

## Laser Ablation Versus Radiofrequency Ablation for Benign Non-Functioning Thyroid Nodules: Six-Month Results of a Randomized, Parallel, Open-Label, Trial (LARA Trial)

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**Background:** No direct prospective studies comparing laser ablation (LA) and radiofrequency ablation (RFA) for debulking benign non-functioning thyroid nodules (BNTNs) exist. We aimed at comparing the efficacy and safety of both techniques in patients with solid or predominantly solid BNTN.

**Methods:** This six-month, single-use, randomized, open-label, parallel trial compared the following primary endpoints between the RFA and LA groups six months after treatment: (i) nodule volume reduction expressed as a percentage of nodule volume at baseline; (ii) proportion of nodules with more than 50% reduction (successful rate). We enrolled subjects with a solitary BNTN or dominant nodule characterized by pressure symptoms/cosmetic problems or patients without symptoms who experienced a volume increase >20% in one year. Nodules underwent core needle biopsy for diagnosis. Patients were randomly assigned (1:1) to receive LA or RFA. Safety was assessed in all randomly assigned participants.

**Results:** Sixty patients were randomly assigned to receive either RFA or LA (1:1) between January 2016 and November 2018. Both groups were similar in basal nodule volume, thyroid function, histology, symptoms/cosmetic score, and procedure time. At six months, the nodule volume reduction was 64.3% (95% confidence interval, CI 57.5–71.2) in the RFA group and 53.2% ([CI 47.2–95.2];  $p=0.02$ ) in the LA group. This effect was also confirmed in the linear regression model adjusted for age, baseline volume, and proportion of cellular component (LA vs. RFA percent change  $\Delta = -12.8$ ,  $p=0.02$ ). No significant difference was observed in success rate six months after treatment (RFA vs. LA: 86.7% vs. 66.7%,  $p=0.13$ ) or in thyrotropin level between the groups. Although improved, no significant difference was observed between RFA and LA for compressive symptoms (RFA: 2.13 vs. 3.9,  $p < 0.001$ ; LA: 2.4 vs. 3.87,  $p < 0.001$ ) and cosmetic score (RFA: 1.65 vs. 2.2,  $p < 0.001$ ; LA: 1.85 vs. 2.2,  $p < 0.001$ ). The adverse event rates (local pain, dysphonia, thyrotoxicosis, fever, hematoma) were 37% ( $n=11$ ) and 43% ( $n=13$ ) for RFA and LA, respectively, with no requirement for hospitalization.

**Conclusion:** Although the success rate was similar in the RFA and LA groups, RFA achieved a significantly larger nodule volume reduction at six months.

**Keywords:** laser ablation, radiofrequency ablation, thyroid nodule

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## Introduction

**N**ODULAR THYROID DISEASE is a common clinical problem and its prevalence increases with age and with more widespread use of thyroid ultrasonography. Although most thyroid nodules are benign and only require periodic monitoring, some may require treatment for associated compressive symptoms and/or cosmetic symptoms. Thyroid surgery, the main therapeutic approach for compressive thyroid nodules, may be associated with several drawbacks such as a neck scar, hypothyroidism, and hypoparathyroidism (1–3). Therefore, minimally invasive image-guided ablation is becoming increasingly common as an alternative to surgery for treating benign thyroid nodules (BTNs) (4,5). A recent study suggested that image-guided ablation may be proposed as a first-line treatment for solid non-functioning thyroid nodules that are benign on cytology when they become symptomatic (6). To date, the most common techniques used and tested are radiofrequency ablation (RFA) and laser ablation (LA). Both techniques are effective in reducing the volume of benign non-functioning thyroid nodules (volume reduction rates [VRR] range from 45% to 80%) and improving compression and/or cosmetic/symptom scores; these findings have been confirmed for up to 3–5 years after the ablation (7–9). To date, there are no reliable data on factors influencing the VRR of nodules treated by these techniques, although hypotheses on some factors such as volume at baseline, ultrasound (US) features of the nodule, proximity to vital structures, and operator skills have been proposed (10–12).

Previous meta-analysis and retrospective studies reported contradictory results regarding RFA and LA efficacy for treating BTNs (11,13–16). However, there are no direct prospective studies that compare the two techniques. In this head-to-head trial, we compared the efficacy and safety of RFA and LA in patients with non-functioning, solid, or predominantly solid BTN. This six-month, single-use, randomized, open-label, parallel trial compared the following primary endpoints between RFA and LA groups six months after treatment: (i) nodule volume reduction expressed as a percentage of nodule volume at baseline, and (ii) proportion of nodules with more than 50% reduction (success rate).

## Methods

### Study design and patients

The Laser Ablation versus Radiofrequency Ablation (LARA) study was a single-center, six-month, randomized, superiority, open-label, parallel group trial performed at Santa Maria Goretti Hospital (Lazio, Italy). This trial was conducted in compliance with the Declaration of Helsinki, and the trial protocol was approved by the institutional review board and ethics committee (ethic committee Lazio 2, approval number: CE 93321). Patients provided written informed consent before trial-related activities commenced. This trial was registered with ClinicalTrials.gov, number NCT02714946.

