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ORIGINAL RESEARCH

Efficacy and Safety of Radiofrequency Ablation for the Treatment of Autonomously Functioning Thyroid Nodules: A Long-Term Prospective Study

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Objective: This study aims to evaluate the efficacy and safety of RFA in the AFTN treatment after 2 years of follow-up and to find the factors related to treatment responses through TSH level and VRR.

Materials and Methods: This long-term prospective study was conducted from September 2017 to April 2021 on 17 AFTNs treated with RFA. Clinical evaluations, thyroid function tests, thyroid scintigraphy, and ultrasonography examinations were performed at 1 month, 3 months, 6 months, and 24 months after ablation. The primary endpoint was the success rate of RFA in restoring the euthyroidism stage after 24 months of follow-ups; secondary outcomes were VRR and improvements of US parameters, clinical examinations, and complications. The Spearman rank correlation test was used to determine related factors with treatment response variables.

Results: At the 24 months after the procedure, symptom score, cosmetic score, vascularity grade, and nodule volume significantly decreased. The VRR reduced approximately 42.77%, 63.13%, 78.3%, and 95.65% after 1 month, 3 months, 6 months, and 24 months follow-up. All 17 patients were restored euthyroid state without taking ATDs. No major complications were collected. The last TSH level was significantly correlated with the age of patients (Spearman rho = −0.637, p = 0.008). The VRR was significantly correlated with age of patients (Spearman rho = 0.566, p = 0.018) and initial TSH (Spearman rho = 0.485, p = 0.048).

Conclusion: RFA was demonstrated as a safe and effective option for AFTN treatment in long-term follow-up. It can be used as an alternative treatment with encouraging results.

Keywords: radiofrequency ablation, thyroid nodules, autonomously functioning thyroid nodule

Introduction

The autonomously functioning thyroid nodule (AFTN), the prevalence from 0.9% up to 9% of all thyroid nodules, is a predominantly benign neoplasm presenting as a solitary hyperfunctioning nodule, inside healthy thyroid parenchyma.[1,2] Because of the strong concentration of Iodine-131 or 99mTc used as a radiotracer (dose, 50 μCi of Iodine-131) by thyroid scintigraphy, it can be seen as a "hot spot", different from the surrounding thyroid tissue. AFTNs can cause functional abnormalities, from euthyroidism to subclinical hyperthyroidism (pre-toxic nodule) and overt hyperthyroidism (toxic nodule).[3] Thus, after confirming benign thyroid nodule(s), treatment decisions usually depend on the presence of nodule-related clinical hyperthyroidism symptoms, compressive and/or cosmetic issues.[4–8]

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In worldwide and Vietnam, anti-thyroid drugs (ATDs), thyroid lobectomy, or radioiodine (RI) treatment are preferred for treating AFTNs but both have limitations. ATDs decrease thyroid hormone production in the short term and are not effective in the long term.[9] The disadvantage of surgery is a high risk of general anesthesia, secondary hypothyroidism, and ugly scar. Using RI treatment often requires a second treatment session because of the higher risk of failure after the first session by large nodules. Also, young women of childbearing age and patients who can stand living with hypothyroidism may not be suitable with this therapy. In addition, another disadvantage is radiation exposure.[10–13]

In the last few years, radiofrequency ablation (RFA) has been rising from a new treatment way of symptomatic thyroid nodule(s) as a minimally invasive procedure. It has been used for the treatment of not only non-functional benign thyroid nodules but also AFTNs according to recent guidelines.[6,14,15] However, the efficacy of RFA on AFTNs is highly fluctuating in the rate of thyroid function normalization (24–82%) and in the volume reduction rate (VRR) >50%.[16–22]

In Vietnam, RFA has been applied for benign thyroid nodules since 2016. Thus, a few studies about the safety and efficacy of RFA for benign thyroid nodules were available and no study demonstrated its efficacy on AFTNs.[23,24] Therefore, our study aims to evaluate the efficacy and safety of RFA in the AFTN treatment after 2 years of follow-up and to find the factors related to treatment responses through TSH level and VRR.

Materials and Methods

Study Design and Patient's Selection

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Institutional Review Board of Bach Mai hospital and Hanoi Medical University, Hanoi, Vietnam approved this prospective study (number: 62720501) and written informed consent for RFA procedures for AFTN was signed by all patients.

