Thyroid

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Laser Ablation versus Radiofrequency Ablation for benign non-functioning thyroid nodules: Six-month results of a randomised, parallel, open-label, trial (LARA trial)

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ABSTRACT

Background: No direct prospective studies comparing laser ablation (LA) and radiofrequency ablation (RFA) for debulking benign non-functioning thyroid nodules (BNTNs) exist. We aimed to compare 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: (1) nodule volume reduction expressed as a percentage of nodule volume at baseline; (2) 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 (CNB) 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 57.5 - 71.2%) in the RFA group and 53.2% (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 6-month 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: While the success rate was similar in the RFA and LA groups, RFA achieved a significantly larger nodule volume reduction at six months.

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INTRODUCTION

Nodular 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 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: (1) nodule volume reduction expressed as a percentage of nodule volume at baseline, and (2) proportion of nodules with more than 50 % reduction (success rate).

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METHODS

Study design and patients

The laser Ablation versus Radiofrequency Ablation (LARA) study was a single center 6-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: (a) older than 18 years; (b) solitary thyroid nodule or dominating nodule that is well-defined in multinodular goiter; (c) nodule volume ≥5 mL; (d) presence of a solid or predominantly solid nodule (solid portion >80%; (e) 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; (f) confirmation of benign thyroid nodule using one single fine-needle aspiration and thyroid core needle biopsy; and (g) 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 (a) nodules showing ultrasound (US) features suggestive of malignancy; (b) previous treatments for thyroid nodule; (c) pregnancy; and (d) hyper-functioning lesions, evaluated biochemically and/or [^{99m}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 one of two 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 up over time.

Randomisation and masking

Patients were randomly assigned (1:1) using a computer-generated randomisation 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 (fT4), and calcitonin, as well as levels of TgAb and TPOAb were measured at baseline and after 6 months. At enrolment and 6 months after treatment, the patients were asked to rate their compressive symptoms and cosmetic complaints. Compressive symptoms were evaluated using a zero- to ten-point scale, where zero indicated the absence of compression and ten indicated severe compression that caused serious symptoms and which affected the patient's quality of life. Cosmetic concerns were evaluated on a four-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)

US was performed using a 7·5 to 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 x 0·525 (ellipsoid formula). The volume reduction percentage was calculated according to the following formula: volume reduction percentage = [(initial volume - final volume) x 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).

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Core needle biopsy (CNB)

In light of our experience in the available literature (18), we chose core needle biopsy (CNB) to obtain information on the histological architecture of the nodules undergoing ablation. CNB was performed using a 1·1 or 1·6 cm excursion 21-gauge double-action spring-activated needle (Ace-cut, TSK, Vancouver Canada). Before CNB, local anaesthetic 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 centre 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 μm thick sections were collected on polarized slides. For each case, a slide was stained with haematoxylin and eosin (H&E), while the remainders were immunostained with galectin-3, cytokeratin-19, CD56, and hector battifora mesothelial-1 (HBME-1) (Thermo Fisher Scientific, Fremont, CA, USA) 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 20X 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 5 years' experience in thyroid biopsy) performed this procedure.

Minimally invasive image-guided thermal techniques

Laryngoscopy was performed in the study population before intervention to asses vocal cord mobility. The same operator, an experienced interventional radiologist who has

regularly performed RFA (in approx. 200 nodules) and LA for several years (approx. 150), carried out all procedures including the initial diagnostic evaluation 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%, Carbosen) 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) using a trans-isthmic 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 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 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-μm 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 fibbers 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 (3W), 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 performed (*pull-back*

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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 joules 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 fibbers 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 (CEUS)

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 0.812mm (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 above stated ellipsoid formula. CEUS evaluation was performed 3 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: (1) nodule volume reduction expressed as a percentage of nodule volume at baseline, and (2) 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 6 months after the treatment. Other pre-specified secondary endpoints were aimed to (1) explore the hypothesis that histopathological

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features of thyroid nodules could predict the volumetric response to treatment and (2) evaluate 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 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 the standard deviation 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 using mean and standard deviation (SD) for quantitative variables and proportion for categorical variables. Differences between groups were evaluated 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

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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 proportion of cellular component.