Patients were selected based on the following inclusion criteria: (i) older than 18 years; (ii) solitary thyroid nodule or dominating nodule that is well defined in multinodular goiter; (iii) nodule volume  $\geq 5$  mL; (iv) presence of a solid or predominantly solid nodule (solid portion  $>80\%$ ); (v) presence of compression symptoms or cosmetic concerns for which all

patients specifically requested treatment, or an increase in nodule volume  $>20\%$  in one year regardless of symptoms; (vi) confirmation of BTN using one single fine-needle aspiration and thyroid core needle biopsy (CNB); and (vii) normal serum levels of thyroid hormones, thyrotropin (TSH), calcitonin, and absence of anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb). The exclusion criteria were (i) nodules showing US features suggestive of malignancy; (ii) previous treatments for thyroid nodule; (iii) pregnancy; and (iv) hyper-functioning lesions, evaluated biochemically and/or [ $^{99m}\text{Tc}$ ]-pertechnetate scintigraphy.

From January 2016 to November 2018, 60 patients who met the eligibility criteria and gave written informed consent were randomly assigned to 1 of 2 groups of 30 patients to undergo either LA or RFA, with a 1:1 ratio. Each nodule underwent a single treatment session and was followed over time.

### Randomization and masking

Patients were randomly assigned (1:1) by using a computer-generated randomization list to receive RFA or LA treatment. The open-label design was necessary; thus, masking of the clinical staff or assessors was impossible.

### Procedures

**Clinical and biochemical evaluation.** Clinical history was carefully recorded, and a complete physical examination was performed. Serum concentrations of TSH, free thyroxine, and calcitonin, as well as levels of TgAb and TPOAb were measured at baseline and after six months. At enrolment and six months after treatment, the patients were asked to rate their compressive symptoms and cosmetic complaints. Compressive symptoms were evaluated by using a 0–10-point scale, where “0” indicated the absence of compression and “10” indicated severe compression that caused serious symptoms and which affected the patient’s quality of life. Cosmetic concerns were evaluated on a 4-point scale as follows: 1, nodule not visible and not palpable; 2, nodule palpable but not visible; 3, nodule palpable and visible from nearby; and 4, nodule palpable and visible from a distance (17).

**Thyroid ultrasonography.** US was performed by using a 7.5–12 MHz linear probe equipped with color Doppler and power Doppler modules (Technos MPX, Esaote My Lab 50; Novarium SRL, Rapallo, Italy). Baseline volume was calculated by multiplying the three longest diameters perpendicular to each other  $\times 0.525$  (ellipsoid formula). The volume reduction percentage was calculated according to the following formula: volume reduction percentage = [(initial volume – final volume)  $\times 100$ ] / initial volume. Two investigators (V.P. and R.C. with  $>15$  years’ experience with thyroid US) performed the US. The intra- and inter-observer coefficients of variation for sonographic volume assessment were previously defined as 4% and 6%, respectively (10).

**Core needle biopsy.** In light of our experience in the available literature (18), we chose CNB to obtain information on the histological architecture of the nodules undergoing ablation. CNB was performed by using a 1.1 or 1.6 cm

excursion 21-gauge double-action spring-activated needle (Ace-cut; TSK, Vancouver, Canada). Before CNB, a local anesthetic was administered. The needle was inserted into the nodule under US guidance in a freehand fashion. The spring was activated to sample the peripheral and sub-peripheral tissue (11 mm), moving from the center to the periphery of the nodule. One needle pass was made for each biopsy. The core samples obtained were fixed with 10% buffered formalin. There was no complication related to the CNB procedure. Formalin-fixed needle core samples were submitted for automated processing and immersed in paraffin. Serial 4- $\mu$ m-thick sections were collected on polarized slides. For each case, a slide was stained with hematoxylin and eosin, while the remainders were immunostained with galectin-3, cytokeratin-19, CD56, and hector battifora mesothelial-1 (HBME-1) (Thermo Fisher Scientific, Fremont, CA) by using a biotin-free peroxidase method in an automatized instrument (Omnis, Dako). All specimens were evaluated by two blinded experienced pathologists (A.C. and C.T. with >5 years' experience in evaluating core biopsy slides). A complete checklist was used for morphological evaluation, growth pattern, nuclear and cytoplasmic features, colloid characteristics, fibrosis, inflammatory components, and immunophenotypic profile of thyrocytes. The three main components of the core (cells, colloid, and fibrous tissue) were reported in percentages of the sample's composition. This evaluation was performed under microscopic examination at medium power field (using a 20 $\times$  objective). The final value was the mean of the values reported by the pathologists. When the difference between the pathologists' values was higher than 10%, the slides were re-reviewed by both pathologists to reach a consensus. Collected data were reported in the database. Only one investigator (V.P. with five years' experience in thyroid biopsy) performed this procedure.

