Original Investigation

Image-guided Thermal Ablation as a Promising Approach to Both Nontoxic and Toxic Autonomously Functioning Thyroid Nodules

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Rationale and Objectives: Although thermal ablation has been recommended as an alternative therapy option for autonomously functioning thyroid nodules (AFTN), current clinical evidence mainly focuses on toxic AFTN. This study aims to evaluate and compare the efficacy and safety of thermal ablation (percutaneous radiofrequency ablation or microwave ablation) in treating nontoxic and toxic AFTN.

Materials and Methods: AFTN patients who received a single session of thermal ablation with a follow-up period ≥12 months were recruited. Changes in nodule volume and thyroid function, and complications were evaluated. Technical efficacy was defined as the maintenance or restoration of euthyroidism with a volume reduction rate (VRR) ≥80% at the last follow-up.

Results: In total, 51 AFTN patients (age: 43.8±13.9 years, female: 88.2%) with a median follow-up period of 18.0 (12.0-24.0) months were included, where 31 were nontoxic (nontoxic group), and 20 were toxic (toxic group) before ablation. The median VRR was 96.3% (80.1%-98.5%) and 88.3% (78.3%-96.2%) in the nontoxic and toxic groups, respectively, and the respective euthyroidism rates were 93.5% (29/31, 2 evolved to toxic) and 75.0% (15/20, 5 remained toxic). The corresponding technical efficacy was 77.4% (24/31) and 55.0% (11/20, p=0.126). Except for one case of stress-induced cardiomyopathy in the toxic group, no permanent hypothyroidism or other major complications occurred in both groups.

Conclusion: Image-guided thermal ablation is efficacious and safe in treating AFTN, both nontoxic and toxic. Recognition of nontoxic AFTN would be helpful for treatment, efficacy evaluation, and follow-up.

KEY WORDS: Autonomously Functioning Thyroid Nodules; Hyperthyroidism; Radiofrequency Ablation; Microwave Ablation; Treatment Outcome.

Abbreviations: AFTN autonomously functioning thyroid nodules, **EZH1** enhancer of zeste homolog 1, **FNA** fine needle aspiration, **fT3** free triiodothyronine, **fT4** free thyroxine, **GNAS** adenylate cyclase stimulating G α-protein, **HIFU** high intensity focused ultrasound, **LA** laser ablation, **MWA** microwave ablation, **RFA** radiofrequency ablation, **RR** reference range, **TMNG** toxic multinodular goiter, **TA** thermal ablation, **TSH** thyroid-stimulating hormone, **TSHR** thyroid-stimulating hormone receptor, **Tg** thyroglobulin, **TgAb** anti-thyroglobulin antibody, **TPOAb** anti-thyroid peroxidase antibody, **TRAb** thyrotropin receptor antibody, **VRR** volume reduction rate

INTRODUCTION

Autonomously functioning thyroid nodules (AFTN) account for 5%–10% of thyroid nodules, and most of them exhibit a mutation in the thyroid-stimulating hormone receptor (TSHR) gene, the adenylate cyclase stimulating G α-protein (GNAS) gene, or the enhancer of zeste homolog 1 (EZH1) gene, which cause thyrocyte proliferation and thyroid hormone overproduction (1–5). AFTN represent the second most common cause of hyperthyroidism, manifesting as toxic multinodular goiter (TMNG) or toxic adenoma, while it is not uncommon for AFTN patients to present with euthyroidism (1,6–8).

The first-line treatments for toxic AFTN are surgery and radioiodine, which provide effective and definitive treatment

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(2). Nevertheless, some patients refuse these options or are contraindicated (2,7). This favors minimally invasive ultrasound-guided techniques, which include chemical ablation and thermal ablation (TA). Laser ablation (LA), high intensity focused ultrasound (HIFU), microwave ablation (MWA), and radiofrequency ablation (RFA), all of which belong to TA, are the techniques that have been studied previously and shown the benefit of volume reduction and euthyroidism restoration in the treatment of toxic AFTN (9,10). TA therefore has been recommended in different guidelines or consensuses for patients declining or who are contraindicated for surgery or radioiodine therapy (10-13). With the largest sample size of 361, the efficacy and safety of TA approaching toxic AFTN have been discussed previously (2,6,7,14,15). Nonetheless, the treatment outcomes of percutaneous RFA fluctuate across different studies, varying from 52.1% to 86.1% in the volume reduction rate (VRR) and 23% to 94.1% in the thyroid function normalization rate (6). Only one study has been conducted to examine the efficacy of percutaneous MWA in treating toxic AFTN with a VRR of 54.29% and euthyroidism restoration rate of 60.00% at the 6-month follow-up (14).

In addition, AFTN can present with a nontoxic status but may slowly progress into subclinical hyperthyroidism (pretoxic) and hyperthyroidism (toxic), at a rate of 4% per year, especially for older patients, nodules with a maximum diameter >3 cm, and for patients living in iodine-deficient areas (2,16,17). Intervention to prevent this progression might be beneficial, while the literature regarding TA treating nontoxic AFTN with normal thyroid-stimulating hormone (TSH) remains rare. The efficacy and safety of TA as a therapy option for these nontoxic AFTN patients and whether the thyroid function status will affect the efficacy are unknown.

The study aims to evaluate and compare the efficacy and safety of TA (percutaneous RFA or MWA) in treating nontoxic and toxic AFTN.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board (KY-Q-2021-231-01). Informed consent for reviewing the medical records was waived due to the study's retrospective nature. Before ablation, informed consent for TA was obtained from all the patients.

Patients

Patients who received a single session of TA (either percutaneous RFA or MWA) in a single tertiary referral center between April 2016 and September 2021 were chosen. The inclusion criteria were as follows: (i) patients suffered from overactive thyroid functional symptoms (heat intolerance, palpitation, hand tremor, increased appetite, weight loss, hyperactivity, etc.(18)), compressive symptoms, or cosmetic concerns; (ii) presented with AFTN confirmed by ^{99m}Tc pertechnetate scintigraphy showing "hot nodule", and either single nodule or multiple nodules confirmed by ultrasound; (iii) "benign" diagnoses in two separate fine needle aspiration (FNA) cytology tests; and (iv) received only one session of percutaneous RFA or MWA. The exclusion criteria were as follows: (i) patients presented with malignant ultrasonic features (19); (ii) incomplete preoperative data; (iii) AFTN could not be matched with the ablated nodules; and (iv) lost during follow-up or a follow-up period shorter than 12 months.