RESULTS

Baseline characteristics

Sixty subjects who met the eligibility criteria were randomly assigned to RFA or LA (Figure 1). The mean age was 56 +/- 13 (mean +/- standard deviation; SD) years, and the average thyroid nodule volume was 25.4 +/- 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 vs 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 also similar in coagulative necrosis volume and procedure time. Patients who underwent RFA received a larger quantity of energy compared to those in the LA group (53898 +/- 74940 vs 9540 +/- 3573 Joules, respectively, p <0·001).

Histology

Three core needle biopsies 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 whole study population, the mean cellular (50% +/- 18%), colloidal (31% +/- 13%), and fibrotic (19% +/- 10%) component was represented, in that order. No significant differences were found between the two groups in these three baseline characteristics (see Table 1). No nuclear clearing nor irregularity in nuclear membranes were observed in the thyrocytes. Immunohistochemistry resulted consistently in negative staining for galectin3 and HBME1 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% CI: 57·5%–71·2%) reduction in nodule volume vs 53.2% (95% CI: 47·2%–59·2%) in the LA group (p=0·02) at 6 months. A reduction of ≥50% of nodule volume at 6 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 6 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 6 months in RFA (1.98 +/- 0.8 vs 2.1 +/- 1.7 µU/mL, p=0.35) and LA (1.75 +/- 0.6 vs 1.77 +/- 0.6 µU/mL, respectively, p=0.45) groups. At 6 months, the two groups were

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similar regarding TSH levels (RFA, 2.1 +/- 1.7 and LA, 1.77 +/- 0.6 µU/mL, p=0.15). In two RFA and one LA patients, TgAb levels were above the upper limit of normal at 6 months. One LA patient had an elevated TPOAb level, above the normal upper limit at 6 months.

Safety

Adverse events were reported by 11/30 (37%) patients treated with RFA and 13/30 (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, 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 after 90 days the symptoms completely resolved. and methimazole was therefore, no longer needed to control the thyroid function. 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 headache 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.

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, 6 months after treatment, RFA was more effective in reducing thyroid nodule volume compared to LA. However, when assessing the percentage of patients with a reduction in the volume of the nodule of at least 50% at 6 months, no statistically significant differences were found between the two treatment

approaches. Furthermore, we confirmed that both techniques were safe and reduces 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% vs 48% for RFA vs LA at 6 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 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 6 months after treatment; however, there was no statistically significant difference between the two treatment groups. Furthermore, 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 (AACE)/Associazione Medici Endocrinologi (AME) 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 is discordant on the correlation between nodule structure indirectly assessed by US investigation and final nodule volume

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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 ≤ 20%. Furthermore, 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 in order to improve the diagnostic quality and to obtain direct information about the nodule's architecture and composition (30). Core needle biopsy led to two unexpected diagnosis of follicular variant of papillary thyroid carcinomas, which were excluded from the study. Three core needle biopsies 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 (Figure 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 the current study was the role of the nodule's cellularity on RFA treatment with a slight reduction in the overall efficacy observed but this characteristic did not seem to the overall efficacy for LA. A possible interpretation is the difference in bio-impendence of various tissues, in particular the capacitive component of the cell membranes at the frequency of approximately 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. Like 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, which occurred in similar proportions in patients treated with RFA and LA. We had three cases of thyrotoxicosis (one RFA and two LA). [^{99m}Tc]-pertechnetate uptake scans revealed that the ablated nodules were cold and pertechnetate uptake in the rest of the thyroid glands were

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. Furthermore, 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 last 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, 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 to evaluate 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. Furthermore, 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: (a) 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; (b) we did not evaluate the quality of life (assessed by SF-36) before and after the procedure; (c) the same operator performed both RFA and LA which may limit

generalization; and (d) efficacy and safety were evaluated with a short-term follow-up time.

In conclusion, RFA achieved better volume reduction at 6 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.