**Minimally invasive image-guided thermal techniques.** Laryngoscopy was performed in the study population before intervention to assess vocal cord mobility. The same operator, an experienced interventional radiologist who had regularly performed RFA (in  $\sim$ 200 nodules) and LA for several years ( $\sim$ 150), carried out all procedures including the initial diagnostic evaluation by using the same US equipment for guidance. Patients were placed in the supine position with their neck fully extended. Perithyroidal injection of mepivacaine (2–5 mL of 2%, Carboson) and ropivacaine (3 mL, Naropine) was used for pain control.

**Radiofrequency ablation.** The procedure was based on the "moving-shot" technique as described elsewhere (19) by using a trans-isthmus approach with direct nodule puncture. In detail, a radiofrequency generator with an 18-gauge, 10-cm electrode with a 1-cm active tip (RF Medical Co, Ltd., South Korea) was applied by using 55 W of power and adequate exposure time to induce transient multiple hyperechoic zones as a sign of the effectiveness of the ablation. We calculated the treatment time for every RFA session from the initial insertion of the radiofrequency needle into the thyroid nodule to the final assessment of the treatment session.

**Laser ablation.** For this technique, we followed the indications published in a previous study (7). In brief, the

procedure was performed by using a commercially available US system (EchoLaser; ELESTA srl, Florence, Italy) equipped with a dedicated linear transducer operating at 13–4 MHz and with a needle-guided attachment with adjustable angle selection. Under US guidance, 21-gauge introducer needles were inserted with direct nodule puncture along its longest axis. Subsequently, a 300- $\mu$ m flat-tipped quartz optical fiber was introduced and advanced up to the introducer needle tip. The introducer needle was then withdrawn to expose the fiber tip by at least 5 mm in direct contact with the tissue. The fibers were then connected with the laser source operating at 1064 nm with an optical beam-splitting device. The number of 21-gauge applicators (introducer needle and flexible fiber) to be inserted was based on the size and shape of the nodule. Each treatment was performed with a fixed power protocol (3 W), but the illumination time was different on a case-by-case basis according to the size and shape of the target. After the first illumination, the applicator(s) were withdrawn by 2/3 cm and subsequent illumination was performed (pull-back technique) until the whole target was illuminated. Each illumination time ranged from a minimum of 400 seconds to a maximum of 600 seconds to keep the total energy applied between 1200 and 1800 J per fiber. Depending on the size of the nodule, one to three illuminations were applied in each session. LA was used on an average of two fibers by employing the pull-back technique. We calculated the treatment time for every LA session from the initial insertion of the LA needle into the thyroid nodule to the final assessment of the treatment session.

**Contrast-enhanced ultrasonography.** Extrapolating the data obtained in other organs, contrast-enhanced ultrasonography (CEUS) is considered a useful and reliable technique to evaluate the actual coagulation zone induced immediately after the ablation maneuver (20,21). The double contrast-imaging model was adopted with contrast-tuned imaging. The mechanical index was 0.03. The second-generation contrast agent SonoView was used (Bracco, Milan, Italy). Twenty-five milligrams of SonoView was diluted with 5 mL saline (0.9% NaCl), and a microbubble suspension was created by vibrating for 30 seconds. The suspension was injected as a bolus through the antecubital vein with a 0.812 mm (20G) needle; 2.4 mL of each injection was then flushed with 5 mL saline. The dynamic perfusion of the lesion was continuously observed for 90 seconds, and the images were stored. Residual viable tissue was determined by means of signal enhancement within the ablated lesion. The size of the non-enhanced area on CEUS was measured, and the volume was calculated by the ellipsoid formula stated earlier. CEUS evaluation was performed three days after LA and RFA treatments to calculate the necrosis volume.

### Outcomes

This trial compared the following primary endpoints between the RFA and LA groups six months after treatment: (i) nodule volume reduction expressed as a percentage of nodule volume at baseline, and (ii) proportion of nodules with more than 50% reduction (success rate). Secondary endpoints were the changes in TSH levels and AbTg positivity from the baseline to six months after the treatment. Other pre-specified secondary endpoints were aimed at (i) exploring the

hypothesis that histopathological features of thyroid nodules could predict the volumetric response to treatment and (ii) evaluating whether baseline volume of thyroid nodules may represent a predictive factor in volumetric response to treatment. Safety endpoints included the number and severity of treatment-related adverse events in both groups over the study period. Adverse events were recorded during each contact with site staff (all visits from randomization to follow-up). Major and minor complications were as defined by the Society of Interventional Radiology (22). A major complication was defined as one that, if left untreated, might threaten the patient's life, lead to substantial morbidity or disability, or result in a lengthened hospital stay. In this study, major complications included a transient or permanent voice change (dysphonia) and thyrotoxicosis. All other complications, such as hematoma, fever, and severe pain that needed medication for relief, were considered minor. Side effects were defined as untoward consequences that did not require therapy or prescription medications; they included mild, transient post-procedural pain, and discomfort.