Inclusion criteria included: (1) presence of an AFTN (as low serum TSH level and/or increased serum total triiodothyronine/free thyroxine (T3/FT4) levels and thyroid scintigraphy); (2) benign thyroid nodule(s) was confirmed by the sonographic result and two different times of US-guided fine-needle aspiration cytology (US-FNAc);[25] (2) restore euthyroid stage before RFA procedures; (3) refusal or had contraindications to do surgery or RI. This study was excluded if any of the following criteria were met: (1) high risk of malignant features of AFTNs during sonographic examination (according to ACR-TIRADS 4 to 5) or FNA cytology (according to Bethesda Class III to VI); (3) current severity of thyrotoxicosis or high risk of thyroid storm; (4) pregnancy; and (5) patients lost to follow-up.

From September 2017 to April 2021, 17 patients using RFA treatment were enrolled in this study.

Measurement and Assessment

Pre-Ablation Evaluations

Before the procedure, clinical examination, US, thyroid scintigraphy using Iodine-131 or 99mTc, 2 times of US-guided FNAc, and the laboratory studies were done. At the initial time, the compressive symptom was evaluated by asking patients via a visual analog scale (from 0 to 10), and a cosmetic score was followed as clinical examination: 1, no palpable mass; 2, a palpable mass but no cosmetic problem; 3, cosmetic problem on swallowing only; 4, readily detected cosmetic problem.[26] Only one radiologist with more than 5 years of US experience performed real-time ultrasonography (Voluson E8 Ultrasound System, GE Healthcare, USA) with an 8 to 12 MHz linear probe. Nodule(s) was assessed the position (left/isthmus/right lobe), size, solid/mixed echoic/cystic proportions, echogenicity, vascularity grade of thyroid nodules (according to a 5-point scale where no signal in the tumor, considering as grade 0; a few spotty signals in the tumor, considering as grade 1; signals in <25% of the tumor, considering as grade 2; signals from 25% to 50% of the tumor, considering as grade 3; and signals in >50% of the tumor, considering as grade 4)[17] and the volume of the AFTN was calculated using the formula: $V = \pi abc/6$ - where a, b, c are the 3 diameters, V is volume. Ultrasound-guided FNA was done by a licensed radiologist (TM Le) and pathologist with more than 5 years of experience. Thyroid function (thyroid-stimulating hormone (TSH), free thyroxine (FT4) level, and triiodothyronine (T3)) were obtained. The normal ranges of serum TSH, FT4, and T3 are 0.27–4.42 microIU/mL, 12–22 pmol/L, and 1.3–3.1 nmol/l, respectively. Before the RFA procedure, we explained this therapy carefully to each patient.

Radiofrequency Ablation Procedure

The same radiologist (TM Le) performed all the RFA procedures at the outpatient department of the Radiology Center, Bach Mai Hospital, Hanoi, Vietnam. After local anesthesia by injecting 2% lidocaine at the needle-puncture site and thyroid capsule with a supine position and mild neck extension, an 18 gauge internally

cooled electrodes (5mm, 7mm, or 10mm in active tips) connected to a radiofrequency generator (VIVA RF Generator, STARmed Co., Ltd., Korea) was used to puncture into the nodule under US guidance. Theoretically, AFTN was ablated by 2 basic techniques: the transisthmic approach and the moving-shot technique. To protect important structures, hydro-dissection by slowly injecting 5% dextrose was used in a few cases. AFTN was ablated completely when the transient hyperechoic zone was presented.[25–27] In the case of the predominantly solid nodule(s), the nodule was ablated after fluid aspiration. Patients were evaluated for complications and discharged after 60 minutes of follow-up without complications.

Follow-Up of the Patients

Patients were followed up at 1 month, 3 months, 06 months, and 24 months after the treatment session. US evaluation, thyroid function tests (TSH, FT4, and T3), thyroid scintigraphy (Iodine-131 or 99mTc), symptom score, and cosmetic score were evaluated at every visit time. On US re-examination, we evaluated changes in the nodular diameters, volume, and vascularity grade. VRR of the treated nodule was calculated based on the formula:

$$\text{VRR}(\%) = \frac{(\text{Baseline volume} - \text{posttreatment volume})}{\text{Baseline volume}} \text{ X100\%}$$

In thyroid scintigraphy evaluation, three categories of thyroid nodules were determined: hot nodule, considered as type 1; nodule takes up Iodine-131 or 99mTc similar to extra-nodular thyroid tissue, considered as type 2; and cold nodule or invisible status, considered as type 3.[17] If the nodule's portion with vascularity was detected on color Doppler ultrasound images and VRR is too small, additional treatment sessions should be considered because of the potential for regrowth. Also, specific complaints were recorded in the follow-up period.