The patients were assigned to the nontoxic group or toxic group (both subclinical hyperthyroidism and hyperthyroidism, and those who needed antithyroid drugs to maintain euthyroidism) according to their respective thyroid function status.

Ultrasonic Evaluation

All nodules were evaluated by SonixSP (Ultrasonix Medical Corporation, Burnaby, Canada) ultrasound apparatus with a 10 MHz 38 mm linear array transducer before ablation. The composition (solid, mixed), maximum diameter (cm), and volume (cm3) of each nodule were recorded. The nodule volume was calculated by the formula $V=\pi abc/6$, where V represents volume, *a* means the largest diameter, and *b* and *c* are the two other orthogonal diameters.

Clinical Evaluation

Serum levels of TSH (reference range [RR]: 0.560-5.910 μIU/mL), free triiodothyronine (fT3, RR: 3.53-7.37 pmol/L), and free thyroxine (fT4, RR: 7.98-16.02 pmol/L) were tested by chemoluminescence immunoassay (Beckman Coulter, Inc., Chaska, USA). Electro-chemiluminescence immunoassay(Roche Diagnostics GmbH, Mannheim, Germany) was used to determine the serum levels of thyroglobulin (Tg, RR: 3.50-77.00 ng/mL), anti-thyroglobulin antibody (TgAb, RR: 0.00-115.00 IU/mL), anti-thyroid peroxidase antibody (TPOAb, RR: 0.00-34.00 IU/mL) and thyrotropin receptor antibody (TRAb, RR: 0.30-1.75 IU/L).

FNA Evaluation

Only patients with results of "benign (Bethesda II [20])" in two separate sessions of ultrasound-guided FNA cytology were qualified for ablation.

Ablation Procedure

Two same skilled endocrinologists performed all the ablation procedures. For nodules with mixed composition, the cystic fluid would be aspirated first, while for solid nodules, ablation was performed directly. The maximum ablation area was aimed to be achieved while avoiding damage to adjacent critical structures.

TA was performed with the patient supine and shoulders elevated with mild neck extension. Conscious sedation was

achieved through local ultrasound-guided 2% lidocaine injection. An RFA system (VRS01, STARmed, Seoul, Korea) and an internally cooled 18-gauge electrode with an active 7 mm tip (18-07s07F, STARmed, Seoul, Korea) were used. Also, an MWA system (MTC-3C, Weijing RAD Medical Center, Nanjing, China) and a distilled water-cooled shaft antenna with a 70 mm shaft and 1.6 mm tip (MTC-3CA-II 18, Weijing RAD Medical Center, Nanjing, China) were used. Under ultrasound guidance, the electrode or antenna was inserted into the thyroid nodule using the transisthmic approach, and the nodule was ablated with the "moving-shot" technique. After ablation, patients were required to be closely observed for 12-24 hours.

The ablation techniques, ablation proportion (%), rated power (W), and ablation duration (minutes) were recorded. The ablation proportion was calculated as the percentage taken up by the volume of the transient hyperechoic zones confirmed by ultrasound in the volume of the entire nodule.

Follow-up

The patients were assessed at 1 (V_{1m}), 6 (V_{6m}), and 12 (V_{12m}) months during the first year after ablation, and after that, they were followed once every six months. Changes in the maximum diameter of the nodule, nodule volume, and VRR (%) were recorded. VRR was calculated by the formula VRR= $[(V_0-V_n)/V_0]\times 100\%$, where V_0 represents the initial volume while V_n represents nodule volume at the visit. The TSH, fT3, fT4, Tg, TgAb, TPOAb, and TRAb levels were measured at every follow-up, and the thyroid function status was then categorized accordingly. Thyroid scan would be performed at 12 months after ablation, if available.

In line with the guideline, technical efficacy in this study was defined as the combined achievement of restoration or maintenance of normal thyroid function and VRR ≥80% after ablation at the last follow-up (10). The inefficacious treatment outcome was defined as either criterion being unmet, including completely inefficacious (neither criterion was met) and partly inefficacious (inefficacious in VRR or inefficacious in function).

Complication Assessment

Ablation-related complications were assessed and documented with the reporting standards of the Society of Interventional Radiology (SIR), where the major complication was defined as event leading to substantial morbidity and disability, while all other complications were considered minor (21).

Statistical Analysis

Normally distributed continuous variables are presented as the mean ± standard deviation (SD), while skewed distributed continuous variables are shown as the median and interquartile ranges (IQR). Categorical variables are reported as counts and percentages. Differences between the baseline and postoperative parameters were tested with the Wilcoxon signed-rank test. Differences in the status of euthyroidism were tested with McNemar's test (baseline vs. postablation) and with the Chi-square test (efficacious vs. inefficacious). The Mann-Whitney U test was used to compare within-group data (nontoxic vs. toxic, efficacious vs. inefficacious). The Friedman test was used to test the difference in the VRR and TSH levels between the different time points, and Post Hoc test was used to conduct pairwise comparisons with Bonferroni adjustment. All analyses were performed with SPSS (Version 26.0, Armonk, NY: IBM Corp), and a two-sided P value less than 0.05 was considered statistically significant.

RESULT

Baseline Clinical Characteristics

As demonstrated in Figure 1, 66 patients were chosen in total, 15 were excluded, and 51 were included in the final analysis. The median follow-up period was 18.0 (12.0-24.0) months, and the patients' baseline data and operational parameters are shown in Table 1. Of the included patients, 88.2% (45/51) were females, and the mean age was 43.8±13.9 years. The maximum diameter was 2.99±1.06 (range: 0.936-5.533) cm, and the median nodule volume was 5.55 (2.25-10.58) cm3. Forty-four (86.3%) patients received RFA, seven (13.7%) received MWA, and the median ablation proportion was 90.0% (90.0%-95.0%).