### Statistical analysis

The trial was powered for volume reduction superiority of RFA compared with LA. Based on published data, we expected at least a 10% difference in nodule volume reduction between the RFA and the LA group (15). We calculated that a sample size of 30 participants per group was needed to have a power of about 90%, with a type I error rate of 5%, by estimating that the standard deviation (SD) would be as large as the expected difference. With the same sample size, we could detect with a power of 80% a standardized difference of 0.36

(i.e., a medium-sized difference according to Cohen J) (23) in the success rate in the two groups.

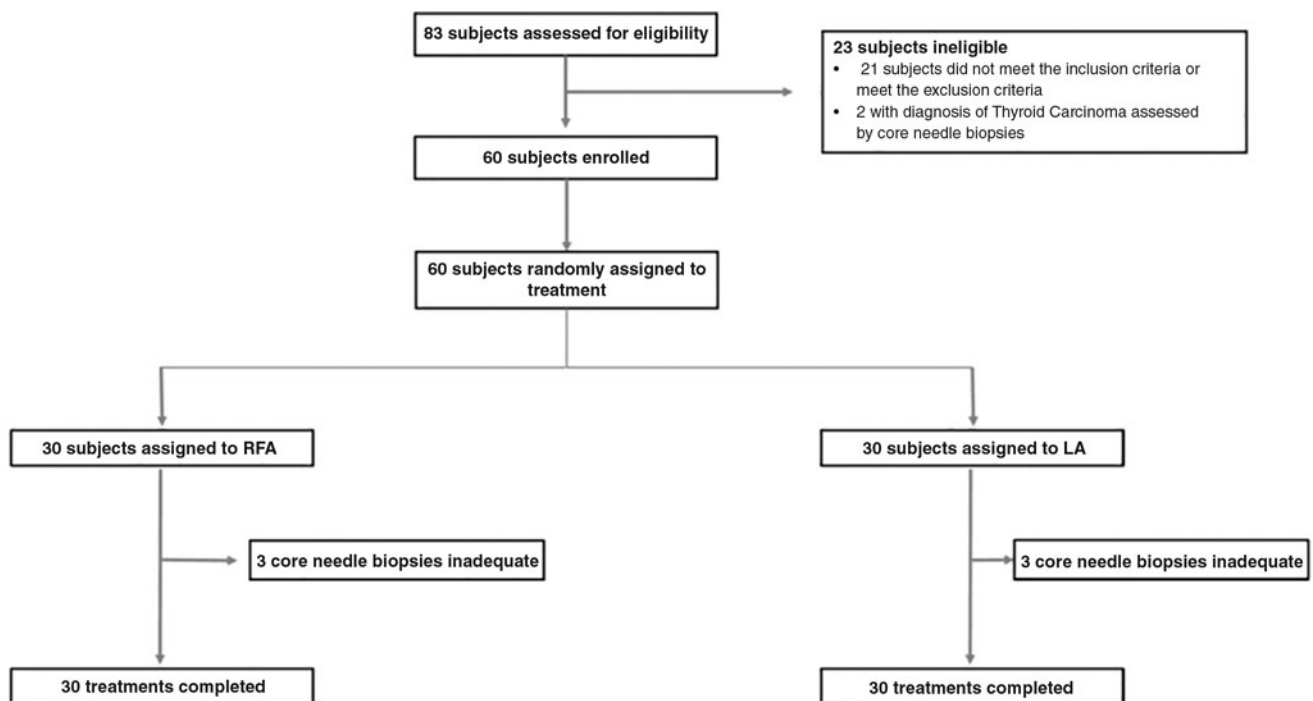
Data are reported by using mean and SD for quantitative variables and proportion for categorical variables. Differences between groups were evaluated by using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

Pearson's correlation coefficient was calculated to quantify the linear relationship between nodule characteristics and percent reduction in nodule volume. The difference in the percent reduction between groups was also evaluated in a linear regression model adjusted for age, baseline volume, and percent of cellular component. As this latter variable was related to nodule reduction in the RFA group only, we hypothesized that it could act as an effect modifier in the relationship between treatment and nodule reduction. Accordingly, we also fitted a model including an interaction term between treatment and the proportion of cellular component.

## Results

### Baseline characteristics

Sixty subjects who met the eligibility criteria were randomly assigned to RFA or LA (Fig. 1). The mean age was  $56 \pm 13$  (mean  $\pm$  SD) years, and the average thyroid nodule volume was  $25.4 \pm 22.3$  mL. The nodule volume, thyroid function, and histology were similar in the two groups at baseline; however, patients enrolled in the RFA group were older, with a mean age of 59 versus 53 years ( $p=0.08$ ) (Table 1). At baseline, no subjects showed TgAb and TPOAb levels above the upper limit of normal. The two groups were



\* 3 core needle biopsies for both treatment groups were inadequate, therefore we conducted the analysis to evaluate the impact of the nodule composition on VRR on 27 subjects for group.

FIG. 1. Screening and enrollment of subject into the randomized clinical trial.