Efficacy Outcome

Our primary endpoint was to evaluate the success rate of RFA in restoring the euthyroidism stage (clinical symptoms, serum TSH concentration, and scintigraphy evaluation) 24 months after the procedure. Secondary endpoints include VRR and improvements in vascularity grade on US, symptoms, and cosmetic scores.

Safety Outcome

Complications of RFA were followed as the recommendations of the international working group on image-guided tumor ablation.[28] Substantial morbidity and disability that increases the level of care, hospital admission, hemorrhage need a blood transfusion, and permanent voice change were considered major complications. Pain, transient voice change, vomiting, and skin burns were identified as minor complications.

Patient Characteristics and Other Factors

Patient information included age (continuous variable), sex (categorical variable: male and female), the severity of thyrotoxicosis symptoms (categorical variable: pretoxic nodule (subclinical hyperthyroidism), and toxic nodule (overt hyperthyroidism)). Treatment characteristics included ablation time (continuous variable: minute), RF power (continuous variable: Walt), and the number of RFA sessions (continuous variable).

Statistical Analysis

All statistical analyses were done using SPSS version 20.0 for Windows. Continuous variables were shown as means ± SD; categorical variables were calculated as frequencies or percentages. The number of RFA's complications and their percentage were calculated as the safety outcome. To evaluate the RFA efficacy, our purpose is to calculate the VRR, symptoms, and cosmetic scores during the follow-up period (1 month, 3 months, 6 months, and 24 months post-ablation) and to calculate the rate of patients who restored euthyroidism through serum TSH concentration in every follow-up period. To compare the changes in symptom score, cosmetic score, thyroid function tests (TSH, FT4, T3), nodule volume, largest diameter, VRR, and vascularity grade from the initial time to 1 month, 3 months, 6 months, and 24 months after the procedure, a general linear model with multiple repeated measurements was performed.

The relationship of patient's characteristics (age), nodular characteristics (position, initial volume, initial largest diameter, TSH, solid composition, cosmetic score, symptom score, and vascularity grade), and procedure's parameters (number of treatment session, RF power, and ablation time) with treatment response variables (TSH level and VRR) was calculated using the Spearman rank correlation test. Statistical significance was defined as p-value <0.05.

Results

From September 2017 to April 2021, 17 patients with 17 AFTNs were enrolled in this study.

Baseline Characteristics of the Patients and Nodules

The baseline demographic information of the patients and nodules are shown in Table 1. In this study, the patients were 15 women and 2 men, whose mean age was 46.47 ± 13.11 years (range 28–66). The mean symptom score, cosmetic score, and vascularity grade were 3.47, 3.59, and 3.12, respectively. At the pre-ablation time, the mean largest diameter AFTN was 38.59 ± 9.70 mm (range 22.0–55.0) with a mean volume of 13.07 ± 8.45 mL (range 2.2–35.5). Among the 17 treated thyroid nodules, there were 10 solid (58.8%) and 7 mix solid nodules (41.2%). Thyroid functions include mean concentrations of TSH, FT4, and T3 were 0.10 mUI/mL, 16.31ng/dL, and 2.59 nmol/l, respectively. Seven subjects had respectively toxic and others had pre-toxic nodules.

