Image-guided thermal ablation in autonomously functioning thyroid nodules. A retrospective multicenter three-year follow-up study from the Italian Minimally Invasive Treatment of the Thyroid (MITT) Group

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Abstract

Objectives To report the results of a multicenter retrospective evaluation of the clinical outcomes of thermal ablation (TA) in a large series of autonomously functioning thyroid nodules (AFTN) with a follow-up protracted up to 3 years.

Methods Patients treated with single TA for an AFTN in Italy were included. Changes in nodule volume, TSH values, and ongoing anti-thyroid therapy were assessed at the 2-, 6-, 12-, 24-, and 36-month follow-up controls. Complications and need of any additional therapy after TA were also registered.

Results A total of 361 patients (244 females, 117 males, median age 58 years, IQR 46–70 years) were included. Nodule volume was significantly reduced at all time points ($p < 0.001$) (median volume reduction 58% at 6-month and 60% at 12-month). Serum TSH values increased significantly at all time points. After TA, anti-thyroid therapy was withdrawn in 32.5% of patients at 2 months, in 38.9% at 6 months, and in 41.3% at 12 months. A significant difference in the rate of patients who withdrawn medical therapy at 12 months was registered between small (< 10 mL) (74%), medium (49%), or large (> 30 mL) nodules (19%). A single major complication occurred (0.25%). Additional treatments were needed in 34/361 (9.4%) of cases including 4 (1.1%) surgical treatment.

Conclusions Image-guided thermal ablation offers a further safe and effective therapeutic option in patients with AFTN. Clinical outcomes are significantly more favorable in small than in large size AFTN.

Key Points

- *Thermal ablations (TA) can be safely and effectively used in patients with autonomously functioning thyroid nodules (AFTN).*
- *TA results in a clinically significant nodule volume reduction that is paralleled by TSH level normalization and anti-thyroid drug therapy discontinuation (after TA anti-thyroid therapy was withdrawn in 41.3% at 12 months).*
- *Clinical outcomes after TA are more favorable in small nodules, and when a large amount of thyroid nodule tissue is ablated.*

Keywords Thyroid nodule · Nodular goiter · Laser therapy · Radiofrequency ablation

Abbreviations

AFTN	Autonomously functioning thyroid nodules
LA	Laser ablation
MITT	Minimally invasive treatments of the thyroid
RAI	Radioiodine ablation
RFA	Radiofrequency ablation
TA	Thermal ablation
TSH	Thyroid stimulating hormone
US	Ultrasound

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Introduction

Autonomously functioning thyroid nodules (AFTN) represent up to 10% of thyroid nodular diseases and are the second cause of hyperthyroidism, either subclinical or overt, after Graves' disease [1].

Radioiodine ablation (RAI) and surgical resection are the established definitive treatments for AFTN, while antithyroid drugs may be used temporarily, for hyperfunction control, or, in the long term, when the final therapies are contraindicated or refused by patients [1, 2]. Surgery is effective but is expensive, may be associated with major complications, and, as for RAI, may be followed by late hypothyroidism. Moreover, patients are not amenable to RAI in case of pregnant or breastfeeding women and in other specific clinical conditions [3, 4].

Minimally invasive treatments (MIT), including ethanol and thermal ablations (TA), are used in the treatment of benign thyroid nodules with favorable outcomes in terms of volume reduction and local symptom improvement [5–9]. Presently, the use of TA in patients with AFTN is reported only in small clinical series with ill-defined enrollment criteria, short-term follow-up, and controversial outcomes [10–13]. So, even if TA is described as providing promising results in nodule volume reduction and thyroid function normalization, its role in the management of AFTN remains unsettled [14]. A meta-analysis of the available data suggested that MIT achieve serum thyroid stimulating hormone (TSH) normalization in 57 to 71% of patients with AFTN. Still, the relationships between treatment modalities, baseline nodule volume, severity of hyperthyroidism, and clinical outcomes remain not clearly defined [15]. Most important, limited data are available about the real-world practice on this issue.