Contributors

Study concept, design and obtained funding: RC, CMP, AL, RC, SM, AC, AP. Executed the study: RC, VP, MI, GC, CT, AC. Statistical analysis: CP, CMP. Drafting manuscript: RC, CMP, PP, AL, AC, AP. Data interpretation and critical revision of the manuscript for important intellectual content, writing of the report and approval of the final version: RC, CMP, AL, AG, CP, AC, AP, PP, RC and AP 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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References

1. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, Paschke R, Valcavi R, Vitti P, Nodules AAATFoT 2016 American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules--2016 Update. Endocr Pract **22**:622-639.

2. Linos D, Economopoulos KP, Kiriakopoulos A, Linos E, Petralias A 2013 Scar perceptions after thyroid and parathyroid surgery: comparison of minimal and conventional approaches. Surgery **153**:400-407.

3. Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ, 3rd, Shaha AR, Shindo ML, Snyder SK, Stack BC, Jr., Sunwoo JB, Wang MB 2018 American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. Thyroid **28**:830-841.

4. Cesareo R, Palermo A, Pasqualini V, Cianni R, Gaspa G, Manfrini S, Pacella CM 2017 Radiofrequency ablation for the management of thyroid nodules: A critical appraisal of the literature. Clinical endocrinology **87**:639-648.

5. Mauri G, Nicosia L, Della Vigna P, Varano GM, Maiettini D, Bonomo G, Giuliano G, Orsi F, Solbiati L, De Fiori E, Papini E, Pacella CM, Sconfienza LM 2019 Percutaneous laser ablation for benign and malignant thyroid diseases. Ultrasonography **38**:25-36.

6. Papini E, Pacella CM, Solbiati LA, Achille G, Barbaro D, Bernardi S, Cantisani V, Cesareo R, Chiti A, Cozzaglio L, Crescenzi A, De Cobelli F, Deandrea M, Fugazzola L, Gambelunghe G, Garberoglio R, Giugliano G, Luzi L, Negro R, Persani L, Raggiunti B, Sardanelli F, Seregni E, Sollini M, Spiezia S, Stacul F, Van Doorne D, Sconfienza LM, Mauri G 2019 Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group. Int J Hyperthermia **36**:376-382.

7. Papini E, Rago T, Gambelunghe G, Valcavi R, Bizzarri G, Vitti P, De Feo P, Riganti F, Misischi I, Di Stasio E, Pacella CM 2014 Long-term efficacy of ultrasound-guided

laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. The Journal of clinical endocrinology and metabolism **99**:3653-3659.

8. Negro R, Greco G 2019 Unfavorable Outcomes in Solid and Spongiform Thyroid Nodules Treated with Laser Ablation. A 5-Year Follow-up Retrospective Study. Endocr Metab Immune Disord Drug Targets **19**:1041-1045.

9. Deandrea M, Trimboli P, Garino F, Mormile A, Magliona G, Ramunni MJ, Giovanella L, Limone PP 2019 Long-Term Efficacy of a Single Session of RFA for Benign Thyroid Nodules: A Longitudinal 5-Year Observational Study. The Journal of clinical endocrinology and metabolism **104**:3751-3756.

10. Cesareo R, Pasqualini V, Simeoni C, Sacchi M, Saralli E, Campagna G, Cianni R 2015 Prospective study of effectiveness of ultrasound-guided radiofrequency ablation versus control group in patients affected by benign thyroid nodules. The Journal of clinical endocrinology and metabolism **100**:460-466.

11. Pacella CM, Mauri G, Cesareo R, Paqualini V, Cianni R, De Feo P, Gambelunghe G, Raggiunti B, Tina D, Deandrea M, Limone PP, Mormile A, Giusti M, Oddo S, Achille G, Di Stasio E, Misischi I, Papini E 2017 A comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules: a propensity score matching analysis. Int J Hyperthermia **33**:911-919.

12. Deandrea M, Garino F, Alberto M, Garberoglio R, Rossetto R, Bonelli N, Spiezia S, De Santis M, Monti S, Deiana MG, Vincenzo T, Cugini C, El Dalati G, Limone PP 2019 Radiofrequency ablation for benign thyroid nodules according to different ultrasound features: an Italian multicentre prospective study. European journal of endocrinology / European Federation of Endocrine Societies **180**:79-87.