Table 1 Baseline Characteristics of the Patients and Nodules

Characteristics	Summary Statistics (N = 17)
Number of patients	17
Number of nodules	17
Age (years) [(mean ± SD) (range)]	46.47 ± 13.11 (28–66)
Female [n (%)]	15 (88.2)
Nodule position [n (%)]	
Left	9 (52.)
Isthmus	1 (5.9)
Right	7 (41.2)
Mean nodule volume (mL) [(mean ± SD) (range)]	13.07 ± 8.45 (2.2–35.5)
Mean largest nodule diameter (mm) [(mean ± SD) (range)]	38.59 ± 9.7 (22.0–55.0)
Internal nodule component [n (%)]	
Solid	10 (58.8)
Mix solid	7 (41.2)
FT4 (ng/dL) [(mean ± SD) (range)]	16.31 ± 5.79 (5.86–28.00)
T3 (nmol/L) [(mean ± SD) (range)]	2.59 ± 1.19 (1.21–5.70)
TSH (mIU/mL) [(mean ± SD) (range)]	0.10 ± 0.18 (0.005–0.69)
Toxic [n (%)]	7 (41.2)
Pretoxic [n (%)]	10 (58.8)
Vascularity grade [(mean ± SD) (range)]	3.12 ± 0.78 (2–4)
Cosmetic score [(mean ± SD) (range)]	3.59 ± 0.79 (1–4)
Symptom score [(mean ± SD) (range)]	3.47 ± 1.91 (0–6)

Abbreviations: SD, standard deviation; FT4, free thyroxine; TSH, thyroid-stimulating hormone; T3, triiodothyronine.

Characteristics of RFA Treatment and Complications

Table 2 shows our treatment characteristics and complications. 88.2% of patients had been treated by only one RFA session and others (11.8%) were used 2 RFA sessions. The ablation time and RF power ranged from 10 to 40 minutes (mean ± SD, 23.35 ± 8.81 minutes) and from 30 to 40 W (mean ± SD, 33.82 ± 4.85 W), respectively.

During RFA, slight pain and a heat sensation in the electrode puncture site that radiated to the chest and shoulder were reported in most patients. No major complications were collected.

The Treatment Efficacy and Its Related Factors

The treatment clinical outcomes and US evaluations are summarized in Figure 1A–F. At the 24 months after the procedure, symptom score, cosmetic score, and vascularity grade significantly decreased from 3.47 to 0.06 (symptom score), from 3.59 to 1.19 (cosmetic score), and from 3.12 to 0.12 (vascularity grade) with $p < 0.0001$. A significant decline of the mean largest diameter was observed from 38.59 ± 9.69 mm at an initial time, 31.41 ± 7.69 mm at 1-month post-ablation, 27.0 ± 8.4 mm at 3 months, 22.23 ± 6.35 mm at 6 months, and 12.47 ± 5.01 mm with $p < 0.0001$. The nodule volume ($p < 0.0001$) was seen rapid decrease from an initial time (13.07 ± 8.44 mL) to 1 month (7.3 ± 4.19 mL), 3 months (4.88 ± 3.34 mL), 6 months (2.75 ± 1.82 mL), and 24 months (0.498 ± 0.45 mL). This represents approximately 42.77%, 63.13%, 78.3%, and 95.65% of the VRR after 1 month, 3 months, 6 months, and 24 months follow-ups.

Table 2 Characteristics of Nodule Treatment

Characteristics	Summary Statistics (N = 17)
RFA session [n (%)]	
1 time	15 (88.2)
2 times	2 (11.8)
RF power (Walt) [(mean ± SD) (range)]	33.82 ± 4.85 (30–40)
Ablation time (minute) [(mean ± SD) (range)]	23.35 ± 8.81 (10–40)

Abbreviations: SD, standard deviation; RFA, radiofrequency ablation.