For these reasons, we report the results of a multicenter retrospective study evaluating the clinical outcomes of TA in a large series of AFTN treated in different centers and with a follow-up protracted up to 3 years.

Materials and methods

Study design

This is a multicenter study retrospectively evaluating patients with AFTN who were treated with TA in Italy. The study was conducted in accordance with the declaration of Helsinki, and the protocol was approved by the Institutional Review Board of all enrolled hospitals. The study protocol was presented at the 2nd meeting of the minimally invasive treatments thyroid (MITT) group, held in Milan in February 2019 [16, 17], and 10 thyroid referral centers contributed to data accrual.

Inclusion criteria

(1) Diagnosis of AFTN based on the combined results of thyroid ultrasound (US) examination, thyroid scintiscan with 99mTc, and serum thyroid hormones profile; (2) no previous treatment with RAI, ethanol ablation, TA, or surgery besides the hyperfunction control with oral drug therapy; (3) treatment of a single AFTN with a single TA session, performed either with laser (LA) or radiofrequency (RFA); (4) informed consent of the patient. The indication to TA and the modalities of treatment were established according to local criteria and resources and to patients' preferences.

Ablation techniques

The RFA and LA procedures were performed under US monitoring according to the described techniques [18–22].

Variables

For each patient, the following baseline data were collected: age, sex, date of treatment, nodule location, nodule volume at ultrasound examination, serum thyroid stimulating hormone (TSH) value, previous or ongoing anti-thyroid pharmacological therapy, TA method (RFA or LA), and the suppression of normal thyroid parenchyma at 99mTc thyroid scintiscan.

Data concerning treatment were as follows: technical success (defined as an ablated nodule volume > 80%), occurrence and type of major and minor complications, and side effects [23]. Treatment tolerability was measured on a Likert scale ranging from 0 to 10, where 0 relates to unbearable pain and 10 corresponds to no discomfort during treatment [23]. Nodule volume, TSH values, and ongoing anti-thyroid therapy were assessed at the 2-, 6-, 12-, 24-, and 36-month follow-up controls and compared to baseline as unchanged, increased, decreased, or withdrawn, respectively. Any additional therapy performed after TA was also registered.

Technique efficacy was defined as > 80% volume reduction at 12 months. Clinical success was defined as the normalization of serum TSH and the suspension of oral antithyroid therapy at the last follow-up control.

The durability of AFTN volume and thyroid function changes after TA were assessed until 3 years.

Statistical analysis

Data analysis assessed the variations after thermal ablation of nodule volume, serum TSH, and anti-thyroid drug therapy over time. A carry over approach was adopted for the inclusion of all treated patients in the analysis. Thus, in case of missing data at follow-up, the last available value was considered [24]. As a control, analyses were also performed based only on available data at each specific follow-up and all the observations were confirmed. Results were stratified according to baseline nodule volume according to the following cut-offs: small ≤ 10 mL, medium > 10 to ≤ 30 mL, and large > 30 mL. A further stratification of the outcomes was based on the employed ablative technique and the completeness of the ablation.

For continuous data, normal distribution was assessed by Shapiro–Wilk test and the following analyses were performed accordingly. One-way ANOVA or Kruskal–Wallis test was applied to test differences among different time points, while two-way ANOVA was adopted to measure the influence of specific variables during time. These analyses were coupled with the appropriate post hoc tests (Dunn's or Bonferroni's) to evaluate differences among specific datasets. Chi-square test was applied to categorical data. Analyses were performed using Prism 5.0 (GraphPad Software). Data are reported as median and interquartile range, if not otherwise specified. p values < 0.05 were considered statistically significant [25].