Before ablation, 31 (60.78%) patients were nontoxic (nontoxic group); 20 (39.22%) were toxic (toxic group, six toxic and 14 pretoxic, one toxic adenoma, and the rest were TMNG). A total of 15.0% (3/20) of the patients received antithyroid drug therapy in the toxic group before ablation. In addition to higher TSH levels ($p<0.001$), the nontoxic group had a smaller maximum diameter and nodule volume [2.69±1.03 cm vs. 3.46±0.93 cm, $p=0.008$, 4.72 (1.47-8.28) cm3 vs. 8.10 (4.35-13.85) cm3, $p=0.014$] than the toxic

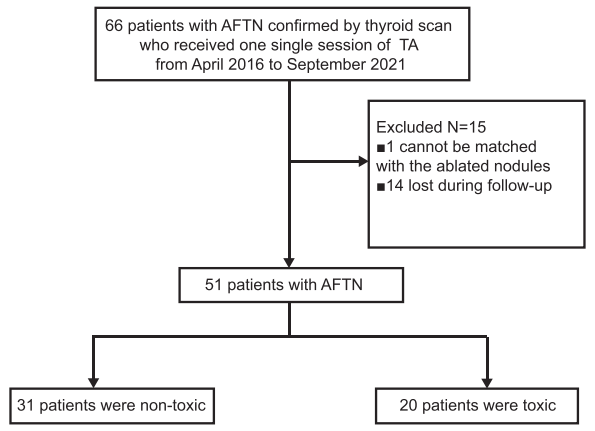

Figure 1. Flowchart demonstrating the patients inclusion process. AFTN: autonomous functioning thyroid nodules; TA: thermal ablation.

TABLE 1. Baseline Clinical Statistics, Operational Parameters and Postoperative Data

		Nontoxic (N = 31)		Toxic (N = 20)		Total (N = 51)	
		Baseline	The last visit	Baseline	The last visit	Baseline	The last visit
Age (y)		43.0±14.2	-	45.1±13.7	-	43.8±13.9	-
Gender (N, %)	Male	5 (16.1)	-	1 (5.0)	-	6 (11.8)	-
	Female	26 (83.9)	-	19 (95.0)	-	45 (88.2)	-
Nodule composition (N, %)	Solid	21 (67.7)	-	11 (55.0)	-	32 (62.7)	-
	Mixed	10 (32.3)	-	9 (45.0)	-	19 (37.3)	-
Maximum diameter (cm) [a,c,d,e]		2.69±1.03	1.18±0.95	3.46±0.93	1.65±0.92	2.99±1.06	1.37±0.96
Nodule volume (cm3) [a,c,d,e]		4.72 (1.47-8.28)	0.19 (0.03-1.02)	8.10 (4.35-13.85)	1.28 (0.13-1.91)	5.55 (2.25-10.58)	0.53 (0.05-1.75)
Elevated Tg (N, %) [d,e,f]		13 (41.9)	2 (6.5)	9 (45.0)	2 (10.0)	22 (43.1)	4 (7.8)
Positive TgAb (N, %) [f]		2 (6.5)	3 (9.7)	3 (15.0)	4 (20.0)	5 (9.8)	7 (13.7)
Positive TPOAb (N, %) [f]		1 (3.2)	4 (12.9)	3 (15.0)	4 (20.0)	4 (7.8)	8 (15.7)
Positive TRAb (N, %) [f]		0 (0.0)	3 (9.7)	0 (0.0)	1 (5.0)	0 (0.0)	4 (7.8)
fT3 (pmol/L) [d,e]		5.21 (4.78-5.67)	5.08 (4.53-5.50)	5.71 (4.73-6.72)	5.33 (4.56-5.62)	5.40 (4.78-5.94)	5.10 (4.56-5.56)
fT4 (pmol/L) [b]		11.39 (10.37-12.22)	11.64 (10.40-12.30)	10.61 (9.49-12.96)	10.43 (9.50-11.68)	11.05 (10.16-12.48)	11.11 (10.06-12.01)
TSH (μIU/mL) [a,b,c,d,e]		0.914 (0.647-1.230)	1.355 (1.159-1.605)	0.185 (0.015-0.300)	0.858 (0.571-1.608)	0.630 (0.278-1.038)	1.270 (0.831-1.605)
Ablation technique (N, %)	RFA	26 (83.9)	-	18 (90.0)	-	44 (86.3)	-
	MWA	5 (16.1)	-	2 (10.0)	-	7 (13.7)	-
Ablation proportion (%)		90.0 (90.0-95.0)	-	90.0 (90.0-95.0)	-	90.0 (90.0-95.0)	-
Rated power (W)		35.0 (30.0-35.0)	-	32.5 (30.0-35.0)	-	35.0(30.0-35.0)	-
Ablation duration (mins)		9.8 (4.3-22.0)	-	16.9 (10.8-20.9)	-	15.3 (5.1-21.3)	-
Follow-up period (months)		-	18.0 (12.0-21.0)	-	20.5 (12.3-34.0)	-	18.0 (12.0-24.0)
Euthyroidism (N, %) [c,e]		31 (100.0)	29 (93.5)	0 (0.0)	15 (75.0)	31 (60.8)	44 (86.3)
Subclinical hyperthyroidism (N, %)		0 (0.0)	2 (6.5)	14 (70.0)	5 (25.0)	14 (27.5)	7 (13.7)
Hyperthyroidism (N, %)		0 (0.0)	0 (0.0)	6 (30.0)	0 (0.0)	6 (11.8)	0 (0.0)
VRR (%)		-	96.3 (80.1-98.5)	-	88.3 (78.3-96.2)	-	92.6 (78.3-98.2)
Technical efficacy (N, %)		-	24 (77.4)	-	11 (55.0)	-	35 (68.6)

a The comparisons of baseline maximum diameter (p=0.008), nodule volume (p=0.014) and TSH level ($p<0.001$) were significant between nontoxic and toxic patients.

b The comparisons of fT4 level (p=0.019) and TSH level (p=0.02) after ablation were significant between nontoxic and toxic patients.

c The comparisons of maximum diameter ($p<0.001$), nodule volume ($p<0.001$), TSH level ($p<0.001$) and euthyroidism status ($p<0.001$) were significant between baseline and postabaltion data in the toxic group.

d The comparisons of maximum diameter ($p<0.001$), nodule volume ($p<0.001$), Tg elevation (p=0.003), fT3 level (p=0.021) and TSH level (p=0.002) were significant between baseline and postabaltion data in the nontoxic group.

e The comparisons of maximum diameter ($p<0.001$), nodule volume ($p<0.001$), Tg elevation ($p<0.001$), fT3 level (p=0.009), TSH level ($p<0.001$) and euthyroidism status (p=0.002) were significant between baseline and postabaltion data in the whole cohort.

f N represents the number of patients recognizing as elevated/positive in respective parameters, whose respective parametric levels were greater than the corresponding upper limits of reference range.