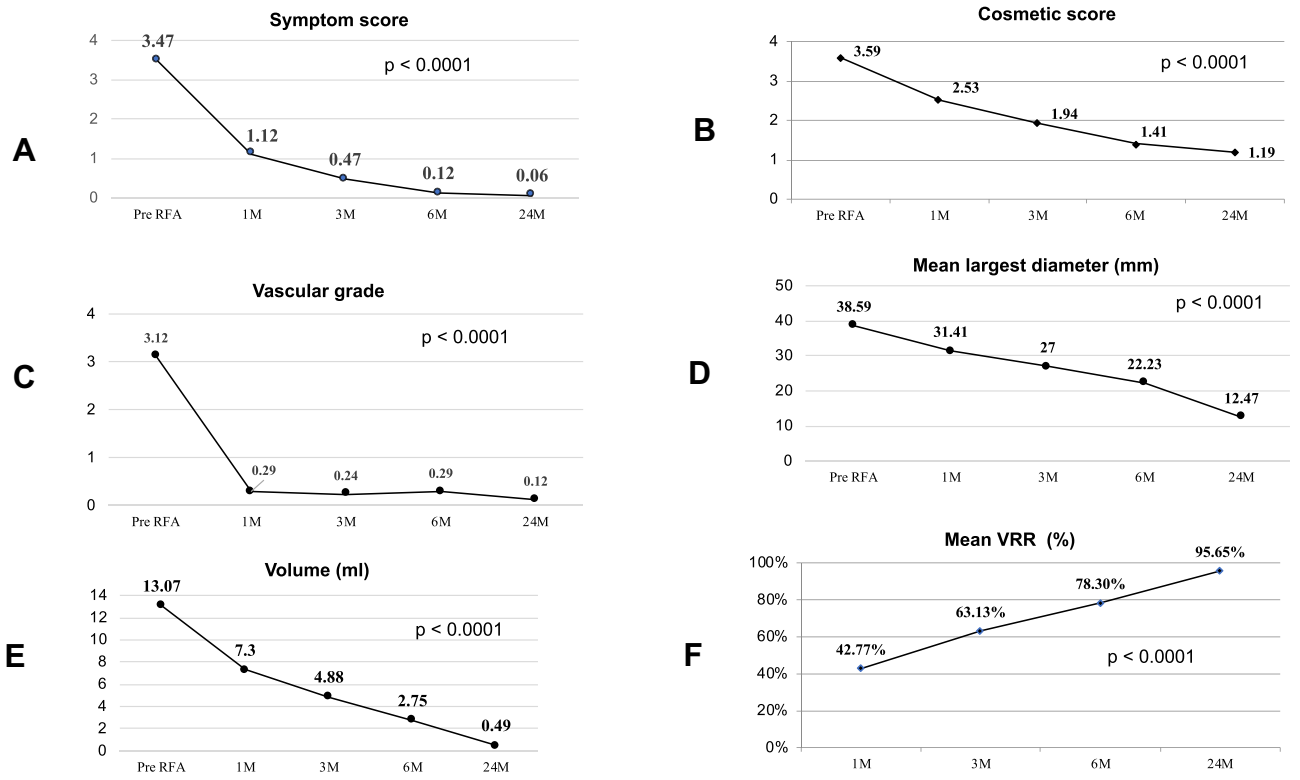

Figure 1 The treatment clinical outcomes and ultrasound evaluations. The symptom score (**A**), cosmetic score (**B**), and vascularity grade (**C**) significantly decreased. The mean largest diameter (**D**) and the nodule volume (**E**) were seen rapid decrease from an initial time to 24 months. This represents increase of the VRR (**F**) after 1 month, 3 months, 6 months, and 24 months follow-ups.

Figure 2A–C shows laboratory results in every period follow-up. A significant improvement of mean T3, FT4, and TSH was observed at the last follow-up. Mean TSH concentration increased from 0.101 mUI/mL to 1.69 mUI/mL. This represents the reduction of mean T3 post-ablation from 2.59 nmol/l at the initial time to 2.05 nmol/l at 24 months follow-up ($p < 0.05$). Especially, mean FT4 significantly decreased from initial to 3 months post-ablation before slightly increased at 6 months and 24 months post-ablation. All 17 patients were restored euthyroid state that was evaluated by serum TSH concentration and thyroid scintigraphy at the last time follow-up without taking ATDs.

Factors Affecting the Responses of Serum TSH and VRR

The last TSH level was significantly correlated with the age of patients (Spearman rho = −0.637, p = 0.008). In addition, the VRR was significantly correlated with age of patients (Spearman rho = 0.566, p = 0.018) and initial TSH (Spearman rho = 0.485, p = 0.048).

Other factors had no significant correlation with serum TSH and VRR in our study.

Representative Typical Cases

A 54-year-old woman complained about a left neck tumor, dysphagia, and hyperthyroidism symptoms. Thyroid ultrasonography showed a right solid nodule with the volume of approximately 6.7 mL (Figure 3A). Cosmetic score, symptom score, and vascularity grade (Figure 3B) were 4, 5, and 3, respectively. The pre-ablation sonographic images, thyroid scintigraphy (Figure 3C), thyroid function tests, and 2 times of US-FNAc show a benign right AFTN.