13. Ha EJ, Baek JH, Kim KW, Pyo J, Lee JH, Baek SH, Dossing H, Hegedus L 2015 Comparative efficacy of radiofrequency and laser ablation for the treatment of benign thyroid nodules: systematic review including traditional pooling and

Thyroid

Laser Ablation versus Radiofrequency Ablation for benign non-functioning thyroid nodules: Six-month results of a randomised, parallel, open-label, trial (LARA trial) (DOI: 10.1089/thy.2019.0660)

bayesian network meta-analysis. The Journal of clinical endocrinology and metabolism **100**:1903-1911.

14. Mauri G, Cova L, Monaco CG, Sconfienza LM, Corbetta S, Benedini S, Ambrogi F, Milani V, Baroli A, Ierace T, Solbiati L 2017 Benign thyroid nodules treatment using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA). Int J Hyperthermia **33**:295-299.

15. Cesareo R, Palermo A, Benvenuto D, Cella E, Pasqualini V, Bernardi S, Stacul F, Angeletti S, Mauri G, Ciccozzi M, Trimboli P 2019 Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A systematic review and meta-analysis. Rev Endocr Metab Disord **20**:37-44.

16. Trimboli P, Castellana M, Sconfienza LM, Virili C, Pescatori LC, Cesareo R, Giorgino F, Negro R, Giovanella L, Mauri G 2019 Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: A systematic review and meta-analysis. Endocrine.

17. Baek JH, Kim YS, Lee D, Huh JY, Lee JH 2010 Benign predominantly solid thyroid nodules: prospective study of efficacy of sonographically guided radiofrequency ablation versus control condition. Ajr **194**:1137-1142.

18. Pyo JS, Sohn JH, Kang G 2016 Core Needle Biopsy Is a More Conclusive Follow-up Method Than Repeat Fine Needle Aspiration for Thyroid Nodules with Initially Inconclusive Results: A Systematic Review and Meta-Analysis. J Pathol Transl Med **50**:217-224.

19. Jeong WK, Baek JH, Rhim H, Kim YS, Kwak MS, Jeong HJ, Lee D 2008 Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol **18**:1244-1250.

20. Meloni MF, Andreano A, Zimbaro F, Lava M, Lazzaroni S, Sironi S 2012 Contrast enhanced ultrasound: Roles in immediate post-procedural and 24-h evaluation of the effectiveness of thermal ablation of liver tumors. J Ultrasound **15**:207-214.

Thyroid
Laser Ablation versus Radiofrequency Ablation for benign non-functioning thyroid nodules: Six-month results of a randomised, parallel, open-label, trial (LARA trial) (DOI: 10.1089/thy.2019.0660)
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21. Kim JH, Baek JH, Lim HK, Ahn HS, Baek SM, Choi YJ, Choi YJ, Chung SR, Ha EJ, Hahn SY, Jung SL, Kim DS, Kim SJ, Kim YK, Lee CY, Lee JH, Lee KH, Lee YH, Park JS, Park H, Shin JH, Suh CH, Sung JY, Sim JS, Youn I, Choi M, Na DG, Guideline Committee for the Korean Society of Thyroid R, Korean Society of R 2018 2017 Thyroid Radiofrequency Ablation Guideline: Korean Society of Thyroid Radiology. Korean J Radiol **19**:632-655.

22. Sacks D, McClenny TE, Cardella JF, Lewis CA 2003 Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol **14**:S199-202.

23. Cohen J 1988 Statistical power analysis for the behavioral sciences (2nd ed) Hillsdale, N.J. : L. Erlbaum

24. Papini E, Guglielmi R, Bizzarri G, Graziano F, Bianchini A, Brufani C, Pacella S, Valle D, Pacella CM 2007 Treatment of benign cold thyroid nodules: a randomized clinical trial of percutaneous laser ablation versus levothyroxine therapy or follow-up. Thyroid **17**:229-235.

25. Gambelunghe G, Fede R, Bini V, Monacelli M, Avenia N, D'Ajello M, Colella R, Nasini G, De Feo P 2013 Ultrasound-guided interstitial laser ablation for thyroid nodules is effective only at high total amounts of energy: results from a three-year pilot study. Surgical innovation **20**:345-350.