Results

Baseline characteristics

The study population included 361 patients (244 females, 117 males) with a median age of 58 years (interquartile range 46–70 years) treated between January 2013 and November 2018. Nodules were in the right lobe in 200/361 cases (55.4%), in the left in 152/361 (42.1%), and in the isthmus in 9/361 cases (2.5%). Prior to TA treatment, the median nodule volume was 9.9 mL (interquartile range: 7.9–14.6 mL) and the median serum TSH was 0.09 mIU/L (range: 0.01–0.225 mIU/L). At 99mTc thyroid scintiscan, the surrounding thyroid parenchyma was suppressed in 272/361 (75.5%), while a partial radioisotope uptake was still present in normal tissue in 82 (24.5%) cases. At baseline, 252/361 patients (69.8%) were taking anti-thyroid therapy, while 109/361 patients (30.2%) were on clinical surveillance.

Nodules were treated with LA in 243/361 cases (67.3%) and with RFA in 118 cases (32.7%) according to local resources and operators' expertise. Data about 86 patients were available at the 2-month control, while data regarding 345, 290, 242, and 132 patients were available for the 6-, 12-, 24-, and 36-month follow-up, respectively.

Treatment outcomes

Nodule volume Technical success was achieved with the two modalities of TA in 194/361 (53.7%) cases. Nodule volume was significantly reduced vs baseline at all time points ($p < 0.001$) and the median volume reduction was 58% at the 6-month and 60% at the 12-month controls. The percentage volume reduction at the different time points of follow-up is reported in Fig. 1a, and the patients' laboratory data are reported in Table 1. No significant difference was found in the percentage volume reduction between the nodules defined at baseline as small, medium, and large (Fig. 1b and Table 2). The 12-month mean volume reduction was 77% for the RFA and 56% for the LA treated patients, respectively (Fig. 1c). A significant difference in percentage nodule volume reduction was registered at all time points in favor of RFA versus LA patients ($p < 0.001$). In particular, at 36-month, volume reduction was -60.3% (IQR: -67.3%, -52.2%) and -83.8% (IQR: -92.1%, -72.4%) in patients treated with LA and RFA, respectively.

A higher volume reduction was found at all time points in patients treated with technical success ($\geq 80\%$ nodule ablation) vs patients without technical success but resulted as statistically significant only at the 6-month control ($p < 0.01$) (Fig. 1d). At this time point, the volume reductions were 61% and 50%, respectively. Technique efficacy was achieved in 51/361 (15.5%) cases.

Thyroid function changes Serum TSH values increased significantly at all time points compared to pre-treatment levels: baseline, 0.09 (IQR 0.01–0.22 mIU/L); 2 months, 0.90 (IQR 0.22–1.42 mIU/L); 12 months, 1.10 (IQR 0.54–1.80 mIU/L) ($p < 0.001$ for all). Mean TSH level further increased from the 12-month control onwards (Fig. 2a). No significant differences of TSH values at the different time points of follow-up were observed between patients treated with RFA vs LA ($p = 0.828$, Fig. 2b). Patients' laboratory data are reported in Table 1.

The increase in TSH values at the 2-, 6-, and 12-month controls was significantly greater in patients treated with technical success. Specifically, serum TSH values at 12 months were 1.15 (0.66–1.90 mIU/L) vs 0.50 (0.20–1.18 mIU/L) in the two groups, respectively (Fig. 2c).

Pharmacologic treatment After TA, anti-thyroid therapy was withdrawn in 32.5% of patients at 2 months, in 38.9% at 6 months, and in 41.3% at 12 months. The drug withdrawal rate at 12-month did not change significantly

