The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 6, 1692–1701
doi:10.1210/clinem/dgab102
Clinical Research Article

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Laser Ablation Versus Radiofrequency Ablation for Thyroid Nodules: 12-Month Results of a Randomized Trial (LARA II Study)

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Abbreviations: BNTN, benign nonfunctioning thyroid nodule; LA, laser ablation; RFA, radiofrequency ablation; VRR, volume reduction rate.

Received: 6 December 2020; Editorial Decision: 12 February 2021; First Published Online: 20 February 2021; Corrected and Typeset: 19 April 2021.

Abstract

Context: Radiofrequency ablation (RFA) seems to achieve a significantly larger nodule volume reduction rate (VRR) than laser ablation (LA) in benign nonfunctioning thyroid nodules (BNTNs)

Objective: To compare the efficacy and safety of both treatments at 12-month follow-up in patients with solid or predominantly solid BNTN.

Methods: This was a single-center, 12-month, randomized, superiority, open-label, parallel-group trial conducted in an outpatient clinic. Sixty patients with a solitary BNTN or dominant nodule characterized by pressure symptoms/cosmetic problems were randomly assigned (1:1 ratio) to receive either a single session of RFA or LA. Twenty-9 patients per group completed the study. The main outcome measures were VRR and proportion of nodules with more than 50% reduction (technical success rate).

Results: At 12 months, VRR was 70.9 ± 16.9% and 60.0 ± 19.0% in the RFA and LA groups, respectively ($P = .024$). This effect was confirmed in the linear regression model that was adjusted for age, sex, nodule baseline volume, and proportion of cellular components (RFA treatment: $\beta = .390$; $P = .009$). No significant between-group difference was observed in the technical success rate at 12 months after treatment. A statistically significant

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

improvement was observed from the baseline to the 12-month follow-up for compression (RFA: 4.6 ± 2.6 and 1.3 ± 0.8, $P < .001$; and LA: 4.6 ± 2.1 and 1.6 ± 0.8, respectively, $P < .001$) and cosmetic (RFA: 3.4 ± 0.6 and 1.3 ± 0.5, $P < .001$; and LA: 3.4 ± 0.5 and 1.4 ± 0.6, $P < .001$) scores although the between-group differences were not significant.

Conclusion: RFA achieved a significantly larger nodule volume reduction at 12 months; however, the technical success rate was similar in the RFA and LA groups.

Key Words: Radiofrequency ablation, laser ablation, thyroid, thyroid nodules, technical success rate, nodule volume reduction

Nodular thyroid disease is the most common endocrine disorder, and incidental thyroid nodules are increasingly discovered due to the widespread utilization of neck ultrasound scanning in clinical practice. Thyroid surgery is associated with operative risk and some detrimental effects; therefore, minimally invasive image-guided ablation is an alternative treatment option to surgery (1) or, in unusual clinical settings, a first-line treatment for solid nonfunctioning thyroid nodules (BNTNs) (2). Techniques for image-guided percutaneous ablation of BNTNs include radiofrequency (RFA), laser (LA), microwave, and high-intensity–focus ultrasound (1). Increasingly, evidence suggests that RFA (3, 4) and LA (5) are the most common techniques that have been tested for BNTN management because of clinically significant, long-lasting BNTN volume reduction and improved cosmetic and/or symptom scores (6, 7). Both RFA and LA can effectively manage autonomously functioning thyroid nodules (8-10) but further studies are needed to achieve higher evidence on the efficacy of thermal ablation of autonomously functioning thyroid nodules.

A novel single-use, randomized open-label parallel trial was conducted to demonstrate that RFA results in a larger volume reduction rate (VRR) than LA at 6 months after treatment without differences in the technical success rate (proportion of nodules with >50% reduction) (11). This study aimed to compare the efficacy and safety of RFA and LA in patients with solid or predominantly solid BNTN at 12 months after treatment based on the following primary endpoints: (1) nodule volume reduction expressed as a percentage of the nodule volume at baseline and (2) the technical success rate.

Materials and Methods

Study Design and Patients

The study design was described previously (11). The LA versus RFA (LARA) study was a single-center, 12-month, randomized, superiority, open-label, parallel-group trial performed at Santa Maria Goretti Hospital (Lazio, Italy). The trial was conducted in compliance with the principles of the Declaration of Helsinki, the trial protocol was approved by the Institutional Review Board and Ethics Committee (Ethics Committee Lazio 2, approval number: CE 93321), and the participants provided written informed consent before commencing trial-related activities. This trial was registered with ClinicalTrials.gov (NCT02714946). The inclusion criteria were as follows: (1) age >18 years; (2) solitary thyroid nodules or dominating nodules that are well defined in multinodular goiter; (3) nodule volume ≥5 mL; (4) solid or predominantly solid nodule (solid portion >80%); (5) compression symptoms or cosmetic concerns for which the patients specifically requested treatment, or >20% increase in nodule volume in 1 year, regardless of symptoms; (6) confirmation of benign thyroid nodules in a single fine-needle aspiration and thyroid core needle biopsy; and (7) normal serum levels of thyroid hormones, thyrotropin, and calcitonin, with the absence of antithyroglobulin antibodies and antithyroid peroxidase antibodies. The exclusion criteria included the following: (1) nodules showing ultrasonographic features suggestive of malignancy; (2) earlier treatment for thyroid nodules; (3) pregnancy; and (4) hyperfunctioning lesions, evaluated biochemically and/or with [^{99m}Tc]-pertechnetate scintigraphy.