Tg, thyroglobulin; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody;fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; VRR, volume reduction rate; RFA, radiofrequency ablation; MWA, microwave ablation.

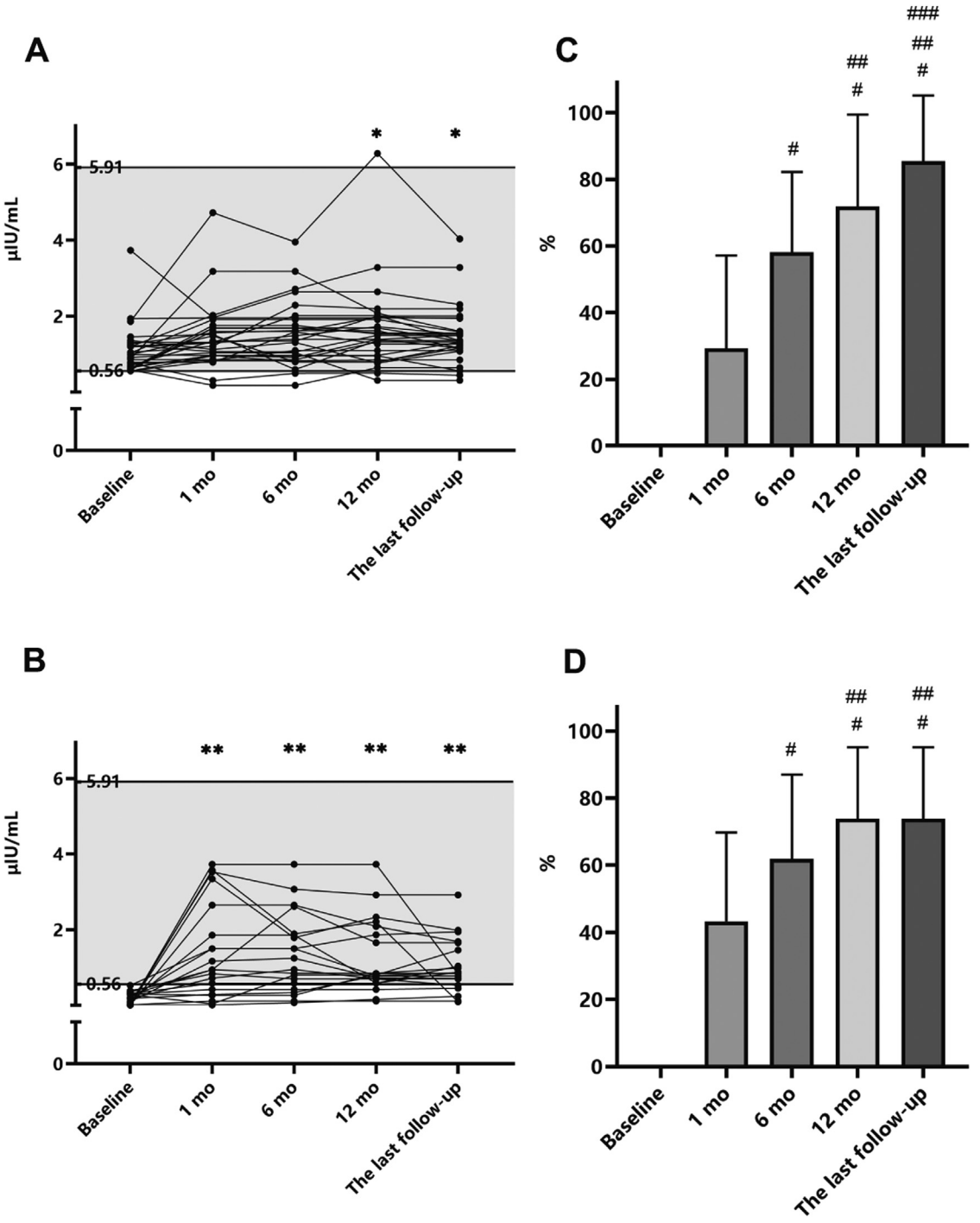

Figure 2. Changes of TSH level and VRR at baseline and in every follow-up[a]. a: The changes of VRR and TSH level ($p<0.001$) were significant across different time points. A: Changes of TSH level across different time points of follow-up in the nontoxic group; B: Changes of TSH level across different time points of follow-up in the toxic group; C: Changes of VRR across different time points of follow-up in the nontoxic group; D: Changes of VRR across different time points of follow-up in the toxic group. *: $p<0.05$ compared to baseline in the nontoxic group (A). **: $p<0.001$ compared to baseline in the toxic group (B). #: $p<0.001$ compared to baseline in the nontoxic group (C); $p<0.001$ compared to baseline in the toxic group (D). ##: $p<0.001$ compared to V_{1m} in the nontoxic group (C); $p<0.05$ compared to V_{1m} in the toxic group (D). ###: $p<0.001$ compared to V_{6m} in the nontoxic group (C). Data about 50, 28 and 32 patients were available at the V_{1m}, V_{6m}, and V_{12m}, respectively and the missing data were replaced by the last available value. The two horizontal solid lines and middle light grey area signify the normal reference range of TSH levels (0.56-5.91 μIU/mL). VRR: volume reduction rate; TSH: thyroid-stimulating hormone.

group. The other baseline and operational parameter comparisons between these two groups were not significant.

Treatment Outcomes

The postoperative data are shown in Table 1, and the VRR and TSH level changes are shown in Figure 2.

In the nontoxic group, none of the patients became hypothyroid at the last visit, and 93.5% (29/31) of the patients showed preservation of euthyroidism. Two (6.5%) patients, each became pretoxic at V_{1m} and V_{12m}, respectively, which lasted until the last visit, while another one patient became pretoxic at V_{1m} and regained euthyroidism at V_{12m}. The change in thyroid function status at the last follow-up was not significant compared to baseline (p=0.492), whereas the TSH level increased significantly since V_{12m} (p=0.001, Fig 2A). The decline in the nodule volume was significant (p<0.001), which decreased from 4.72 (1.47-8.28) cm3 to 0.19 (0.03-1.02) cm3. The increment of VRR across different time points was also significant (p<0.001), where the VRR was significantly elevated compared to the baseline at V_{6m}, V_{12m}, and the last visit (Fig 2C). The median VRR in this group at the last visit was 96.3% (80.1%-98.5%), and the percent of patients with VRR ≥ 80% and technical efficacy were both 77.4% (24/31).