26. Lim HK, Lee JH, Ha EJ, Sung JY, Kim JK, Baek JH 2013 Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. Eur Radiol **23**:1044-1049.

27. Lee GM, You JY, Kim HY, Chai YJ, Kim HK, Dionigi G, Tufano RP 2019 Successful radiofrequency ablation strategies for benign thyroid nodules. Endocrine **64**:316-321.

28. Ben Hamou A, Ghanassia E, Espiard S, Abi Rached H, Jannin A, Correas JM, Do Cao C, Kyheng M, Vantyghem MC, Monpeyssen H 2019 Safety and efficacy of thermal ablation (radiofrequency and laser): should we treat all types of thyroid nodules? (dagger). Int J Hyperthermia **36**:666-676.

29. Dossing H, Bennedbaek FN, Hegedus L 2019 Long-term outcome following laser therapy of benign cystic-solid thyroid nodules. Endocr Connect.

30. Jung CK, Baek JH 2017 Recent Advances in Core Needle Biopsy for Thyroid Nodules. Endocrinol Metab (Seoul) **32**:407-412.

31. Amini M, Hisdal J, Kalvøy H 2018 Applications of bioimpedance measurement techniques in tissue engineering J Electr Bioimp **9**:142-158.

32. Ahmed M, Brace CL, Lee FT, Jr., Goldberg SN 2011 Principles of and advances in percutaneous ablation. Radiology **258**:351-369.

33. Pacella CM, Francica G, Di Lascio FM, Arienti V, Antico E, Caspani B, Magnolfi F, Megna AS, Pretolani S, Regine R, Sponza M, Stasi R 2009 Long-term outcome of cirrhotic patients with early hepatocellular carcinoma treated with ultrasound-guided percutaneous laser ablation: a retrospective analysis. J Clin Oncol **27**:2615-2621.

34. Arienti V, Pretolani S, Pacella CM, Magnolfi F, Caspani B, Francica G, Megna AS, Regine R, Sponza M, Antico E, Di Lascio FM 2008 Complications of laser ablation for hepatocellular carcinoma: a multicenter study. Radiology **246**:947-955.

35. Jung SL, Baek JH, Lee JH, Shong YK, Sung JY, Kim KS, Lee D, Kim JH, Baek SM, Sim JS, Na DG 2018 Efficacy and Safety of Radiofrequency Ablation for Benign Thyroid Nodules: A Prospective Multicenter Study. Korean J Radiol **19**:167-174.

Thyroid
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Table 1. Baseline study cohort characteristics

	Laser (SD)	RFA (SD)	P-value
Age (yrs)	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 (µU/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)	53898 (47494)	<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

Table 2. Correlation between nodule characteristics and volume reduction at 6 months

	RFA	**LA**
	***r* coefficient (P-value)**	***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 (%)	**-0.41 (0.03)**	-0.066 (0.76)
Fibrotic component (%)	0.366 (0.06)	0.192 (0.38)
Colloidal component (%)	0.042 (0.83)	-0.213 (0.32)

RFA, radiofrequency ablation

LA, laser ablation

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Table 3. Linear regression models for percent reduction of nodule at 6 months

	Model 1		Model 2	
	β coefficient	**P-value**	**β 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

RFA, radiofrequency ablation

LA, laser ablation

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Table 4. All complications and side effects observed in trial.

Type of complications (SIR Class) [a]	Intra-procedural		Immediate post-procedural (within 24 h)		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**)							14	14
Hyperthyroidism					1 (**3**)		1 (**3**)	1 (**3**)	90	90
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	

a. Society of Interventional Radiology (SIR) guidelines criteria.