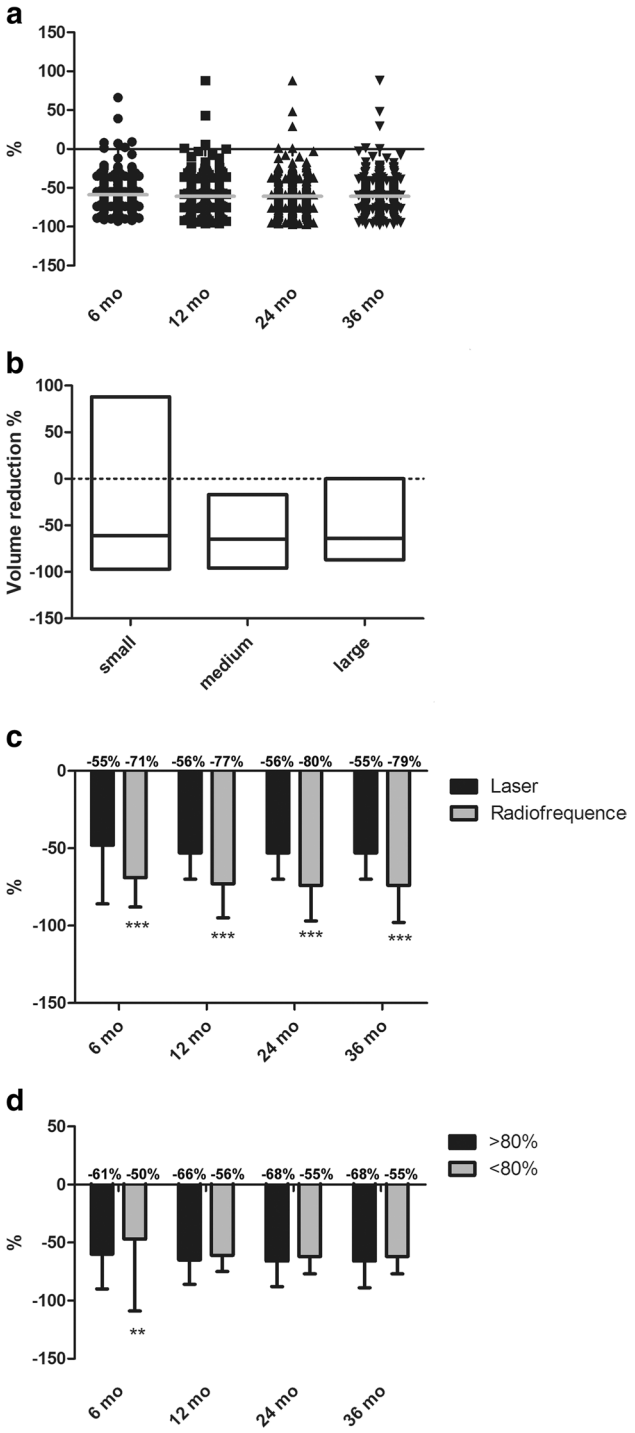

Fig. 1 Graphic representation of volumetric reduction of AFTN treated with thermal ablation, stratified according to: **a** different time points of follow-up; **b** nodule size at baseline; **c** method of ablation; **d** technical success. ** indicates $p < 0.01$; *** indicates $p < 0.001$

at the 24- and 36-month follow-up (42.5%, at both time points). Additionally, medical treatment prescription was decreased in 4.8%, 14.3%, and 13.9% of patients at the 2-, 6-, and 12-month control, respectively. The decrease in pharmacological therapy remained nearly stable at the following 24- and 36-month controls (13.9% and 11.5%, respectively) ($p < 0.001$) (Fig. 3a).

A significant difference in the rate of patients who withdrawn medical therapy 12 months after TA was registered between the nodules classified at baseline as small (74%), medium (49%), or large size (19%). The rate of anti-thyroid therapy requirement decreased at 12-month more frequently in large (48%) than in medium (20%) and small nodules (3%) ($p < 0.001$, Fig. 3b).

At 12 months, drug therapy was withdrawn or reduced in 60.0% of patients who underwent RFA and 53.6% of those treated with LA, with no significant statistical difference between the two modalities of treatment ($p = 0.238$).