TABLE 1. BASELINE STUDY COHORT CHARACTERISTICS

	<i>Laser (SD)</i>	<i>RFA (SD)</i>	<i>p-Value</i>
Age (years)	59.3 (11.7)	53.3 (14.3)	0.08
Baseline volume (mL)	24.7 (24)	26 (20.9)	0.89
Cellular component (%)	49.2 (18)	50.1 (18)	0.79
Colloidal component (%)	31.7 (13.8)	31.3 (12.8)	0.77
Fibrotic component (%)	19.8 (18.8)	18.6 (18.7)	0.44
Symptoms score	4.5 (2.1)	4.5 (2.5)	0.75
Cosmetic score	3.4 (0.5)	3.4 (0.6)	0.67
TSH ( $\mu$ U/mL)	1.75 (0.6)	1.98 (0.8)	0.52
ft4 (ng/dL)	1.29 (0.22)	1.25 (0.279)	0.54
Necrosis volume (mL)	16.2 (10.4)	21.0 (14.5)	0.15
Total energy (J)	9540 (3573)	53,898 (47,494)	<0.001
Energy delivered/volume (J/mL)	496 (209)	2011(95)	0.01
Time (minutes)	23 (8)	16 (13)	0.13

SD, standard deviation; RFA, radiofrequency ablation; TSH, thyrotropin; ft4, free thyroxine.

also similar in coagulative necrosis volume and procedure time. Patients who underwent RFA received a larger quantity of energy compared with those in the LA group ( $53,898 \pm 74,940$  vs.  $9540 \pm 3573$  J, respectively,  $p < 0.001$ ).

### Histology

Three CNBs in each treatment group were inadequate; therefore, we conducted an analysis to evaluate the impact of the nodule composition on VRR in 27 participants per group. Microscopic examination of the biopsies revealed thyroid parenchyma with follicular architecture showing various degree of follicle sizes, colloid characteristics, and stromal fibrosis. In the whole study population, the mean cellular ( $50\% \pm 18\%$ ), colloidal ( $31\% \pm 13\%$ ), and fibrotic ( $19\% \pm 10\%$ ) component was represented, in that order. No significant differences were found between the two groups in these three baseline characteristics (Table 1). No nuclear clearing nor irregularity in nuclear membranes were observed in the thyrocytes. Immunohistochemistry consistently resulted in negative staining for galectin3 and HBME-1 in all observed cases, while focal positivity for CK19 was detected in the thyrocytes limited to the fibrous septa in a few cases. There was no difference in the markers evaluated and VVR.

### Nodule volume change

As shown in Figure 2, participants in the RFA group had a 64.3% [95% confidence interval, CI 57.5–71.2] reduction in nodule volume versus 53.2% [CI 47.2–59.2] in the LA group ( $p = 0.02$ ) at six months. A reduction of  $\geq 50\%$  of nodule volume at six months was obtained in 76.7%, 86.7% in RFA, and 66.7% in LA group ( $p = 0.13$ ). Figure 3 shows the technical success rate at different cut-off values of nodule reduction at six months.

The volume reduction obtained with either of the two methods did not correlate with the baseline nodule volume or coagulative necrosis volume. Among patients treated with RFA, we found a correlation between the proportion of cellular component and the proportional volume reduction, while no correlation was present between histology and volume reduction in the LA group (Table 2).

The difference in volume reduction between both study groups was confirmed in a linear regression model adjusted

for age, baseline volume, and proportion of cellular component (LA vs. RFA percent change  $\beta = -12.8$ ,  $p = 0.018$ ). Concordant results were obtained in a model that also included an interaction term between treatment and proportion of cellular component (Table 3).