From January 2016 to November 2018, 60 patients who met the eligibility criteria and provided written informed consent were randomly assigned in a 1:1 ratio to 1 of 2 groups (n = 30 patients each) who underwent either LA or RFA. Each nodule received a single treatment session and was followed up over time. Twenty-nine participants in each group completed the 12-month study follow-up (excluding 1 participant who relocated to another Italian region and 1 who transferred to a different endocrinological outpatient clinic) (Fig. 1).

Randomization and Masking

Patients were randomly assigned (in a 1:1 ratio) using a computer-generated randomization list to receive either RFA or LA treatment. As the open-label design was essential for this study, masking the allocation from the clinical staff or assessors was not feasible.

Procedures

Clinical and biochemical determinations, thyroid ultrasonography, contrast-enhanced ultrasonography, and histological evaluations were described previously (11).

Minimally invasive image-guided thermal techniques

Preintervention laryngoscopy was performed in the study population to assess vocal cord mobility. A single operator, an experienced interventional radiologist who has regularly performed RFA (~200 nodules) and LA (~150 procedures) for several years, performed all procedures, including the initial diagnostic evaluation, using the same ultrasonography equipment for guidance. Patients were placed supine with their neck fully extended. A perithyroidal injection of mepivacaine (2-5 mL of 2% Carbosen®, Galenica Senese, Italy) and ropivacaine (3 mL of Naropine®, Aspen Pharma Trading Limited, Ireland) was used for anesthesia.

Radiofrequency ablation

The RFA was based on the "moving-shot" technique as described elsewhere (12) using a transisthmic approach with direct nodule puncture. A radiofrequency generator with an 18-gauge, 10-cm electrode with a 1-cm active tip (RF Medical Co, Ltd South Korea) was used with 55 W power and adequate exposure time to induce transient multiple hyperechoic zones, indicative of effective ablation. The treatment time for every RFA session was calculated from the initial insertion of the radiofrequency needle into the thyroid nodule to the final assessment of the treatment session.

Laser ablation

For LA, we followed the indications as published previously (13). We used a commercially available ultrasound system (EchoLaser, ELESTA srl, Florence, Italy) equipped with a