The attainment of euthyroidism was significantly more frequent in patients whose treatment achieved technical success. Pharmacologic therapy was withdrawn in 71% and drug dosage was reduced 6% of them. Conversely, patients who did not attain technical success withdrew medical treatment in 14% and decreased the daily drug dosage in 67% of cases ($p < 0.001$, Fig. 3c). Overall, clinical success was achieved in 50.7% of patients at 3 years. Clinical success was more frequent in patients treated with RFA (57.6%) than LA (46.9%), but this difference was not statistically significant ($p = 0.056$).

Safety, tolerability, and need for additional treatments A single major complication occurred in 361 patients (0.25%). One case of dysphonia occurred immediately after treatment and persisted, without recovery, until the 36-month follow-up. Local, self-resolving, hematoma occurred immediately after treatment in 8/361 patients (2.2%) and was considered a minor complication because it did not request specific treatment. Mild pain after treatment was reported by 48/361 patients (13.2%) and was classified as a side effect due to it lasting less than 24 h and not requiring opioid painkillers. The mean treatment tolerability was rated as 8.6 ± 1.9/10 on the Likert scale.

One case of severe thyrotoxicosis was registered at the 6-month follow-up after medical therapy withdrawal. No case of late hypothyroidism occurred. Additional treatments were needed in 34/361 (9.4%) of cases. Eighteen (4.9%) patients underwent RAI, 12 (4.3%) patients underwent a subsequent successful TA, and 4 (1.1) patients underwent surgical treatment.

Discussion

A robust evidence demonstrates the efficacy and safety of TA, with either LA or RFA, in the treatment of symptomatic, cytologically benign, thyroid nodules [5–8, 26]. Currently,

Table 1 Modifications over time of nodule volume, TSH, and pharmacological treatment in AFTN after thermal ablation

	Baseline	2 months	6 months	12 months	24 months	36 months
Nodule volume (mL)	9.9 (7.95–14.65)	9.1 (6.2–12.1)	4.2 (2.9–7.2)	4.0 (2.5–6.65)	4.0 (2.3–6.65)	4.0 (2.3–6.65)
Delta vs baseline		−8.1%	−57.6%	−59.6%	−59.6%	−59.6%
p-value vs baseline		$p<0.01$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$
TSH (mIU/L)	0.09 (0.01–0.225)	0.8 (0.20–1.375)	0.9 (0.325–1.6)	0.99 (0.4–1.7)	1.00 (0.475–1.6)	1.00 (0.42–1.5)
Delta vs baseline		788.9%	900.0%	1000.0%	1011.1%	1011.1%
p-value vs baseline		$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$
p-value vs 2 months			0.826	$p<0.01$	$p<0.001$	$p<0.01$
Pharmacological therapy (%)						
Withdrawn		32.5%	38.9%	41.3%	42.5%	42.5%
Reduced		4.8%	14.3%	13.9%	13.9%	11.5%
Unchanged		62.3%	46.4%	44.4%	43.3%	45.6%
Increased		0.4%	0.4%	0.4%	0.4%	0.4%

Data are provided as median (interquartile range). Data regarding nodule volume and TSH variation refer to 361 patients. Data regarding variations of pharmacological therapy refer to 252 patients

Table 2 Modifications over time of nodule volume, TSH, and pharmacological treatment stratified according to baseline volume size