In the toxic group, the rise in TSH level was significant at different time points compared to the baseline (p<0.001, Fig 2B), at the last visit, 75.0% (15/20) of the patients became euthyroid, and thyroid function normalization was significant compared to baseline (p<0.001). Anti-thyroid drug therapy was withdrawn in 66.7% (2/3) of the patients at V_{1m} and was unchanged in the rest one patient. The mean nodule volume decreased significantly from 8.10 (4.35-13.85) cm3 to 1.28 (0.13-1.91) cm3 (p<0.001). The VRR increment across different time points reached statistical significance (p<0.001) as well, and the VRR was significantly increased compared to baseline at V_{6m}, V_{12m}, and the last visit (Fig 2D). The median VRR at the last follow-up was 88.3% (78.3%-96.2%) and 70.0% (14/20) of the patients had a VRR ≥ 80%. Technical efficacy was achieved in 55.0% (11/20) of the patients.

When comparing treatment outcomes between these two groups at the different time points, as illustrated in Table 2, differences of maximum diameter and nodule volume after ablation, VRR, TSH level, and technical efficacy were not significant (p>0.05), but a more favorable trend was noted in the nontoxic group. At the last follow-up, higher TSH and fT4 levels in the nontoxic group were noted (p<0.05).

At the last follow-up, the overall nodule volume decreased significantly from 5.55 (2.25-10.58) cm3 to 0.53 (0.05-1.75) cm3 (p<0.001). There were 86.3% (44/51) of patients being euthyroid (p=0.002), and 7 (13.7%, 2 in the nontoxic group and 5 in the toxic group) patients being toxic and there was no hypothyroid patient. The technical efficacy was 68.6% (35/51) in the whole cohort. Typical thyroid scan images before and after ablation are presented in Supplementary Figure 1.

TABLE 2. Comparison of Treatment Outcomes Between Nontoxic and Toxic Patients With AFTN

	Baseline			V_{1m}			V_{6m}			V_{12m}			The last visit		
	Nontoxic	Toxic	p Value	Nontoxic	Toxic	p Value	Nontoxic	Toxic	P Value	Nontoxic	Toxic	P Value	Nontoxic	Toxic	P Value
Maximum diameter (cm)	2.69±1.03	3.46±0.93	**0.008**	2.27±0.88	2.69±1.08	0.154	1.94±0.99	2.22±0.93	0.298	1.58±1.08	1.91±0.90	0.249	1.18±0.95	1.65±0.92	0.091
Nodule volume (cm3)	4.72 (1.47-8.28)	8.10 (4.35-13.85)	**0.014**	2.04 (0.91-5.38)	4.68 (2.71-6.35)	0.165	1.44 (0.23-3.87)	2.50 (0.81-5.46)	0.280	0.53 (0.09-3.14)	1.67 (0.30-3.08)	0.183	0.19 (0.03-1.02)	1.28 (0.13-1.91)	0.076
VRR (%)	0	0	1.000	33.1 (1.9-49.6)	34.5 (27.3-59.2)	0.210	53.2 (42.3-79.4)	63.4 (35.2-83.7)	0.643	82.0 (50.3-96.2)	73.5 (61.3-91.7)	0.847	96.3 (80.1-98.5)	88.3 (78.3-96.2)	0.847
TSH (μIU/mL)	0.914 (0.647-1.230)	0.185 (0.015-0.300)	**<0.001**	1.314 (0.970-1.694)	0.946 (0.324-2.451)	0.239	1.396 (0.920-1.911)	1.100 (0.464-1.883)	0.307	1.500 (0.958-1.980)	0.796 (0.618-2.034)	0.090	1.355 (1.159-1.605)	0.858 (0.571-1.608)	**0.020**
Technical efficacy (N, %)	0 (0.0)	0 (0.0)	/	0 (0.0)	2 (10.0)	0.165	7 (22.3)	6 (30.0)	0.750	16 (51.6)	7 (35.0)	0.253	24 (77.4)	11 (55.0)	0.064
Follow-up period (months)	-	-	/	-	-	/	-	-	/	-	-	/	18.0 (12.0-21.0)	20.5 (12.3-34.0)	0.258

Data about 50, 28 and 32 patients were available at the V_{1m}, V_{6m}, and V_{12m}, respectively and the missing data were replaced by the last available value.
AFTN, autonomously functioning thyroid nodules; V_{1m},V_{6m}, and V_{12m}: visit at the 1-month, 6-month, 12-month after ablation; TSH, thyroid-stimulating hormone; VRR, volume reduction rate.

TABLE 3. Comparison Between Technically Efficacious and Inefficacious Treatment Outcomes