### Symptoms and cosmetic scores

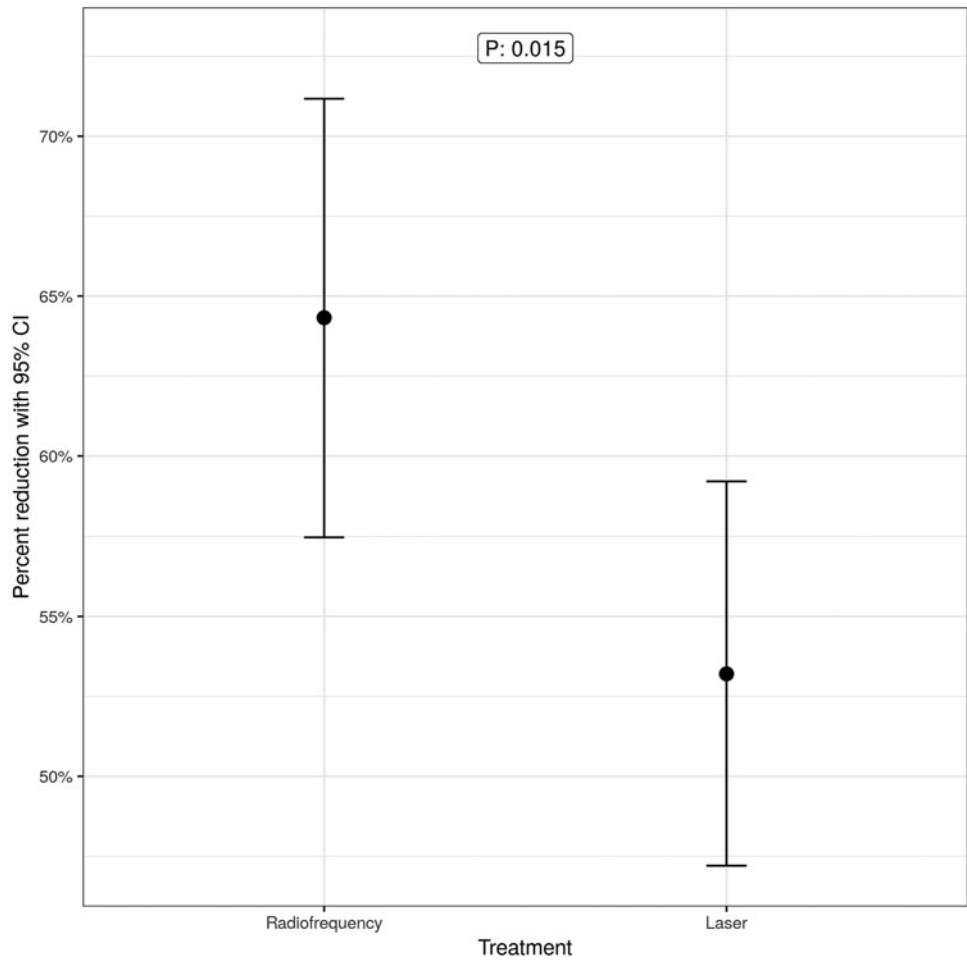
Compression symptom (mean reduction points:  $-3$  vs.  $-2.8$ ) and cosmetic concern ( $-1.9$  vs.  $-2$  points) scores were not significantly different between RFA and LA groups, respectively, at the end of the study.

### Thyroid function change

Thyroid function did not significantly change before and after treatment and at last follow-up. In particular, we did not record any significant TSH difference between the baseline and at six months in RFA ( $1.98 \pm 0.8$  vs.  $2.1 \pm 1.7$   $\mu$ U/mL,  $p = 0.35$ ) and LA ( $1.75 \pm 0.6$  vs.  $1.77 \pm 0.6$   $\mu$ U/mL, respectively,  $p = 0.45$ ) groups. At six months, the two groups were similar regarding TSH levels (RFA,  $2.1 \pm 1.7$  and LA,  $1.77 \pm 0.6$   $\mu$ U/mL,  $p = 0.15$ ). In two RFA and one LA patients, TgAb levels were above the upper limit of normal at six months. One LA patient had an elevated TPOAb level, above the normal upper limit at six months.

### Safety

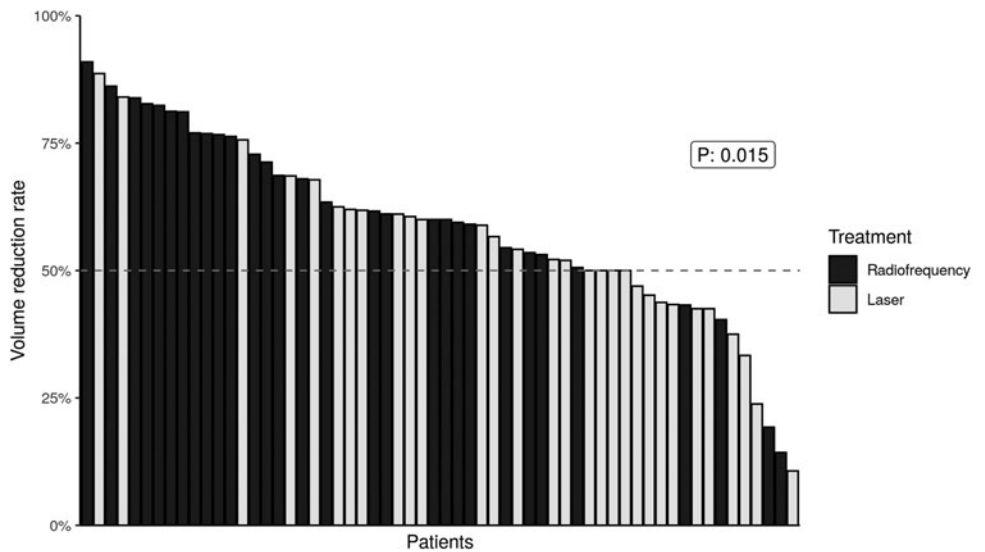
Adverse events were reported by 11 out of 30 (37%) patients treated with RFA and by 13 out of 30 (43%) patients treated with LA (Table 4). No adverse event led to premature treatment discontinuation, and no subject required hospitalization. Local pain, the most frequent side effect experienced during the procedure, occurred in similar proportions of patients treated with RFA (20%) and LA (17%). In the peri-procedural period, the frequency of major complications was similar between treatment groups. One subject experienced dysphonia in each group within 14 days from the beginning of oral glucocorticoid therapy, and the symptoms resolved in both subjects. One subject in the RFA group (39 days after the procedure) and two subjects in the LA group (28 and 37 days after the procedure) experienced thyrotoxicosis: Oral glucocorticoid, beta-blockers, and methimazole were started and



**FIG. 2.** Thyroid nodule volume change at six months after treatment.

after 90 days the symptoms completely resolved. Among the minor complications, three patients in the RFA group and two patients in the LA group experienced hematoma (anterior region of the neck) that resolved within 10 days of the procedure. One subject in the RFA group complained of head-

ache immediately after the procedure, with relief after one hour of paracetamol administration. Three patients in the LA group experienced fever (>37°C) within 30 days of the procedure; paracetamol and antibiotic therapies (amoxicillin and clavulanic acid) were administered.