Nodule volume (mL)	Baseline	2 months	6 months	12 months	24 months	36 months
Small	8.20 (6.00–9.10)	8.00 (4.60–9.10)	3.50 (2.00–4.40)	3.30 (2.00–4.20)	3.30 (2.00–4.20)	3.30 (2.00–4.20)
Delta vs baseline		−2%	−57%	−60%	−60%	−60%
Medium	13.80 (11.00–18.00)	11.10 (10.00–14.60)	5.80 (4.20–8.20)	4.90 (3.60–7.50)	4.80 (3.60–7.70)	4.80 (3.50–7.80)
Delta vs baseline		−20%	−58%	−64%	−65%	−65%
Large	42.10 (35.4–64.00)	38.00 (31.3–62.00)	20.00 (13.30–38)	13.00 (10.00–29.00)	13.00 (9.9–29.2)	13.00 (10.00–29.00)
Delta vs baseline		−10%	−52%	−69%	−69%	−69%
TSH (mIU/L)	Baseline	2 months	6 months	12 months	24 months	36 months
Small	0.11 (0.04–0.22)	0.88 (0.30–1.21)	0.91 (0.58–1.40)	0.99 (0.61–1.44)	1.01 (0.61–1.48)	1.03 (0.67–1.50)
Medium	0.06 (0.00–0.21)	0.80 (0.10–1.60)	0.96 (0.24–1.81)	1.01 (0.24–1.80)	0.97 (0.30–1.78)	0.90 (0.30–1.50)
Large	0.04 (0.00–0.40)	0.25 (0.01–0.92)	0.40 (0.20–0.80)	0.80 (0.49–1.54)	0.80 (0.52–1.78)	0.80 (0.3–1.22)
Therapy						
		2 months	6 months	12 months	24 months	36 months
Small						
Withdrawn		56.9%	67.2%	74.1%	74.1%	74.1%
Reduced		6.9%	5.2%	3.4%	3.4%	3.4%
Unchanged		36.2%	27.6%	22.4%	22.4%	22.4%
Increased		0.0%	0.0%	0.0%	0.0%	0.0%
Medium						
Withdrawn		41.9%	47.0%	48.7%	50.4%	50.4%
Reduced		5.1%	19.7%	19.7%	17.9%	14.5%
Unchanged		52.1%	32.5%	30.8%	30.8%	34.2%
Increased		0.9%	0.9%	0.9%	0.9%	0.9%
Large						
Withdrawn		4.8%	19.0%	19.0%	23.8%	23.8%
Reduced		9.5%	47.6%	47.6%	57.1%	47.6%
Unchanged		85.7%	33.3%	33.3%	19.0%	28.6%
Increased		0.0%	0.0%	0.0%	0.0%	0.0%

Data are provided as median (interquartile range)