		Nontoxic		*p* Value	Toxic		*p* Value	Overall		*P* Value
		Technically efficacious (N = 24)	Inefficacious (N = 7)		Technically efficacious (N = 11)	Inefficacious (N = 9)		Technically efficacious (N = 35)	Inefficacious (N = 16)	
Age (y)		36.0±13.7	54.0±12.9	0.065	45.0±15.1	43.0±12.3	0.570	41.3±14.0	51.0±12.4	0.053
Gender (N, %)	Male	2 (8.3)	3 (42.9)	0.062	1 (9.1)	0	1.000	3 (8.6)	3 (18.8)	0.360
	Female	22 (91.7)	4 (57.1)		10 (90.9)	9 (100)		32 (91.4)	13 (81.3)	
Nodule composition (N, %)	Solid	15 (62.5)	6 (85.7)	0.379	5 (45.5)	6 (66.7)	0.406	20 (57.1)	12 (75.0)	0.350
	Mixed	9 (37.5)	1 (14.3)		6 (54.5)	3 (33.3)		15 (42.9)	4 (25.0)	
Euthyroidism (N, %)		24 (100.0)	7 (100)	/	0 (0.0)	0 (0.0)	/	24 (68.6)	7 (43.8)	0.126
Maximum diameter (cm)		2.73±0.99	3.75±1.12	0.236	3.36±0.83	3.47±1.09	0.882	2.87±1.04	3.26±1.07	0.231
Nodule volume (cm3)		3.53 (1.01-6.39)	10.27 (1.97-14.46)	**0.033**	9.05 (3.96-14.16)	7.03(4.31-13.05)	0.710	4.90 (2.12-8.28)	9.70 (6.56-9.25)	0.059
Elevated Tg (N, %)[a]		9 (37.5)	4 (57.1)	0.413	5 (45.5)	4 (44.4)	1.000	14 (40.0)	8 (50.0)	0.554
Positive TgAb (N, %)[a]		1 (4.2)	1 (14.3)	0.406	1 (9.1)	2 (22.2)	0.566	2 (5.7)	3 (18.8)	0.309
Positive TPOAb (N, % [a]		1 (4.2)	0 (0.0)	1.000	1 (9.1)	2 (22.2)	0.566	2 (5.7)	2 (12.5)	0.581
Positive TRAb (N, %)[a]		0 (0.0)	0 (0.0)	/	0 (0.0)	0 (0.0)	/	0 (0.0)	0 (0.0)	/
fT3 (pmol/L)		5.45 (4.81-5.72)	4.9 2(4.49-5.06)	0.167	5.76 (5.10-7.51)	5.66 (4.61-6.64)	0.656	5.51 (4.88-5.86)	4.99 (4.59-6.27)	0.388
fT4 (pmol/L)		11.74 (10.61-12.65)	10.49 (9.76-11.05)	**0.048**	10.46 (9.33-12.78)	10.64 (9.40-18.65)	0.603	11.41 (10.21-12.77)	10.62 (9.8-11.79)	0.287
TSH (μIU/mL)		0.867 (0.634-1.221)	1.200 (0.770-1.933)	0.216	0.190 (0.060-0.283)	0.180 (0.010-0.347)	0.882	0.647 (0.283-1.038)	0.460 (0.056-1.129)	0.356
Ablation technique	RFA	20 (83.3)	6 (85.7)	1.000	10 (90.9)	8 (88.9)	1.000	30 (95.7)	14 (87.5)	1.000
	MWA	4 (16.7)	1 (14.3)		1 (9.1)	1 (11.1)		5 (14.3)	2 (12.5)	
Ablation proportion (%)		92.5 (90.0-98.8)	90.0 (80.0-95.0)	0.317	90.0 (90.0-95.0)	90.0 (87.5-99.0)	0.824	90.0 (90.0-95.0)	90.0 (85.0-97.3)	0.509
Rated power (W)		35.0 (30.0-35.0)	35.0 (32.5-35.0)	0.473	32.5 (30.0-35.0)	35.0 (30.0-35.0)	0.456	32.5 (30.0-35.0)	35.0 (30.6-35.0)	0.278
Ablation duration (mins)		8.5 (3.5-19.3)	21.4 (14.0-27.5)	0.054	17.2 (13.7-22.0)	15.2 (9.2-18.3)	0.370	12.0 (4.6-21.0)	18.2 (9.4-21.7)	0.361
VRR (%)		97.4 (90.5-99.1)	60.2 (36.0-70.1)	<**0.001**	89.7 (85.8-96.5)	78.3 (61.1-96.8)	0.095	96.5 (87.2-98.5)	71.2 (48.1-78.3)	<**0.001**

a N represents the number of patients recognizing as elevated/positive in respective parameters, whose respective parametric levels were greater than the corresponding upper limits of reference range.

Tg, thyroglobulin; TgAb, anti-thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody;fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; VRR, volume reduction rate; RFA, radiofrequency ablation; MWA, microwave ablation.

Comparison Between Technically Efficacious and Inefficacious Treatment Outcomes

As demonstrated in Table 3, the differences in the baseline data and operational parameters between the patients with technically efficacious and inefficacious treatment outcomes were not significant ($p>0.05$). However, a smaller baseline nodule volume was found in the patients of the nontoxic group with technical efficacy ($p=0.033$). In addition, the total technical efficacy for percutaneous RFA and MWA was 68.2% (30/44) and 71.4% (5/7), respectively ($p=1.000$).

At the last visit, 31.6% (16/51) of the patients did not achieve technical efficacy. However, only two patients (6.5% and 10.0%, respectively) in each group were completely inefficacious. There were 16.3% (5/31) and 20.0% (4/20) of patients inefficacious in VRR in the nontoxic and toxic groups, respectively, and 15.0% (3/20) of the patients inefficacious in function in the toxic group. The median VRR of these 16 patients at the last follow-up was 71.2% (range:26.3%-99.3%). Concrete treatment outcomes are illustrated in Figure 3.

There were 13.7% [7/51, 6.5% (2/31) in the nontoxic group, and 25% (5/20) in the toxic group] of the patients being dysthyroid at the last follow-up, as illustrated in Supplementary Table 1. Nodule volume of them ranged from 0.50 cm3 to 39.31 cm3 at baseline. Six of them received RFA, and one received MWA. Four of them had a VRR< 80% (median VRR 45.60%, range: 26.31%-67.77%), and all of them became pretoxic at the last follow-up.

Complications

Most of the patients experienced temporary pain during the procedure at the neck, and none had had the ablation stopped. One nontoxic patient suffered from temporary subclinical hypothyroidism detected at V_{12m} and self-resolved at the last follow-up (56 months after ablation). Except for one case of stress-induced cardiomyopathy after MWA with an excellent prognosis after receiving prompt and effective treatment from cardiologists in a toxic patient, there was no other major complication, as demonstrated in Figure 3.

DISCUSSION

As the second most common cause of hyperthyroidism, AFTN are composed of TMNG and toxic adenoma, where TMNG has a higher prevalence, and occurs more commonly in the elderly (1,8,18,22). In addition to causing hyperthyroidism, AFTN patients can also present as euthyroidism and are at risk of converting into hyperthyroidism (2,23). Image-guided TA has already been recommended as an alternative therapy option for those toxic AFTN patients who are contraindicated for or refused surgery or radioiodine (10). Our study demonstrates that a single session of TA (percutaneous RFA or MWA) is effective in treating both nontoxic and toxic AFTN, where nodule volume decrement and euthyroidism can be encouragingly achieved. The safety of TA (percutaneous RFA or MWA) is reinforced although rare complications might occur.