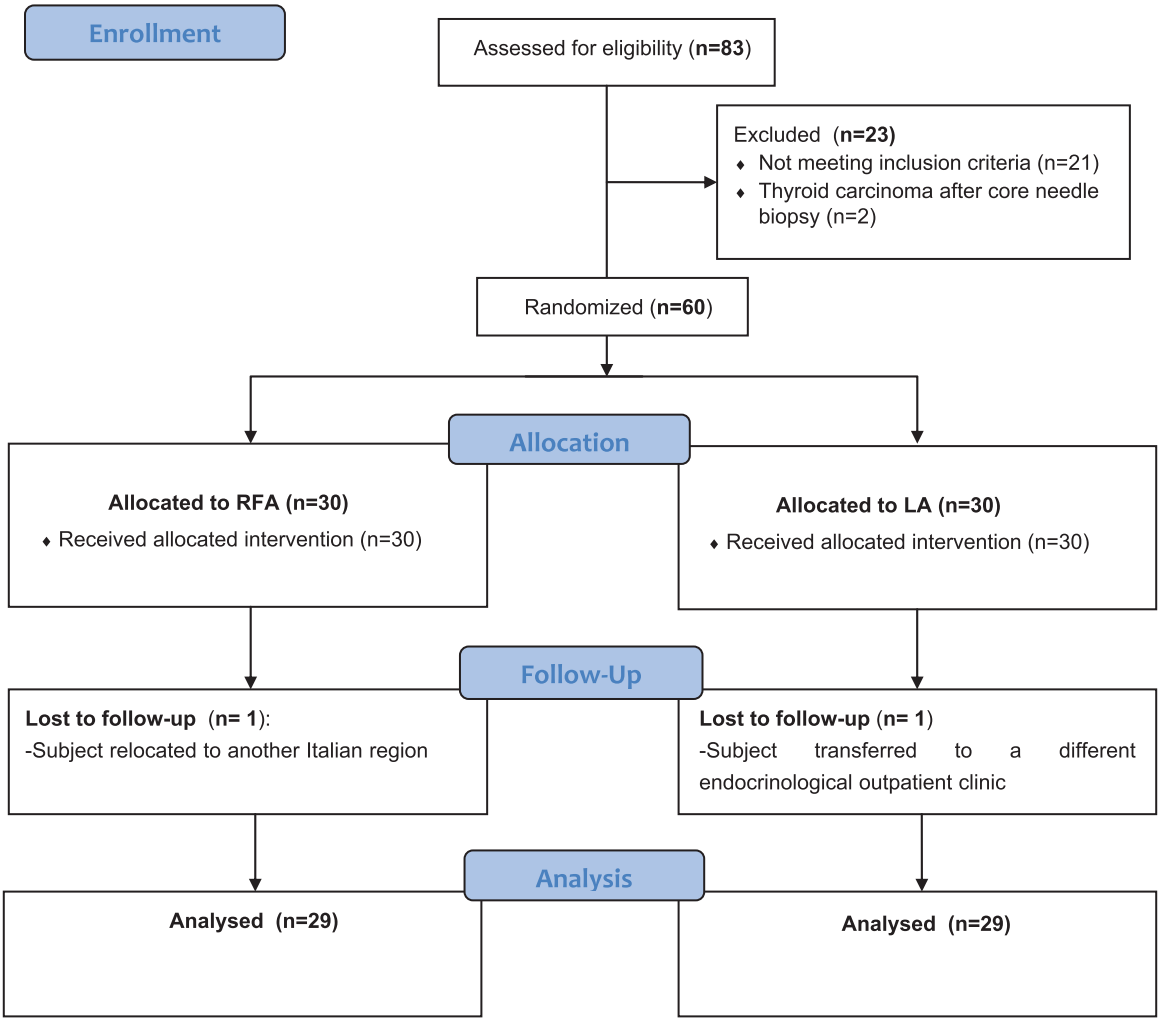


Figure 1. Flow diagram for screening and enrollment of subject into the randomized clinical trial according to CONSORT guidelines.

dedicated linear transducer operating at 13 to 4 MHz, with a needle-guided attachment and adjustable angle selection. Under ultrasound guidance, 21-gauge introducer needles were inserted for direct nodule puncture along the longest axis. A 300-µm flat-tipped quartz optical fiber was introduced and advanced up to the introducer needle tip, and the introducer needle was withdrawn to expose the fiber tip by at least 5 mm in direct contact with the tissue. The fibers were then connected to a laser source, operating at 1064 nm, with an optical beam-splitting device. The number of 21-gauge applicators (introducer needles and flexible fibers) that were inserted depended on the nodule's size and shape. Each treatment was performed with a fixed-power protocol (3 W), although the illumination time varied on a case by case basis by the size and shape of the target. After the first illumination, the applicator(s) were withdrawn by 2 to 3 cm and subsequent illumination was performed (pull-back technique) until the entire target was illuminated. Each illumination time ranged from 400 to 600 seconds to keep the total energy applied between 1200 and 1800 J per fiber. Depending on nodule size, 1 to 3 illuminations were applied in each session. On average, 2 fibers were used in LA by the pull-back technique. The treatment time for each LA session was calculated from the initial LA needle insertion into the thyroid nodule to the final assessment of the treatment session.

Outcomes

This trial compared the following primary endpoints between the RFA and LA groups 12 months after treatment: (1) nodule volume reduction, expressed as a percentage of nodule volume at baseline, and (2) proportion of nodules with more than 50% reduction (technical success rate). The secondary endpoint was the change in thyrotropin levels from baseline to 12 months after treatment. Other prespecified secondary endpoints were aimed to (1) explore the hypothesis that the histopathological features of thyroid nodules could predict the volumetric response to treatment; (2) proportion of nodules with more than 75% volume reduction; (3) safety. Adverse events were recorded during each contact with the site staff (for all visits from randomization to follow-up).

Statistical analysis

The trial was powered for volume reduction superiority of RFA compared with LA and to detect the intergroup difference in the success rate (11). Continuous variables are presented as mean and SD. The differences between the means in the 2 groups were analyzed using an unpaired (after Levene's test to assess equal variance in the subgroups) or paired Student's *t*-test, as appropriate. Nominal variables are shown as numbers and percentages and were analyzed using contingency tables and Fisher's exact or chi-squared test, as appropriate. The bivariate association between VRR and the other study variables was investigated using Pearson's correlation coefficient (r). The independent association of the adopted treatment with the VRR and the technical success rates was tested using multiple, forward, stepwise, linear, and logistic regression models that were adjusted for the patients' age and sex, and for the baseline nodule volume and percentage of cellular component in nodule composition. Logarithmic transformations were performed for the baseline nodule volume variable to obtain a more near-normal data distribution. For all tests, statistical significance was set at an alpha level of $P = .05$.

All statistical analyses were performed using IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics

Sixty patients who met the eligibility criteria were randomly assigned to RFA or LA groups. Two participants (1 each in the RFA and LA groups) who had completed the 6-month follow-up were lost at the 12-month follow-up. Therefore, 58 patients (mean age ± SD: 56.8 ± 13.1 years; females: n = 40, 69.0%) completed the 12-month follow-up and constituted the study population. The study groups were comparable at baseline for all clinical, histological, radiological, and biochemical features that were considered (Table 1). Patients who underwent RFA received a larger quantity of energy than those in the LA group (Table 1).

Nodule Volume Change at 12 Months

Both techniques induced a significant volume reduction at 6 and 12 months after treatment compared with baseline levels (Fig. 2). At the 12-month follow-up, RFA was associated with a statistically significant greater nodule VRR than LA ($P = .024$; Table 2). RFA was independently associated with a higher VRR in linear regression analysis ($\beta = .390$; $P = .009$), whereas none of the other covariates showed a statistically significant association with VRR.