**FIG. 3.** Success rate at different cut-off values of nodule reduction at six months. Dashed red line at 50%, which was used to define successful ablation in this study.

TABLE 2. CORRELATION BETWEEN NODULE CHARACTERISTICS AND VOLUME REDUCTION AT SIX MONTHS

	RFA $r$ Coefficient (p-value)	LA $r$ Coefficient (p-value)
Baseline volume	0.177 (0.35)	0.296 (0.11)
Coagulative necrosis volume	0.069 (0.72)	0.145 (0.45)
Cellular component (%)	<b>-0.41 (0.03)</b>	-0.066 (0.76)
Fibrotic component (%)	0.366 (0.06)	0.192 (0.38)
Colloidal component (%)	0.042 (0.83)	-0.213 (0.32)

Bold indicates statistically significant result.  
LA, laser ablation.

## Discussion

This is the first randomized control trial that compared the efficacy and safety of RFA and LA in a population with non-functioning, solid, or predominantly solid thyroid benign nodules. Our findings showed that, six months after treatment, RFA was more effective in reducing thyroid nodule volume compared with LA. However, when assessing the percentage of patients with a reduction in the volume of the nodule of at least 50% at six months, no statistically significant differences were found between the two treatment approaches. Further, we confirmed that both techniques were safe and reduce local symptoms and cosmetic concerns.

Our findings for VRR are consistent with the results of previous prospective studies (9,10,12,24). In a recent meta-analysis (16), the authors found that RFA was able to result in a VRR of 68% versus 48% for RFA versus LA at six months, respectively. These reduction rates are similar to our findings (64% vs. 53% for RFA and LA, respectively). The energy used to perform the thermal ablation may provide a possible explanation for the different VRR between the two techniques. Indeed, consistent with previous studies (14,25), we used a higher amount of energy with RFA than with LA. Some investigators also suggest that the moving-shot technique may explain the greater effectiveness of RFA, because it enables the treatment of the entire nodule in a safe and effective manner (11,14).

Seventy-seven percent of our entire study population achieved a reduction of at least 50% of the basal volume at six months after treatment; however, there was no statistically significant difference between the two treatment groups.

TABLE 3. LINEAR REGRESSION MODELS FOR PERCENT REDUCTION OF NODULE AT SIX MONTHS

	Model 1		Model 2	
	$\beta$ Coefficient	p- Value	$\beta$ Coefficient	p- Value
LA vs. RFA	-12.816	0.02	-32.3	0.03
Age	0.112	0.55	0.113	0.54
Baseline volume	0.108	0.48	0.122	0.42
Cellular component	-0.246	0.09	-0.430	0.03
Cellular component and treatment	—	—	0.395	0.17

Further, the success rate in our LA group was very similar to that reported in another prospective randomized trial (7). For local symptoms and cosmetic concerns, RFA and LA were equally able to improve symptom and cosmetic scores, confirming that both techniques can be valuable for the management of thyroid nodules symptoms.

We found discrepant results regarding the application time for the two techniques (11,14). In our study, we did not find any significant difference between RFA and LA. According to the American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi and Korean Society of Radiology guidelines (1,21), CEUS should be restricted to defining the size and limits of coagulated necrotic zones after US-guided ablation procedures. No clear evidence exists that demonstrates a significant correlation between coagulative necrosis volume assessed by CEUS and the final VRR (1,21). Our analysis did not provide relevant data to support the assumption that CEUS could be a useful tool to predict the final, post-ablation, volumetric reduction. From the analysis of previous studies focused on the use of LA and RFA, data are discordant on the correlation between nodule structure indirectly assessed by US investigation and final nodule volume reductions (11,12,26–29). Therefore, to avoid potential confounding, we used a very restrictive criterion enrolling patients only with solid or predominantly solid nodules with a fluid component  $\leq 20\%$ . Further, to date, no previous studies have directly evaluated the potential impact of the nodule composition on VRR. In our study population, we used a thin core biopsy instead of the second cytological assessment to improve the diagnostic quality and to obtain direct information about the nodule's architecture and composition (30). CNB led to two unexpected diagnoses of the follicular variant of papillary thyroid carcinomas that were excluded from the study. Three CNBs for both treatment groups were inadequate; therefore, we conducted analysis to evaluate the impact of the nodule composition on VRR in 27 subjects per group (Fig. 1). All the other core biopsies provided opportunities to evaluate the impact, if any, of the nodule's composition and the different ablative techniques.