We applied RFA therapy by using 18 gauge internally cooled electrodes (7mm in active tips). The trans-isthmic approach and the moving-shot technique were used in our procedure.

After 24 months of follow-up, the VRR was relatively 98% and vascularity grade 1(Figure 3D and E). The cosmetic score and symptom score were an improvement. In thyroid scintigraphy, the hot nodule was not detected (Figure 3F).

Discussion

Benign thyroid nodule(s) is not a rare disease.[29] In contrast, AFTN's prevalence is scarce in clinical practice.[1,2] It can cause not only hyperthyroidism symptoms but also

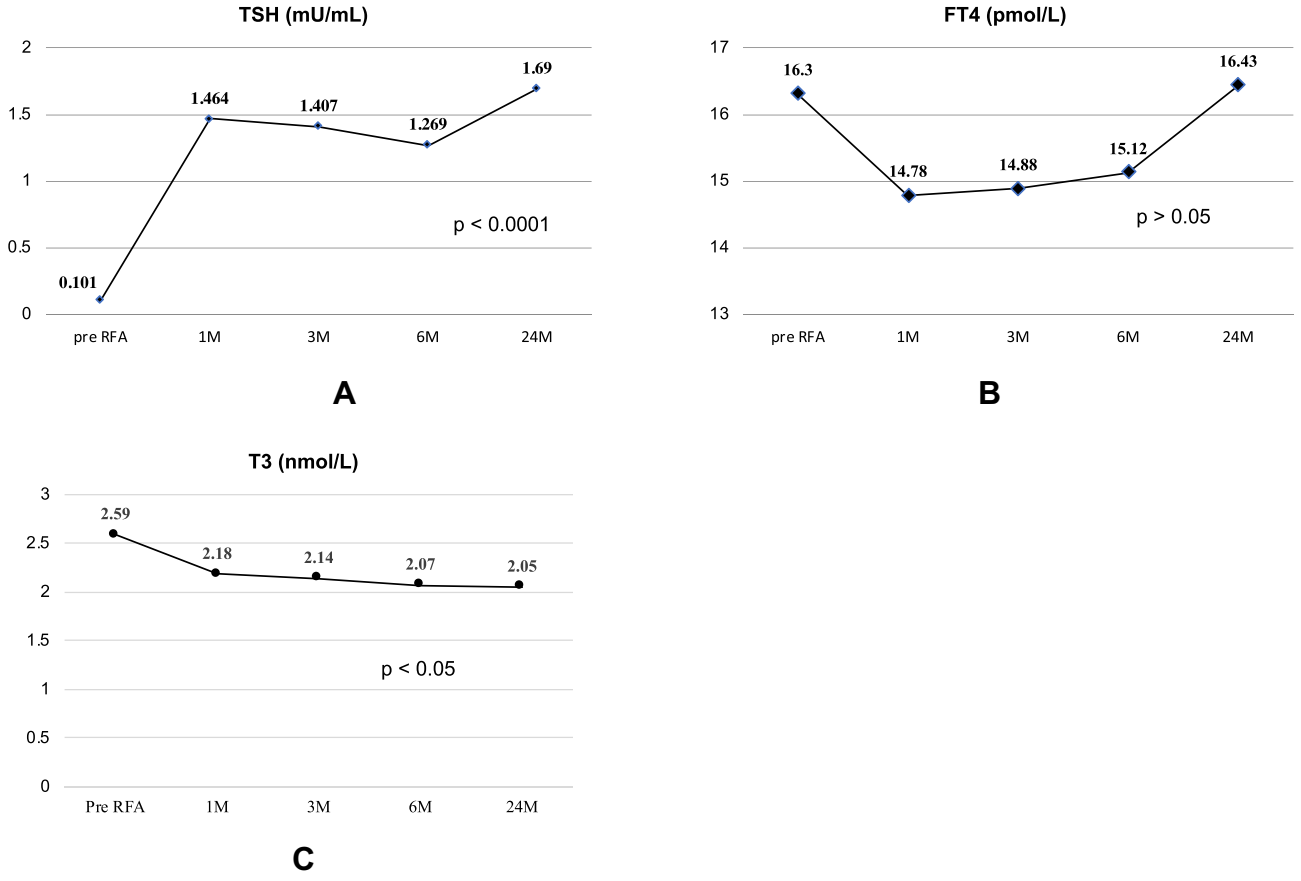

Figure 2 Laboratory results in every follow-up period from initial time to 24 months post-ablation. (**A–C**) A significant improvement of mean T3, FT4, and TSH was observed at the last follow-up.