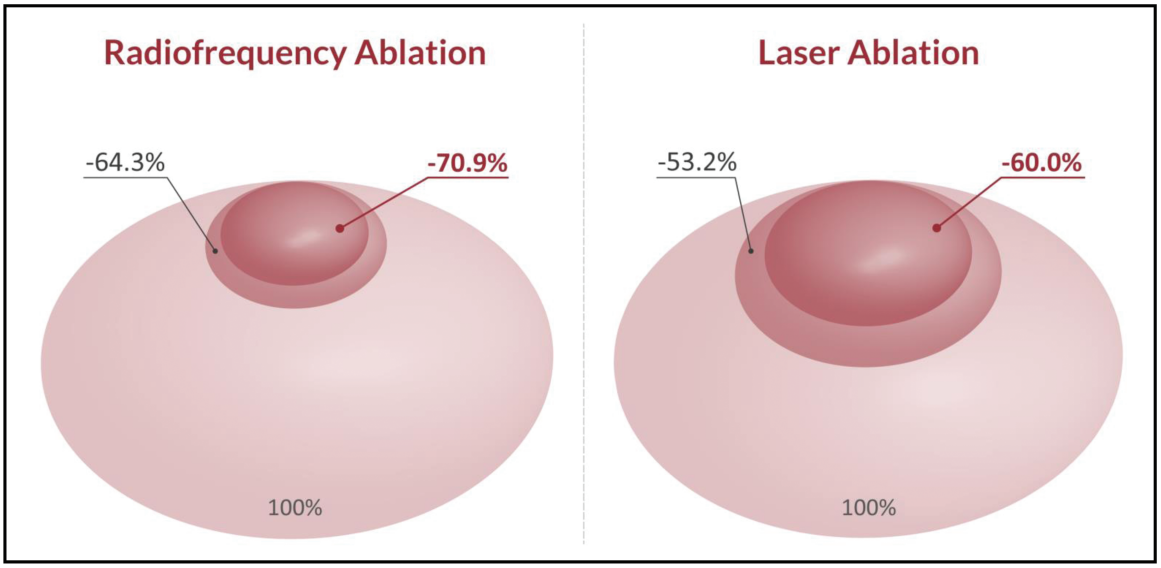
The volume reduction obtained with both methods at 12 months did not correlate with the baseline nodule volume, coagulative necrosis volume, or nodule composition (Table 3).

In the entire study population, a reduction of >50% in nodule volume at 12 months was observed in 26 (89.7%) and 22 (75.9%) patients in the RFA and LA groups (technical success rate), respectively ($P = .149$). A statistically significant inter-group difference was detected at a technical success rate threshold of >75% (RFA: n = 14, 48.3%; LA: n = 4, 13.8%; $P = .005$; Table 2).

Table 1. Baseline characteristics of the enrolled study population

	RFA (n = 29)	LA (n = 29)	*P* value
Age (years)	54.1 ± 13.9	59.5 ± 11.8	.116
Sex (female)	19 (65.5)	21 (72.4)	.570
TSH (μU/mL)	2.0 ± 0.8	1.7 ± 0.6	.202
FT4 (ng/dL)	1.3 ± 0.3	1.3 ± 0.2	.460
Baseline volume (mL)	26.5 ± 21.2	25.1 ± 24.3	.818
Cellular component (%)	49.3 ± 17.9	48.5 ± 18.1	.867
Colloidal component (%)	31.5 ± 13.0	32.2 ± 13.9	.869
Fibrotic component (%)	19.1 ± 18.8	20.0 ± 19.2	.873
Necrosis volume (mL)	21.2 ± 14.7	16.3 ± 10.6	.157
Total energy delivered (J)	54 800.9 ± 48 072.3	9620.7 ± 3608.9	<.001
Energy/nodule volume ratio (J/mL)	2012.6 ± 96.5	497.1 ± 213.1	<.001
Symptoms score	4.6 ± 2.5	4.6 ± 2.1	1.000
Cosmetic score	3.4 ± 0.6	3.4 ± 0.5	.817

Data are presented as mean ± standard deviation or n (%).
Abbreviations: RFA, radiofrequency ablation; LA, laser ablation; TSH, thyroid-stimulating hormone; FT4, thyroxine.



Percentages: volume reduction rates (VRR). Difference in VRR between RFA and LA: 6-months p=0.015; 12-months p=0.024

Figure 2. Graphic representation of mean nodule volume at baseline (light-pink area), 6- (mid-pink area) and 12-month (dark-pink area) follow-up for patients treated with radiofrequency (RFA) and laser (LA) ablation. Percentages: volume reduction rates (VRR). Difference in VRR between RFA and LA: 6 months *P* = .015; 12 months *P* = .024

In the multivariable logistic regression model, RFA was associated with a 12-fold probability to achieve a success rate of >75% after 12 months of treatment (OR 12.250, 95% CI 2.370–63.316; *P* = .003). No statistically significant association was detected for any of the study covariates when a success rate of >50% was considered as a dependent variable.