In the nontoxic group, the median VRR and euthyroidism maintenance rate were 96.3% (80.1%-98.5%) and 93.5%, respectively. *Papini et al.* (10) and *Li et al.* (24) reported a VRR ranging from 69.0% to 78.0% and from 74.6% to 90.5% for the use of percutaneous RFA and MWA in the treatment of benign non-functioning thyroid nodules at the 12-month follow-up, respectively. This study indicates that percutaneous RFA and MWA approaching nontoxic AFTN is similar in VRR achievement when compared to benign non-functioning thyroid nodules. When compared to the toxic group, VRR, euthyroidism status, and technical efficacy of the nontoxic group also showed a more efficacious

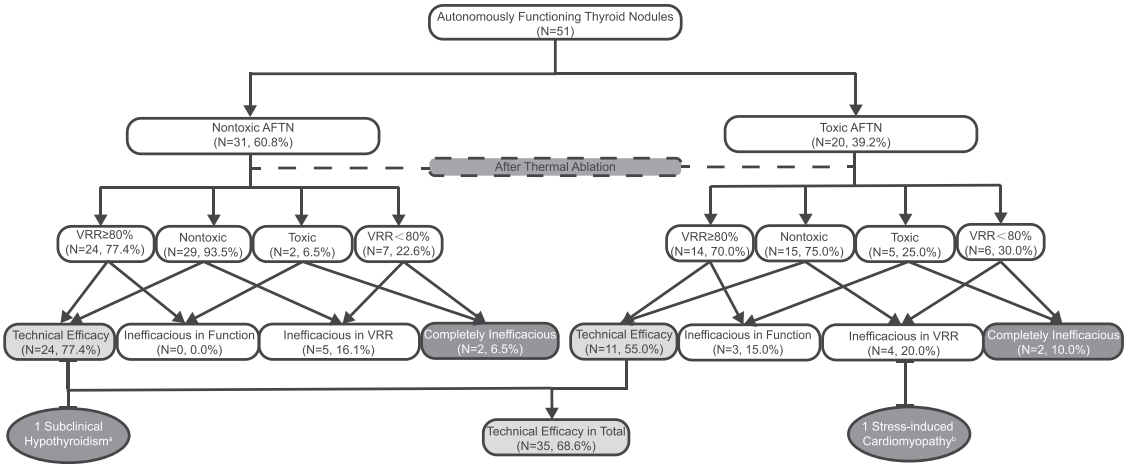

Figure 3. The Follow-up of nontoxic and toxic patients with AFTN after ablation. a: This occurred in one nontoxic patient at the 12th month after ablation and this temporary subclinical hypothyroidism was restored to normal thyroid function status without further intervention at the last follow-up. b: This happened immediately after the procedure of microwave ablation in a pretoxic patient, and this patient was recovered without any comorbidity. AFTN: autonomously functioning thyroid nodules; VRR: volume reduction rate.

trend, although statistical significance was not found. This might indicate the comparable efficacy of TA (percutaneous RFA or MWA) in treating both nontoxic and toxic AFTN patients (77.4% vs. 55.0%, p=0.126). However, it should be noted that the maximum diameter and nodule volume were smaller in this group than in the toxic group, which may contribute to the desirable trend. Hypothyroidism is one of the major concerns for ablated nontoxic AFTN patients, as thyrotoxicosis has not yet occurred. This cohort, however, showed preservation of euthyroidism in 93.5% (29/31) of the patients, and none was hypothyroid at the last visit. Only one patient who received RFA showed temporary and self-resolved subclinical hypothyroidism, which may be associated with the patient's high serum level of TPOAb before ablation rather than ablation itself, as a high level of TPOAb was associated with the possibility of postablation hypothyroidism in toxic AFTN and benign non-functioning thyroid nodules receiving RFA (25–27), where functional compensation of normal thyroid tissue after ablation of the functioning nodule might be inadequate since TPOAb contributes to thyrocyte death (28).

Additionally, nontoxic AFTN patients were at risk of converting to hyperthyroidism (23), as demonstrated in this cohort that two nontoxic AFTN patients progressed into toxic at the last visit, with the association between hyperthyroidism and increased all-cause and cardiovascular mortality (18), intervention of nontoxic AFTN to avoid the progression is reasonable, especially for those suffering from compressive symptoms or cosmetic concerns caused by thyroid nodules, as in this study. Nevertheless, studies of TA approaching nontoxic AFTN are rare (29). Our study indicates that these patients may benefit from TA (percutaneous RFA or MWA) both in nodule shrinkage and euthyroidism maintenance. Moreover, the efficacy criteria of TA treating nontoxic AFTN remain to be further discussed as the current guidelines were mainly developed against toxic AFTN (10).

Patients with thyroid nodules were recommended to perform thyroid scan when TSH was suppressed (30). However, nearly 50% of AFTN patients detected by thyroid scan were presented with normal TSH (23), and these patients might not receive timely intervention. Thus, in addition to the confirmation of the benignity nature of thyroid nodules before ablation (10,11,13), the recognition of the functional autonomy of thyroid nodules would be helpful for treatment, efficacy evaluation, and follow-up (31). In our experience, for nodules ≥ 2 cm and/or presenting with rich intranodular vascularity (32–35), the role of thyroid scan is worthy of emphasis to detect the existence of AFTN early even if the TSH level is normal.

For the toxic group, the median VRR was 88.3% (78.3%–96.2%), and the euthyroidism restoration rate was 75.0%. Previous studies have shown the efficacy of TA in approaching toxic AFTN patients. With the largest sample size of 361 patients, the multicenter study conducted by *Mauri et al.*(15) concluded that TA (LA and RFA) offered an effective therapeutic option for toxic AFTN with median VRR of 60.0% and anti-thyroid therapy withdrawal rate of 41.3% at 12-month after TA, although 9.4% of the patients needed additional treatment. *Cappelli et al.* (36) reported a VRR of 72.9% and thyroid function normalization of 94.1% in 17 patients with toxic nodules at 12 months after a single session of RFA. One recent meta-analysis showed a pooled VRR of 76.5% and a normalization of thyroid function rate of 61.7% for RFA approaching toxic AFTN, with sample sizes ranging from 9 to 44 and follow-up periods varying from 6 to 24 months (6). The technical efficacy was 55.0% in the toxic patients in this study, similar to what was reported previously (about 50% at 12 months after ablation) (10). Our study results were in line with the result of previous studies and even showed superiority compared to some of them, reinforcing the efficacy of TA (percutaneous RFA or MWA) in treating toxic AFTN, although the median preablation nodule volume (8.10 cm3) was relatively small in this study. Moreover, compared to the hypothyroidism rate of 20% in toxic AFTN patients receiving radioiodine therapy (37), no hypothyroidism at the last follow-up developed after ablation in this cohort.