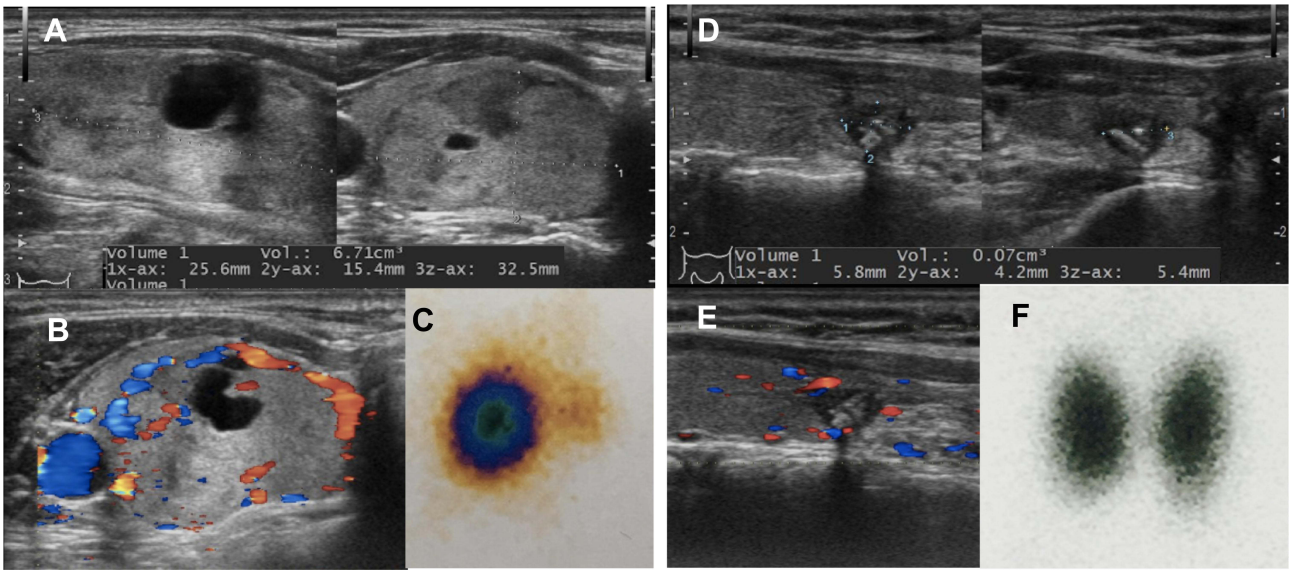

Figure 3 A 54-year-old woman presented with right neck bulging and hyperthyroidism symptoms who underwent radiofrequency ablation for AFTN treatment. (**A**) Initial volume of large thyroid nodule: 15x26x33mm, V~6.7mL. (**B**) Vascularity grade 2 in US. (**C**) At initial time, hot nodule presented in thyroid scintigraphy. (**D**) After 24 months ablation, VRR was 98%, (**E**) Vascularity grade 0. (**F**) Hot nodule was not totally detected in thyroid scintigraphy.

compressive and/or cosmetic problems. Thus, AFTN's treatment is required. Anti-thyroid drugs (ATDs), thyroid lobectomy, or radioiodine (RI) are the most conventional way for treatment but both of them have limitations.[10–13,30] Ethanol ablation and laser ablation have been demonstrated as effective and safe alternatives to traditional therapy for the treatment of AFTNs.[31–34] In addition, RFA has been accepted worldwide as a minimally invasive treatment of benign thyroid nodules including non-functioning nodules and AFTN. Like LA, RFA has proven to be a safe and effective option because of the precision in inducing a well-defined area of necrosis.[17,35]