Nodule Volume Change Throughout the Study Period

A further statistically significant VRR between 6 and 12 months was documented for both RFA (mean ± SD 66.0 ± 16.0% and 70.9 ± 16.9%, respectively; *P* = .001) and LA (54.7 ± 14.2% and 60.0 ± 19.0%, respectively; *P* = .020), and this new VRR variation was similar for the

Table 2. Outcomes at 12 months after nodule ablation treatment

	RFA	LA	*P* value
Nodule residual volume (mL)	7.5 ± 6.4	9.3 ± 6.7	.300
Nodule volume reduction (mL)	18.9 ± 17.4	15.7 ± 20.6	.527
Volume reduction rate (%)	70.9 ± 16.9	60.0 ± 19.0	.024
Nodules with volume reduction >50%	26 (89.7%)	22 (75.9%)	.149
Nodules with volume reduction >75%	14 (48.3%)	4 (13.8%)	.005
TSH (µU/mL)	1.8 ± 0.8	1.7 ± 0.4	.564
TSH variation (µU/mL)[a]	0.2 ± 0.7	0.0 ± 0.6	.325
Symptoms score	1.3 ± 0.8	1.6 ± 0.8	.267
Symptoms score variation[a]	3.2 ± 2.4	3.0 ± 1.7	.659
Cosmetic score	1.3 ± 0.5	1.4 ± 0.6	.369
Cosmetic score variation[a]	2.1 ± 0.7	2.0 ± 0.7	.361

Data are presented as mean ± standard deviation or n (%).
Abbreviations: RFA, radiofrequency ablation; LA, laser ablation; TSH, thyroid-stimulating hormone.
[a]Baseline vs 12-month follow-up.

Table 3. Correlation between nodule characteristics and volume reduction at 12-month follow-up in study groups

	RFA	LA
Baseline volume (mL)	0.044; 0.823 (29)	0.155; 0.422 (29)
Cellular component (%)	–0.251; 0.216 (26)	–0.026; 0.905 (23)
Colloidal component (%)	0.048; 0.816 (26)	–0.360; 0.092 (23)
Fibrotic component (%)	0.205; 0.315 (26)	0.266; 0.231 (22)
Coagulative necrosis volume (mL)	–0.048; 0.803 (29)	–0.062; 0.751 (29)

Data are presented as *r* value; *P* value (n).
Abbreviations: RFA, radiofrequency ablation; LA, laser ablation.

2 groups (RFA: 4.9 ± 6.8%; LA: 5.3 ± 11.6%; $P = .866$; Fig. 3).

The 6- to 12-month analysis of VRR variations for each patient showed that most of them (RFA: n = 20, 69.0%; LA: n = 19, 65.5%) showed a further reduction of the nodule volume, without a statistically significant intergroup difference in VRR variations (RFA: 8.2 ± 4.1%; LA: 11.3 ± 6.1%; $P = .066$). Conversely, 3 patients in each study group showed a new increase in nodule volume, with a similar 6- to 12-month VRR for both groups (RFA: –7.5 ± 9.2%; LA –20.5 ± 10.0%; $P = .172$). In the remaining 13 cases (RFA: n = 6, 20.7%; LA: n = 7, 24.1%), no modification in VRR was documented (Fig. 4).

Thyroid Function, Symptom, and Cosmetic Score Changes

A similar variation in the thyrotropin level was documented for LA and RFA between the baseline and 12-month follow-up (Table 2).

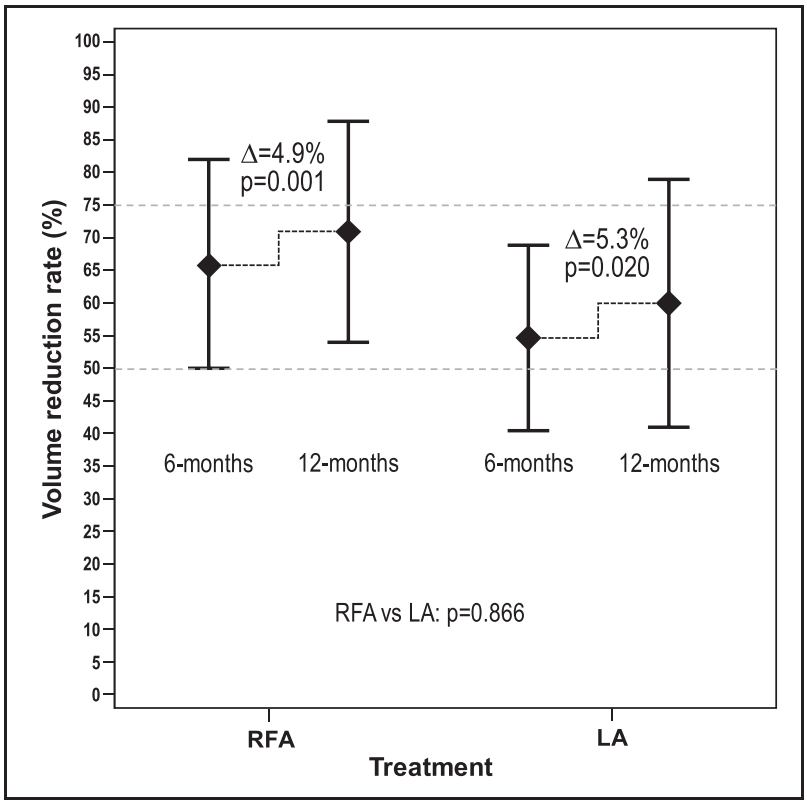
A statistically significant improvement in the compression symptom score from baseline to the 12-month follow-up was observed with both RFA (4.6 ± 2.6 and 1.3 ± 0.8, respectively; $P < .001$) and LA (4.6 ± 2.1 and 1.6 ± 0.8, respectively; $P < .001$). Similar results were documented for the cosmetic score (RFA: baseline: 3.4 ± 0.6; 12 months: 1.3 ± 0.5; $P < .001$ and LA: baseline: 3.4 ± 0.5; 12 months: 1.4 ± 0.6; $P < .001$). However, the intergroup differences were not significant (Table 2). No further significant changes were documented from 6 to 12 months for both cosmetic and compressive symptom scores (Fig. 5).