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FIGURE LEGENDS

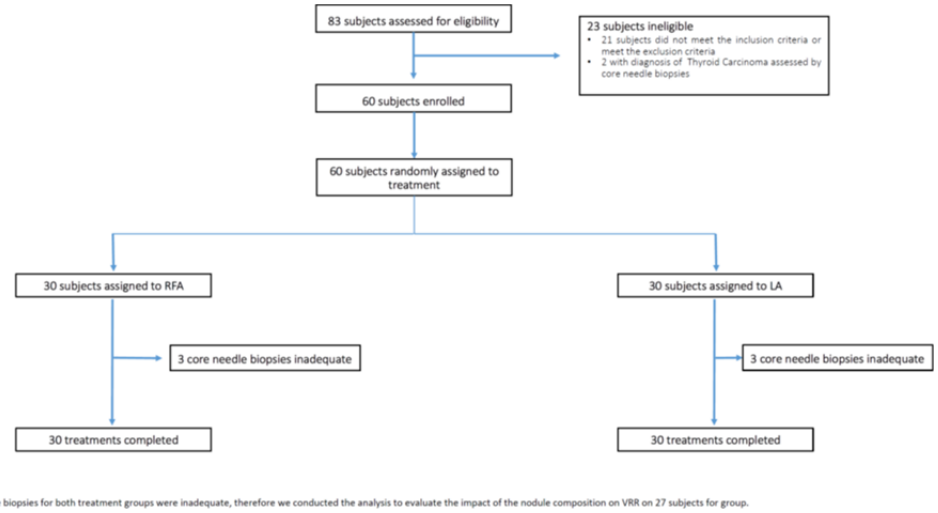

Figure 1. Screening and enrollment of subject into the randomized clinical trial.

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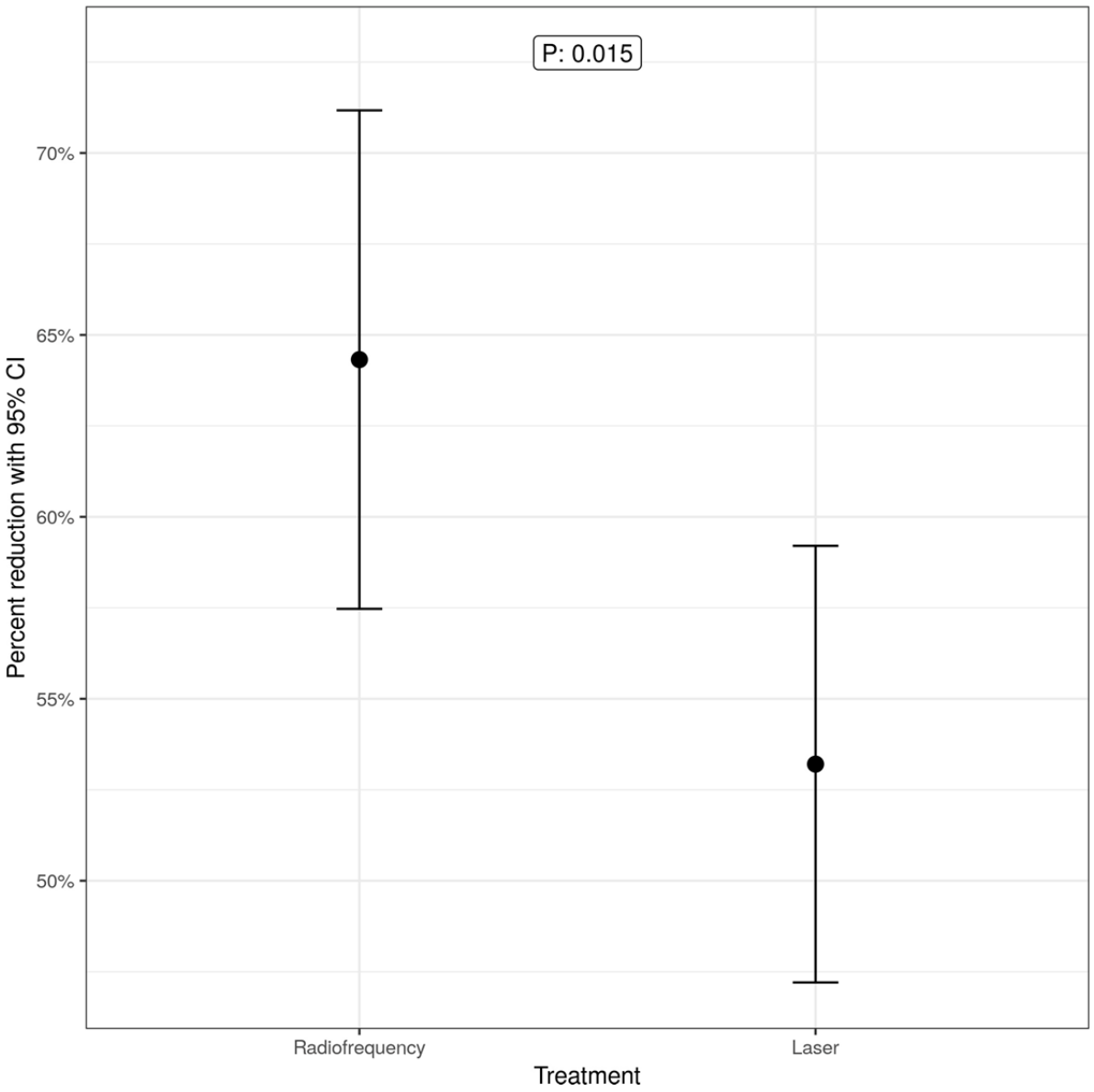

