Clinical Research Article

Percutaneous Ultrasound-Guided Laser Ablation of Benign Thyroid Nodules: Results of 10-Year Follow-Up in 171 Patients

Giovanni Gambelunghe,[1] Elisa Stefanetti,[2] Nicola Avenia,[3] and Pierpaolo De Feo[1]

[1]Endocrine Unit, Clinica Liotti, 06123 Perugia, Italy; [2]Studio Tiroide Prof. De Feo, 06132 Perugia, Italy; and [3]Department of Endocrine Surgery, Azienda Ospedaliero-Universitaria di Terni, 05100 Terni, Italy

ORCiD number: 0000-0002-7149-4867 (G. Gambelunghe).

Abstract

Context: Percutaneous, ultrasound-guided laser ablation is effective in nodular thyroid disease.

Objective: The aim of this study was to evaluate the long-term (10-year) efficacy and safety of laser ablation in the treatment of benign thyroid nodules.

Methods: From 2009 to 2010, 171 patients received a single session of laser ablation. Evaluation of nodule volume was performed before treatment, at 6 months, and every year.

Results: Technique efficacy was achieved in 92% of patients at 1 year. Median nodule volume significantly decreased from 16.7 mL (range, 11.0-97.0 mL) at baseline to 5.0 mL (range, 4.1-32.0 mL) at 1 year, a volume reduction ratio (VRR) of 68%. The benefit of the treatment was durable ($P < 0.001$ vs baseline at all timepoints), with a VRR of 59% after 10 years. No cases of nodule regrowth > 50% were observed at 1 year, although such cases did occur after 4 years (n = 3; 1.7% of the overall cohort) and 7 years (n = 8; 4.7%). There were no further cases of regrowth beyond 7 years. When patients were stratified according to baseline nodule volume (< 15 mL, 15-25 mL, or > 25 mL), durable results were observed across all 3 categories, with the largest, most prolonged effect observed in patients with nodules < 15 mL. Treatment was well tolerated, with only minor, transient complications of fever and local pain, and 98% of patients willing to recommend the treatment.

Conclusion: Percutaneous, ultrasound-guided laser ablation of benign thyroid nodules provides long-term benefits and the treatment is well tolerated.

Key Words: percutaneous laser ablation, ModìLite, EchoLaser, benign nodules, follow-up

Thyroid nodules are commonly seen in clinical practice, with an adult prevalence of 3% to 7% based on findings at palpation, and prevalence estimates ranging from 20% to 76% based on ultrasound examination [1]. Although the majority of thyroid nodules are cytologically benign, asymptomatic, and do not warrant treatment, some nodules will increase in size, producing compressive symptoms or causing cosmetic concerns for the patient. Therefore, in a proportion of patients with benign thyroid nodules, remedial treatment is required.

Alternatives to surgical treatment of benign thyroid nodules are preferable where clinically appropriate, and image-guided ablation of thyroid nodules using laser energy is recommended as a treatment strategy in recent management guidelines. According to recent guidelines on management of thyroid nodules, ultrasound-guided laser ablation (LA) may be considered for the treatment of solid or complex benign thyroid nodules that progressively enlarge, are symptomatic, or cause cosmetic concern [1-3]. The position of image-guided LA within recent management guidelines is based upon a large body of evidence gained over the last 2 decades [4, 5]. Randomized controlled trials have demonstrated the efficacy and safety of image-guided LA when compared with an observational approach [6, 7] and in comparison with treatment with radioiodine [8] or levothyroxine therapy [9]. One randomized comparison of image-guided LA vs radiofrequency ablation (RFA) in solid or predominantly solid thyroid nodules recently reported assessed outcome at 6 months postprocedure and observed similar success rates and safety in the 2 groups [10], while numerous retrospective studies of image-guided LA have added to the evidence base for this procedure [11-14].

The longest follow-up after ultrasound-guided LA for benign nodules reported in the literature is 5 years [15, 16]. In one study, 5-year retrospective follow-up was reported for 104 patients with benign, solid, cold nodules [15]. More recently, 5-year results of LA were compared with those of RFA in a multicenter, retrospective evaluation of 406 patients with benign thyroid nodules [16]. The current literature does not contain reports of the efficacy and safety of the laser procedure over longer follow-up periods. Here, we report the findings from 10 years of follow-up of a cohort of 171 patients with benign thyroid nodules who were treated with a single session of ultrasound-guided LA.