Safety

No further procedure-related complications were documented during the 12-month period.

Discussion

This is the first randomized head to head trial to compare the efficacy and safety of RFA and LA for the management of BNTN. We confirmed that RFA achieved a significantly larger nodule volume reduction at 12 months after thermal ablation treatment. Updated guidelines recommend LTA and RFA as the first-line treatments for thyroid nodules (1). In this study population, VRR at 12 months after RFA confirms findings from previous evaluations (1-year post-treatment VRR ~75%) (7, 14, 15). With regard to the ability of LA to induce significant nodule VRR, our findings are in agreement with the results of previous randomized clinical studies (13, 16). Trimboli et al. reported a slightly lower VRR for LA (52%) than our results (7); however, the technical experience of the operator may partially explain this difference. A randomized multicenter study on LA treatment showed that the VRR changed quite markedly (from 48% to 64%) according to the different centers that performed the procedure (13).



Diamonds: mean. Whiskers: 1 × standard deviation. RFA vs LA: comparison of the extent of volume reduction rate variation between 6 and 12 months in study groups.

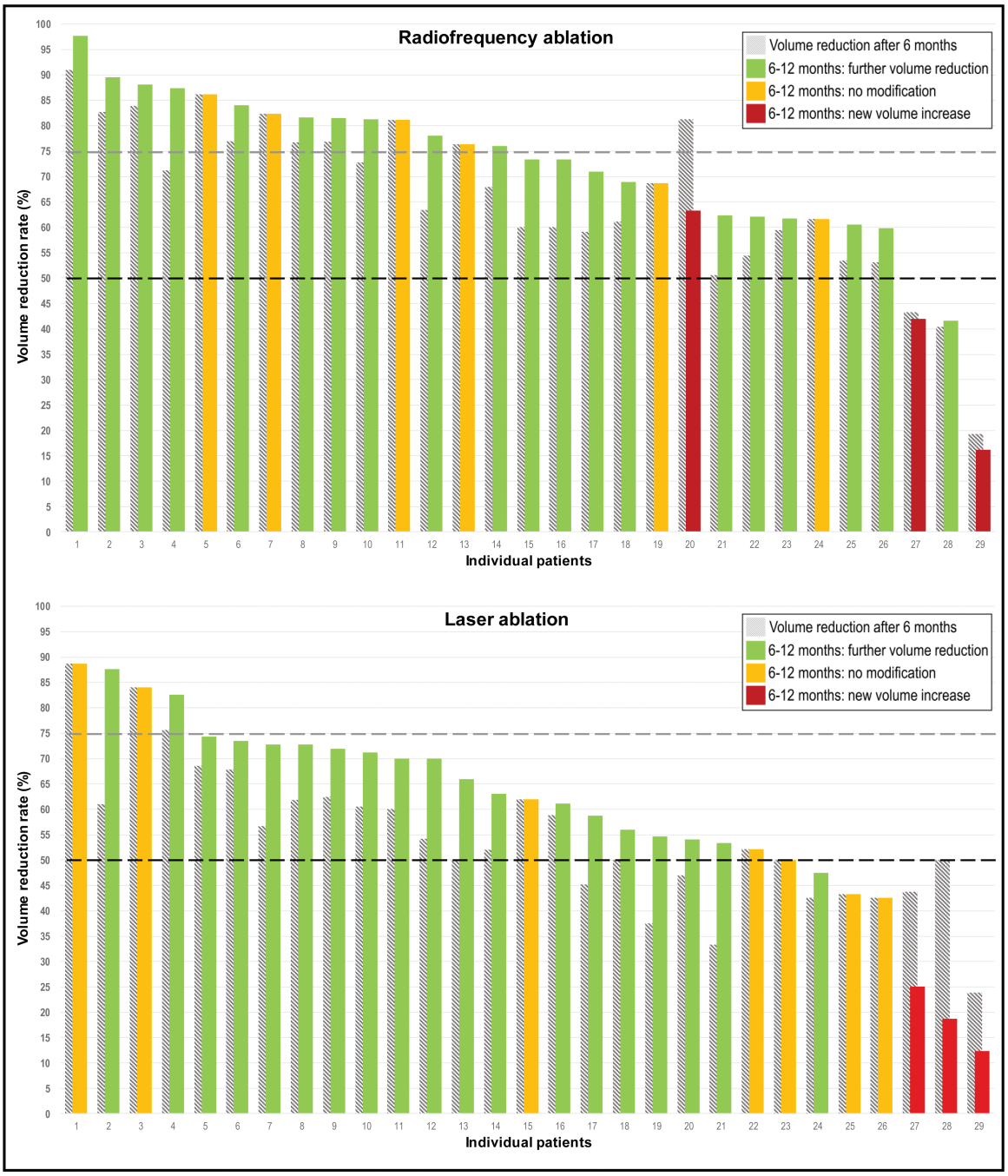
Figure 3. Comparison of nodule volume reduction rate changes between 6- and 12-month follow-up for patients treated with radiofrequency (RFA) and laser (LA) ablation. Diamonds: mean. Whiskers: 1 × standard deviation. RFA vs LA: comparison of the extent of volume reduction rate variation between 6 and 12 months in study groups.