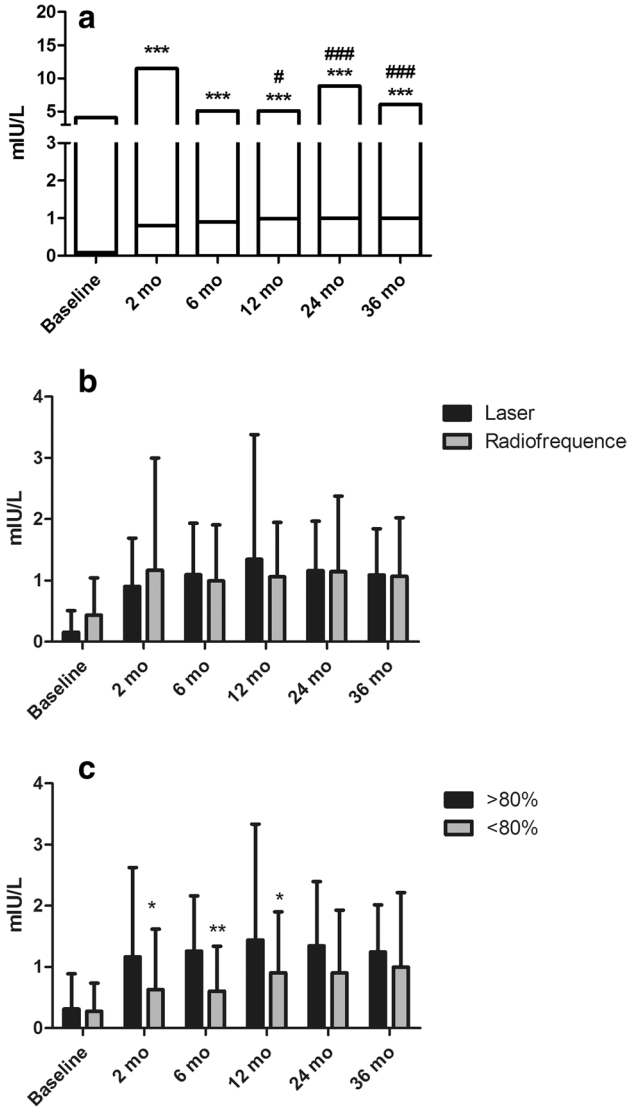

Fig. 2 Graphic representation of TSH modifications of AFTN treated with thermal ablation, stratified according to: **a** different time points of follow-up; **b** method of ablation; **c** technical success. * indicates $p<0.05$ vs baseline; ** indicates $p<0.01$ vs baseline; *** indicates $p<0.001$ vs baseline; # indicates $p<0.05$ vs 2-month follow-up; ## indicates $p<0.01$ vs 2-month follow-up; ### indicates $p<0.001$ vs 2-month follow-up

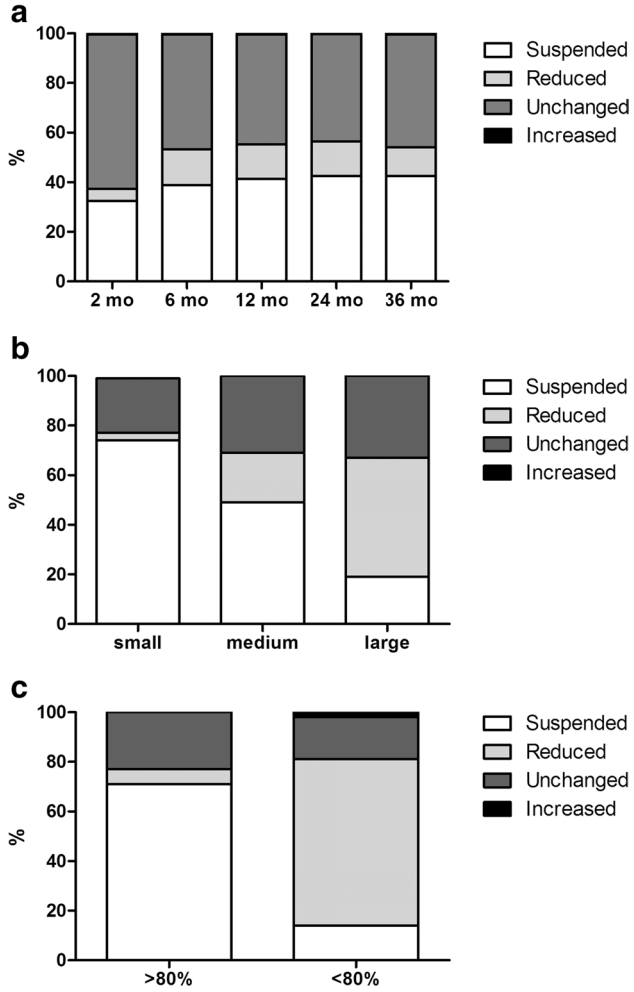

Fig. 3 Graphic representation of therapy modifications of AFTN treated with thermal ablation, stratified according to: **a** different time points of follow-up; **b** nodule size at baseline; **c** technical success. * indicates $p<0.05$ vs baseline; ** indicates $p<0.01$ vs baseline; *** indicates $p<0.001$ vs baseline; # indicates $p<0.05$ vs 2-month follow-up; ## indicates $p<0.01$ vs 2-month follow-up; ### indicates $p<0.001$ vs 2-month follow-up

image-guided minimally invasive procedures are considered an alternative option to surgery for non-functioning thyroid nodules in patients who refuse or are not amenable to surgery [17, 27, 28].

