal ablations are applied for the treatment of papillary thyroid carcinoma as well.<sup>7</sup>

A problem of RFA is the requirement of multiple ablation sessions. The reason is that the volume is slowly reduced or even remained or increased during the follow-up period. This might be due to the incomplete ablation or different effects of RFA in different types of thyroid nodules. In our study, we found that gender and the initial solidity of nodules are significantly associated with the VRR. We could not explain why males had lower VRR than females, this may be because of the relatively small sample size that limits the generalization of this result, thus a larger study is needed to confirm this. However, the association between the solidity of thyroid nodules and VRR has been demonstrated in other studies.<sup>15-18,20-24</sup> The more cystic of the nodules leads to higher VRR, which is explained by the aspiration of cystic fluid inside the nodules during the RFA procedure. Although gender and solidity of the nodules were significantly associated with VRR, they showed no association with the risk of having multiple RFA sessions in our study. We found only one risk factor of having multiple RFA sessions which is the initial size of the nodules represented by the initial volume: larger nodule has a higher risk of having multiple RFA sessions. Some other studies showed similar results and the reason may be the incomplete ablation in the case of a large nodule.<sup>23,24</sup> This result would help clinicians to forecast the risk of multiple sessions before performing RFA to treat BTN.

Limitations of the study are the retrospective single-center design with relatively small sample size and the absence of histological confirmation of BTN which is similar to other



studies without surgery. However, we enrolled patients with the confirmation of benign nodules based on two separate US-FNA cytology results and no suspicion of malignancy on US findings. We also followed up with patients regularly and found no malignant nodules later on.

## CONCLUSION

Radiofrequency ablation is a safe and effective treatment for BTN. The median VRR of the treated nodules reached 56.7, 77, 89.4, and 92.8% at 4, 10, 16, and 22 months after the procedure. Both symptom and cosmetic concerns significantly improved accordingly, while no major complications occurred. We found that gender and solidity of the nodules were associated with VRR, but a large nodule increased the risk of having multiple RFA sessions. Future studies are required to better determine associated factors of the efficacy of RFA and reduce the risk of multiple RFA sessions.

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