The most interesting result of this study was the role of the nodule's cellularity in RFA treatment with a slight reduction in the overall efficacy observed but this characteristic did not seem to be the overall efficacy for LA. A possible interpretation is the difference in bio-impedance of various tissues, in particular the capacitive component of the cell membranes at the frequency of  $\sim 400$  kHz of the RFA treatment. These may cause a reduction in the resistive component, thus leading to lower heat production (31). In contrast, RFA-induced tissue heating, generated by resistive heating from ionic agitation, is strongly dependent on the local electrical conductivity (32). Neither nodule fibrosis nor colloid components showed significant impact on RFA or LA treatments. Similar to microwave ablation, LA is relatively tissue insensitive and therefore it is not influenced by the histological characteristics of the nodule tissue (32).

Findings from our trial confirmed that both techniques are safe. In particular, the overall safety profiles of RFA and LA were quite similar. No adverse events led to premature treatment discontinuation, and no patient required hospitalization. Pain experienced during the procedure was the most frequent adverse event that occurred in similar proportions in patients treated with RFA and LA. We had three cases of

TABLE 4. ALL COMPLICATIONS AND SIDE EFFECTS OBSERVED IN TRIAL

Type of complications (SIR class) <sup>a</sup>	Intra-procedural		Immediate post-procedural (within 24 hours)		Peri-procedural (within 30 days)		Delayed (after 30 days)		Maximum time to recovery (days)	
	LA	RFA	LA	RFA	LA	RFA	LA	RFA	LA	RFA
	Major									
Dysphonia	1 (3)	1 (3)								
Hyperthyroidism					1 (3)		1 (3)	1 (3)	14	14
Minor										
Hematoma	2 (7)	3 (10)							10	10
Side effects										
Local pain	5 (17)	6 (20)							1	1
Headache				1(3)						1
Fever			3 (10)						60	

Bold indicates statistically significant result.

<sup>a</sup>Society of Interventional Radiology (SIR) guidelines criteria.

thyrotoxicosis (one RFA and two LA). [<sup>99m</sup>Tc]-pertechnetate uptake scans revealed that the ablated nodules were cold and pertechnetate uptake in the rest of the thyroid glands was low and irregular. TSH receptor antibodies were negative, ruling out the induction of Grave's disease. Cell lysis due to the thermal ablation might have been the cause of the thyrotoxicosis. Further, in the LA group, three patients experienced fever that successfully responded to the use of paracetamol and antibiotic therapy. On the basis of a robust body of previous studies, we hypothesized that this is an aseptic reaction to the thermal insult of LA (33,34).

Two patients, one treated with RFA and one with LA, showed transient dysphonia, which spontaneously resolved after a few days. Even though vocal cord mobility impairment was suspected as a possible cause for the temporary hoarseness, no mobility impairment was detectable with routine fiber-optic endoscopic examination of the larynx. Because of the spontaneous recovery of the symptoms within a few days, no further assessment of vocal cord function was carried out. Temporary damage due to minimal thermal spread to the perineural soft tissue environment of either superior or inferior laryngeal nerves may have been the cause. In general, our major complication rates for both techniques agree with previous studies (11,35).

In the past few years, several studies have shown the efficacy of these techniques on thyroid nodules but the analysis of several biases such as the lack of randomization, the number of retreatments, and the different type of treated nodules (solid/mixed/cystic) have made the interpretation of the study results difficult. The strength of our study is that this is the first randomized controlled trial that aimed at evaluating the efficacy of the two most commonly used thermal ablation techniques. This was a single-center study, with a single operator, and thyroid nodules were treated once. Further, the structural characteristics of the nodules were homogeneous: all the treated nodules were solid or predominantly solid. Finally, this is the first study that tried to correlate volumetric reduction with thyroid nodule histological characteristics at baseline.

The main limitations of the study are: (i) the trial was not double blinded, but the open-label design was necessary;

therefore, it was not possible to blind the clinical staff or assessors; (ii) we did not evaluate the quality of life (assessed by SF-36) before and after the procedure; (iii) the same operator performed both RFA and LA, which may limit generalization; and (iv) efficacy and safety were evaluated with a short-term follow-up time.

In conclusion, RFA achieved better volume reduction at six months than LA. However, the success rate and safety profile were similar in both groups. Further larger prospective studies with longer follow-up time are needed to confirm our findings.

#### Author Contributions

Study concept, design and obtained funding: R.C., C.M.P., A.L., R.C., S.M., A.C., and A.P. Executed the study: R.C., V.P., M.I., G.C., C.T., and A.C. Statistical analysis: C.P., C.M.P. Drafting the article: R.C., C.M.P., P.P., A.L., A.C., and A.P. Data interpretation and critical revision of the article for important intellectual content, writing of the article, and approval of the final version: R.C., C.M.P., A.L., A.G., C.P., A.C., A.P., P.P., R.C., and 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.

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