Figure 2. Thyroid nodule volume change at 6 months after treatment.

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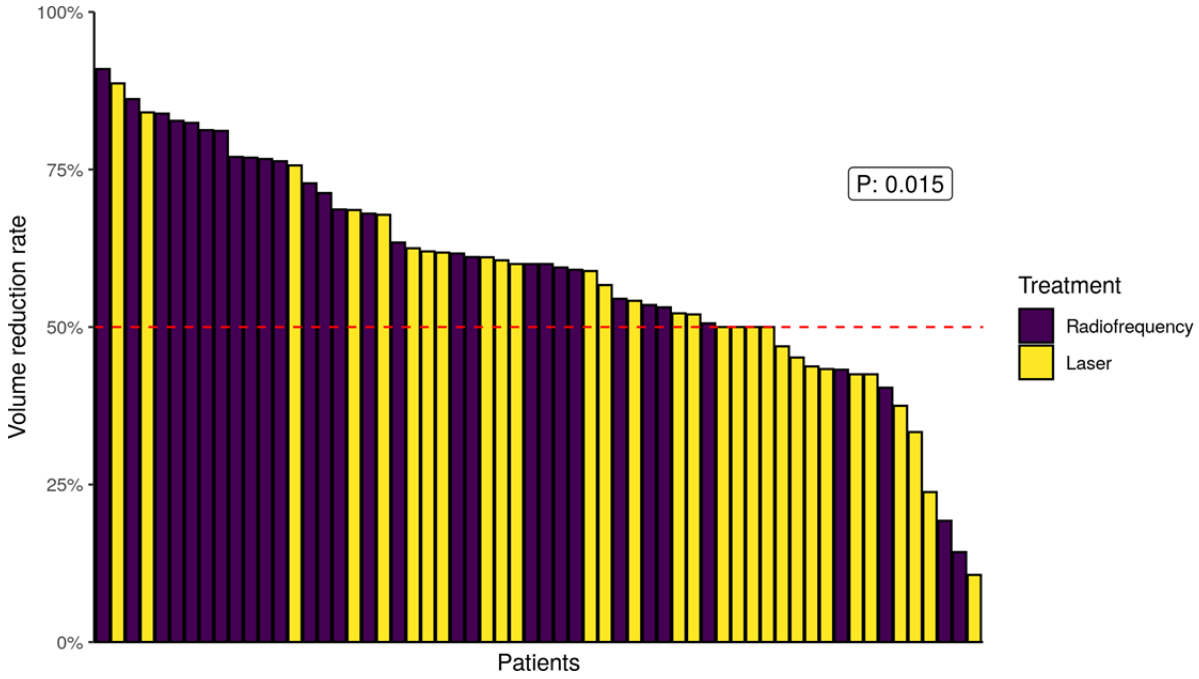

Figure 3. Success rate at different cut-off values of nodule reduction at 6 months. **Dashed red line at 50%, which was used to define successful ablation in the current study.**