When comparing patients with different treatment outcomes, a smaller nodule volume was noted in the patients with technical efficacy in the nontoxic group. In previous studies, nodule volume was found predictive of effectiveness (15,38), where a greater VRR and increment of TSH level were found in the group with smaller nodules (<12 mL). The small nodule volume in our study (<12 mL in both groups) might be the reason for the lack of association between nodule volume and technical efficacy in the toxic group and the whole cohort. However, *Bernardi et al.*(39) also failed to recognize the association where the nodule volume was 17.12 mL. Additionally, in the present study, technical efficacy was defined as both VRR and thyroid function fulfilling the criteria (10); most of the previous studies, however, evaluated the efficacy from either criterion separately (15,29,39–41). From this perspective, the percent of patients with VRR≥ 80% were 77.4% (24/31) and 70.0% (14/20), and those with normal thyroid function were 93.5% (29/31) and 75.0% (15/20) in the nontoxic group and the toxic group, respectively, in this study. More studies evaluating the efficacy from both criteria are needed in order to provide more robust evidence regarding the role of TA as therapy in AFTN.

Genetic mutation of TSHR, GNAS or EZH1 harbored by most of the AFTN stimulates thyrocyte proliferation (3–5). Thus, insufficient ablation at the nodule margin could cause insufficient volume reduction and regrowth (41,42), which may contribute to the failure of thyroid function restoration. In addition, with the higher prevalence of TMNG than toxic adenoma, the possibility of a latent functioning nodule revealing thyrotoxicosis as the functional suppression by the dominant functioning nodule was stopped due to the ablation of the dominant nodule cannot be eliminated in AFTN patients without euthyroidism maintenance/restoration after ablation, and this might also be caused by the occurrence of

new toxic AFTN. In the present study, dysthyroid outcome might partly be caused by insufficient ablation or regrowth of nodule treated with a single session of ablation. This suggests that sufficient ablation of the entire nodule is necessary, or repeated ablation procedures can be considered (15,41). Close surveillance of such patients is fundamental and thyroid scan when needed would be a valuable tool. Intriguingly, 15% (3/20) of the patients in the toxic group improved functionally from "overt toxic" to "pretoxic" at the last follow-up. With longer follow-up, it is likely to witness the normalization of thyroid function as the nodule keeps shrinking (39).

The prevalence of AFTN, especially TMNG, was higher in the elderly (1,43), who are more prone to ablation-related complications with potential underlying diseases. In this study, only one toxic 60-year-old patient was complicated by stress-induced cardiomyopathy immediately after ablation. After receiving prompt and effective treatment, the patient was recovered with an excellent prognosis. There were no other major complications. For minor complications, other than temporary pain during the procedure at the neck, complications such as voice change, nodule rupture, and hematoma reported by previous studies were not observed (6,25,26). This demonstrates the safety and well-tolerance of TA (percutaneous RFA or MWA), which may also relate to the adequate ablation expertise of the medical center (8,44).

There were several limitations in our study. The retrospective nature of our study design may result in selection bias. The diagnosis of AFTN was made largely dependent on thyroid scan, where the false positive result could not be eliminated, although the prevalence previously reported of that was only 5% (45). The sample size of our study was only moderate as a single-center study, which may contribute to the insignificance in some comparisons, but it is similar to, even more than that of most previous single-center studies (ranging from 9 to 44)(6,14). Approximately 21% (14/66) of the patients were lost during follow-up for various reasons, including COVID-19 pandemic, while the overactive thyroid functional symptoms, compressive symptoms or cosmetic concerns were improved compared to baseline, which was obtained through simple phone surveys. With the median period of 18 months, the length of the follow-up period was similar to that of previous studies (ranging from 6-36 months), but a longer follow-up period may provide more insights into the long-term efficacy of TA.

CONCLUSIONS

A single session of TA (percutaneous RFA or MWA) is efficacious and safe as a therapy option for patients with AFTN, both nontoxic and toxic, in significant nodule volume decrement and euthyroidism achievement. The technical efficacy between these two groups of patients was comparable. Additionally, recognition of the functional autonomy of thyroid nodules is also crucial, especially for nontoxic nodules, since it would be helpful for treatment, efficacy evaluation and follow-up. Caution in performing ablation is necessary since the occurrence of rare complications is likely.

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Supplementary Figure 1. Thyroid scan of nontoxic and toxic patients with AFTN before and after ablation.

At baseline, hot nodules demonstrated in the thyroid scan of nontoxic (A, fT3:4.88 pmol/L, fT4:9.16 pmol/L, TSH:0.621 μIU/mL) and toxic (C, fT3:5.63 pmol/L, fT4:9.33 pmol/L, TSH:0.283 μIU/mL) patients with AFTN. After ablation, the disappearance of hot nodules showed in the thyroid scan of nontoxic (B, fT3:5.10 pmol/L, fT4:10.89 pmol/L, TSH:1.561 μIU/mL) and toxic (D, fT3:6.32 pmol/L, fT4:9.53 pmol/L, TSH:1.464 μIU/mL) patients with AFTN.

AFTN: autonomously functioning thyroid nodules, fT3: free triiodothyronine; fT4: free thyroxine; TSH: thyroid-stimulating hormone.

Supplementary Table 1. Clinical characteristics of dysthyroid patients at last follow-up. a: "+" and "-" represent parametric levels were greater than the corresponding upper limits of reference range and in the reference range, respectively.

Tg: thyroglobulin; TgAb: anti-thyroglobulin antibody; TPOAb: anti-thyroid peroxidase antibody; TRAb: thyrotropin receptor antibody; VRR: volume reduction rate; RFA: radiofrequency ablation; MWA: microwave ablation.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.acra.2023.02.002.