Of note, a further significant VRR, similar for both study groups, between 6 and 12 months was documented for both RFA and LA treatments, supporting the durability of the thermal ablation effect over time. In variance from the 6-month results, the volume reduction with both methods at 12 months did not correlate with the basal nodule composition. This might indicate the long-term effect of the vascular injury induced by thermal treatment that leads to an ischemic atrophy in the residual nodular tissue. Indeed, novel ablation techniques have been proposed with artery-first ablation and marginal venous ablation to decrease the incomplete ablation rate and prevent nodule regrowth (17).

Several experts have established that the main therapeutic goal for BNTN thermal ablation includes the technical success rate with the ability to reduce the baseline volume by at least 50% (18). However, only few studies have evaluated the technical success rate as primary endpoint. With regard to the technical success rate endpoint, both techniques achieved very satisfying results without any significant differences at 6 or 12 months in this study population.

These findings are in agreement with the results of previous clinical studies that reported a technical success rate of 63% to 67% for LA (6, 13) and 85% to 90% for RFA (6, 12). Furthermore, a higher threshold (>75%) of VRR to define the technical success rate could help detect the better performance of RFA compared to LA. In our study, the higher is the VRR threshold to define the technical success rate, the higher is the performance of RFA than LA (Fig. 6). However, larger prospective studies are needed to confirm this finding.

We found a wide range of VRR variations in the LA group during the study period (6-12 months), although 3 patients in each study group experienced a new increase in nodule volume. Conversely, a long-term retrospective study on LA treatment showed that 37% of patients experienced nodule regrowth during a 5-year follow-up period, and the rate of nodule regrowth was inversely related to the 12-month VRR (19). Another retrospective long-term study that investigated the efficacy of RFA and LA showed that the rate of recurrence was approximately double in the laser group than in the RFA group.



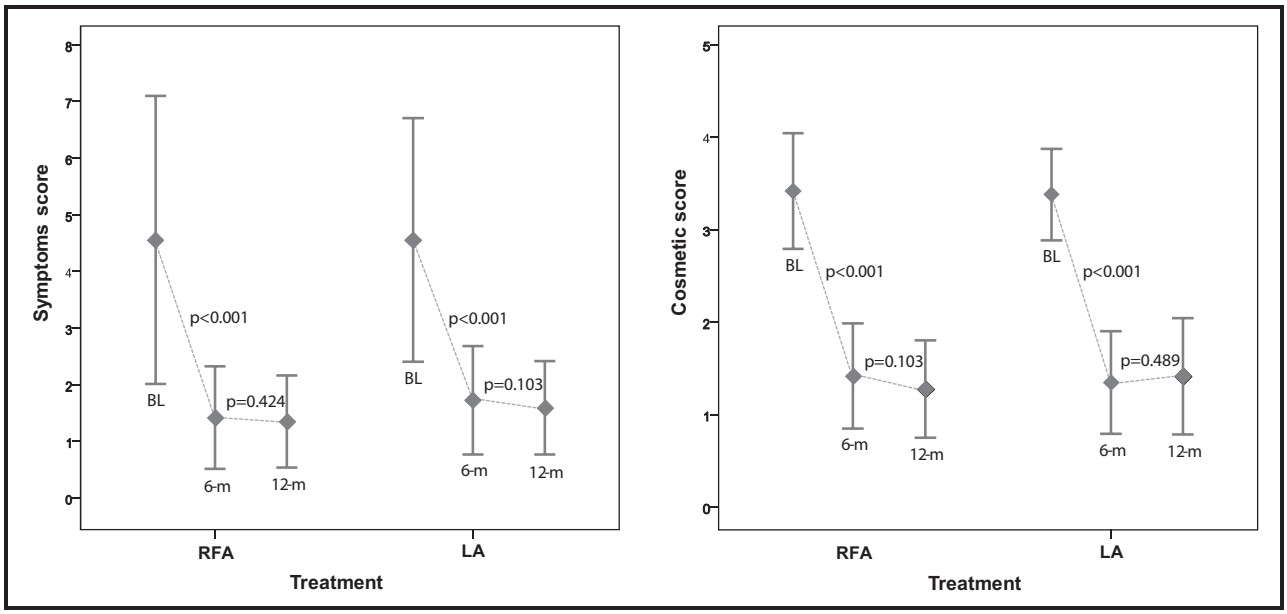
Dashed black line: primary success threshold (VRR > 50%). Dashed grey line: secondary success threshold (VRR > 75%).