Conversely, a limited evidence is available for TA treatments of AFTN and the major thyroid guidelines consider the use of TA as a conclusive treatment only for cases that are not suitable for RAI nor thyroidectomy [17, 27–29]. For this reason, the present study assessed the outcomes in real-world practice of these treatment modalities in Italy. Overall, 361 patients, treated either by RFA or LA, have been included, representing, to the best of our knowledge, the largest clinical series up to now available [10–13]. As only 70% of them were under treatment with anti-thyroid drugs, about one hundred patients were treated with TA in a condition of subclinical hyperthyroidism, a clinical state that frequently is not candidate to treatment with surgery or RAI.

TA of AFTN resulted in 60% mean nodule volume reduction 12 months after treatment and in the normalization of TSH values, with discontinuation of anti-thyroid therapy, in 50.7% of patients. More favorable outcomes were registered

for all variables (nodule volume reduction, serum TSH level, and drug therapy withdrawal) when treatments achieved a nearly complete ablation, defined as technical success (> 80% destruction of the nodule tissue). As only about 50% of cases in our series attained initial technical success, the operators should aim at an almost complete ablation of AFTN for improving the clinical outcomes of TA. So, a repeat treatment can be considered in cases with a < 80% volume ablation after TA.

Clinical results of TA were previously reported as correlated to baseline nodule volume and the percentage of ablated tissue [21, 30–32]. In our series, the percentage of patients that completely withdrew anti-thyroid therapy was significantly higher in the small nodule (< 10 mL) group. These results confirm data from previous smaller studies [21, 30, 31], suggesting a correlation between the attained percentage of coagulative necrosis of nodule tissue and the normalization of thyroid function. Notably, patients with smaller nodules had also the higher percentage volume reduction. So, nodules < 10 mL appear most suited for TA treatment due to their long-term favorable outcomes. Notably, the use of contrast-enhanced ultrasound should be encouraged because it, more clearly defining the residual nodule tissue than B-mode US [33, 34], allows a targeted treatment of the still viable areas.

RFA resulted in a significantly higher nodule volume reduction compared to LA while no significant difference was observed between the two techniques for serum TSH changes and drug therapy reduction or withdrawal. So, even if RFA appear to achieve a higher volume reduction, clinical results appear to be similar between the two techniques.

Finally, the outcomes of TA demonstrated a satisfactory durability. Patients who attained serum TSH normalization at 12 months maintained TSH values within normal limits until the 3-year control.

Limitations of this study are its retrospective design, the collection of data from different centers, with potentially relevant differences in operators' expertise and technical resources, and the amount of energy delivered for each nodule [35, 36]. Conversely, the large series of AFTN, the anonymous collection of data, the use of TA in everyday practice, and the large number of participating centers allow a real-world assessment of thermal ablation outcomes in AFTN.

In conclusion, image-guided thermal ablation offers a further therapeutic option in patients with AFTN. A single TA session results in a clinically significant nodule volume reduction that is paralleled by TSH level normalization and anti-thyroid drug therapy discontinuation in about 50% of patients at 12-month follow-up. Clinical outcomes are significantly more favorable in small (< 10 mL) than in large size (> 30 mL) AFTN.

A significant difference in percentage nodule volume reduction was registered at all time points in favor of RFA versus LA.

As the long-term clinical outcomes are significantly more satisfactory in case of technical success, TA operators should aim at an almost complete ablation of AFTN.

Major complications were exceptionally low, and no case of late hypothyroidism occurred until 3 years. So, these procedures should be especially considered in the treatment of small size AFTN that are generally associated with subclinical hyperthyroidism, in young patients, and in the management of hyperfunctioning lesions in fragile subjects or in pregnant women.

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Declarations

Guarantor The scientific guarantor of this publication is Dr. Giovanni Mauri, MD.

Conflict of interest The authors of this manuscript declare relationships with the following companies: G.M.: consultancy, Elesta SrL; F.S.: speaking fee, HS Hospital Service. All other authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Dr. Marco Viganò has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- observational
- multicenter study

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