In our study, the efficacy and safety of RF ablation for treating AFTN were demonstrated by the ability to restore the euthyroidism stage and VRR from our long-term study in 17 patients that were performed by only radiologist with 5 years of experience. At 1 month, 3 months, 6 months, and 24 months after RFA procedure, both of clinical expression (symptom score and cosmetic score), US evaluations (vascularity grade, largest diameter, nodule volume, and VRR), thyroid scintigraphy, and thyroid function test (TSH, FT4, T3) significantly improved. With efficacy in reducing nodule volume, VRR steadily increased in every follow-up period from 42.77% at one month, 63.13% at 3 months, 78.3% at 6 months, and 95.65% at 24 months post-ablation, respectively. This is in line with the previous findings, where it has been demonstrated that RFA can increase VRR from 33% to 54% after one month post-ablation and from 51% to 75% after six months.[16,17,19–21,36] However, our study showed somewhat superior results compared with other studies that showed 79–84% of VRR after two years of follow-up.[18,36] In addition, our study showed all 17 patients (100%) were restored euthyroidism state which normalized serum TSH and thyroid scintigraphy after 24 months post-ablation without taking ATDs. Also, a significant improvement of mean T3 and FT4 was observed at the last follow-up. Our study exhibited a greater achievement in the percentage of patients with thyroid function normalization than previous studies with 79–86% after 2 years after the procedure.[18,36] Some studies reported that a single RFA session normalized thyroid function in 33% at 3 months post-ablation, 43% at 6 months, and 40–50% at 12 months.[20] Different VRR and rate of thyroid function normalization can be attributed to the difference in the number of sessions performed, the difference in techniques and devices. There are two types of techniques and devices. The first is a fixed-needle technique and a multi-tined expandable electrode. The second is the moving shot technique and a straight type of internally cooled electrode.[16–18]

In our study, patients complained about slight transient pain and a heat sensation during the RFA procedure and no major complications occurred. This is consistent with other previous studies.[17,21] It is demonstrated that RFA is very safe for the treatment of AFTN with experienced radiologists.

Baek et al reported that the only factor affecting the treatment response was the tumor vascularity.[17] In our study, the last TSH level was significantly correlated with the age of patients. In addition, the VRR at 24 months after the procedure was significantly correlated with the age of patients and initial serum TSH concentration. Other factors had no significant correlation with serum TSH and VRR.

Besides RFA, LA and EA have also been introduced as minimally invasive treatments for AFTN. In the review of literature, RFA revealed similar or slightly superior results compared with those of LA (81.7% versus 44–81.9%), with the mean number of treatment sessions appears to be similar (1–2.2 in RF ablation versus 1–2.7 in LA).[21,31,32,37,38] EA has shown good results in normalization of the thyroid function (35.3–91.1%) for AFTN; however, the mean number of treatment sessions is much higher. In addition, the mean volume reductions of EA seem to be inferior to those of RF ablation (43.1–66% versus 52.1–81.7%).[16,17,31,33,34,39–42] With our results of VRR and rate of normalization of the thyroid function, RFA completely confirmed better results than LA and EA.

The strength of our study is the long-term duration of the follow-up period in 24 months. Thus, this study contributes more insights into efficacy and its related factor of RFA in treating AFTN. However, our study has several limitations. Firstly, a prospective study of a single medical center with relatively small sample size is the major limitation. Secondly, some variables including IAR were not collected. Finally, our study was not designed for comparison between RFA and other therapy.

In conclusion, the results of RFA demonstrated as an effective option in the improvement of thyroid function and clinical issues in long-term follow-up for AFTN treatment without major complications. The last TSH level was significantly correlated with the age of patients and the VRR at 24 months after the procedure was significantly correlated with the age of patients and initial serum TSH concentration.

Abbreviations

ACR-TIRADS, American College Of Radiology – Thyroid Imaging Reporting and Data Systems; AFTN, Autonomously

functioning thyroid nodule; CI, Confidence interval; EA, Ethanol ablation; FNA, Fine Needle Aspiration; FT4, Free Thyroxine; IAR, Initial ablation ratio; LA, Laser ablation; RFA, Radiofrequency ablation; RI, Radioiodine; SD, Standard deviation; T3, Triiodothyronine; TSH, Thyrotropin; VRR, Volume Reduction Rate; US, ultrasound.

Data Sharing Statement

Availability of data and materials supporting our findings will be shared upon request.

Ethics Approval and Consent to Participate

Written informed consent form was given to patients. Patients provided informed consent for the case details and any accompanying images to be published.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article was submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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