Figure 4. Comparison between 6- and 12-month nodule volume reduction rate (VRR) for individual patients treated with radiofrequency and laser ablation with technical success rate at different cut-off values. Dashed black line: primary success threshold (VRR > 50%). Dashed grey line: secondary success threshold (VRR > 75%).

This is an important finding as it may indicate a higher risk of being affected by a malignant thyroid nodule in cases with poor response to the ablation treatment (6). All participants of this study group with nodule regrowth underwent ultrasound-guided fine-needle aspiration that ruled out malignancy.

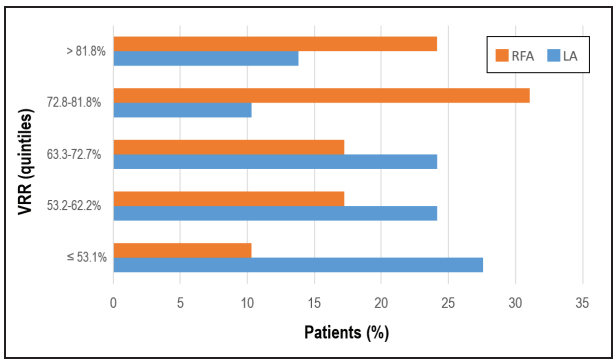
At 1 year after treatment, both techniques further improved the compressive symptoms compared to the baseline and the 6-month analyses, although there was no statistically significant difference between the LA and RFA groups. We confirmed that thermal ablation did not affect thyroid function.

We could not precisely determine why RFA induced a larger VRR compared to LA, although the greater release of energy with RFA could partially explain this result. The finding of the Trimboli and Deandrea study support the



Diamonds: mean. Whiskers: 1 × standard deviation. BL: baseline. 6-m: 6-months. 12-m: 12-months.

Figure 5. Comparison of changes in Symptoms and Cosmetic scores between baseline, 6-months and 12-months follow-up for patients treated with radiofrequency (RFA) and laser (LA) ablation. Diamonds: mean. Whiskers: 1 × standard deviation. BL: baseline. 6-m: 6 months. 12-m: 12 months.



Quintile	Patients n (%) LA	RFA
Q1	8 (27.6)	3 (10.3)
Q2	7 (24.1)	5 (17.2)
Q3	7 (24.1)	5 (17.2)
Q4	3 (10.3)	9 (31.0)
Q5	4 (13.8)	7 (24.1)

Figure 6. Comparison of 12-months nodule volume reduction rate (VRR) – stratified according to VRR quintiles distribution – between patients treated with radiofrequency (RFA) and laser (LA) ablation.

theory that energy per volume >2670 J/mL allows optimization of the technical and clinical successes of BNTN (20). In our RFA group, we administered a mean energy per volume of 2012.6 ± 96.5 J/mL and achieved a similar VRR. Conversely, the greatest VRR for the LA technique could be achieved using at least 400 J/mL energy for thyroid nodules (21-23), and, similarly, we released a similar quantity of energy (mean 497 J/mL). However, in LA, using a higher amount of energy would not be useful because the LA fiber is in direct contact with the nodule tissue and directly releases heat from the tip. Thus, a higher energy would produce a fence of tissue carbonization, thereby limiting the heating effect in the adjacent areas. There is an initial linear correlation between the output power and the delivered energy and the size of the laser-induced lesion, although for the highest values of power and energy delivered, the curves show a plateau that suggests logarithmic behavior (24). In our opinion this point represents an interesting field of development for LA technology since there is an emerging information about the energy per ml as an independent factor associated to the VRR.

Our findings support the safety of both thermal ablation treatments, as the study participants did not experience any other complications compared to what was recorded at 6 months after treatment. In particular, none of our patients required hospitalization.

The main limitations of this study are as follows: (1) non–double-blind study design and (2) no pre- and post-treatment evaluation of the quality of life of the participants.

In conclusion, a randomized head to head clinical trial showed that RFA persistently achieved a larger VRR than LA at 1-year after treatment, despite the similar technical success rates in both groups. Both ablation techniques are safe and do not affect the thyroid function.

Acknowledgments

We thank very much to our friend Claudio Pacella for his unconditional support. We thank "Tendi la mano ONLUS" for financially supporting the language editorial assistance (Editage, www.editage.com). Special thanks are due to Francesca Sanson for her assistance in the realization of figures.

Financial Support: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions: Study concept, design, and obtained funding: R.C., S.M., A.P. Executed the study: R.C., S.M., V.P., C.A., G.S., A.G., P.P., C.P., A.C., A.P. Statistical analysis: G.S., A.P. Drafting manuscript: R.C., A.P., A.C., G.S. Data interpretation and critical revision of the manuscript for important intellectual content, writing of the report and approval of the final version: R.C., S.M., V.P., C.A., G.S., A.G., P.P., C.P., A.C., A.P. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Additional Information

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Disclosures: All the other authors have nothing to disclose.

Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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