Methods

Inclusion criteria for this retrospective study were as follows: diagnosis of benignity obtained through 2 fine-needle aspiration biopsies, solid nodules (fluid component ≤ 10%), normal thyroid-stimulating hormone (TSH), free triiodothyronine and free thyroxine levels, negative anti-TSH receptor antibodies, negative anti-thyroperoxidase and anti-thyroglobulin antibodies, normal calcitonin levels, and the presence of local compression symptoms combined with refusal of surgery or surgical ineligibility. There were no specific exclusion criteria. The study was approved by the local ethics committee and fully informed consent was obtained in writing from all the subjects who met the inclusion criteria.

From 2009 to 2010, 171 patients were treated at Azienda Ospedaliero-Universitaria, Terni with 1 session of ultrasound-guided laser treatment and received a median energy of 510 J (424-680) per mL of tissue. The procedure was performed on an outpatient basis. Laser ablation was performed under sterile conditions, and ultrasound guidance was performed as described by Pacella et al [5] without anesthesia or sedation as we used the symptom of pain or burning as a guide to eventually stop or reduce energy delivery. Either 1 or 2 Chiba needles (21-gauge) were inserted percutaneously into the thyroid lesion under ultrasound guidance using a multifrequency probe (8-13 MHz, Esaote, Genoa, Italy). A 300-µm quartz laser flat-tip fiber was inserted in the needle lumen, with 5 mm of the fiber extending out of the needle. Patients were treated via a 1064 nm continuous-wave laser (EchoLaser ModìLite, Elesta, Calenzano, Florence, Italy). A continuous output power of 3 W was used for variable time, with the fibers pulled back whenever necessary. To avoid damage to adjacent structures, we maintained a distance of at least 15 mm from the tip of the fiber to the distal margin of the lesion and a distance of 10 mm with surrounding cervical structure and nodule capsule margin. All patients received a single treatment. The volume of the nodules treated was measured using the ellipsoid formula [17] before treatment, at 6 months, and every year.

Thyroid function was determined by routine assays before laser treatment and at each follow-up. Compressive symptoms and cosmetic effect were evaluated at Day 0 and after 1, 6, and 12 months and every year using the following scores: 0 = asymptomatic; 1 = mild pressure complaint; 2 = neck constraint; 3 = neck constraint with swallowing difficulty. Cosmetic effect was evaluated as follows: 0 = nodule not visible; 1 = nodule visible with hyperextended neck; 2 = nodule visible at a distance of < 1 m without extending neck; 3 = nodule visible at a distance of > 1 m. After clinical and ultrasound control, patients were asked to complete a structured visual analog questionnaire concerning treatment tolerability. Periprocedural pain was scored from 1 (absence of pain) to 10 (intolerable pain) [7].

Volume reduction ratio (VRR) was defined as the percentage reduction in volume, and it was calculated as follows: VRR = [(initial volume − final volume)/initial

volume × 100]. Technique efficacy was defined as a volume reduction ≥ 50% after 1 year from the treatment. Nodule regrowth was defined as a ≥ 50% nodule volume increase compared with the minimum recorded volume measured at a given follow-up time point [18]. The noncumulative incidence of nodule regrowth was analyzed; that is, for each time point, only new cases of regrowth that had occurred since the previous time point were included.

Statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL). Values for quantitative variables are expressed as median and range, or as mean and SD. Statistical significance was set at $P < 0.05$. The Wilcoxon test was used to check whether the changes in volume between every 2 consecutive follow-up visits were statistically significant. Correlation among the energy deposited, initial nodule volume, and nodule volume reduction in the follow-up period was investigated by means of Spearman's rank correlation and regression analysis.

Results

A total of 171 patients underwent the procedure and were followed for 10 years. Of this group of patients, 42% were male, and the median age was 61 years (range, 28-87 years). Patient characteristics are summarized in Table 1. The duration of the procedure ranged from 14 to 48 minutes.

Technique efficacy was achieved in 92% of patients at 1 year. Figure 1 depicts the durability of the reduction in nodule volume over the course of the follow-up period. Median nodule volume was significantly reduced from 16.0 mL (range, 11.0-97.0 mL) at the pretreatment assessment to 5.0 mL (range, 4.1-32.0 mL) at 1 year, corresponding to a VRR of 68%. The subsequent nodule volumes at 4 years, 7 years, and 10 years were 5.3 mL (range, 4.1-32.0 mL), VRR = 66%; 6.4 mL (range, 4.1-34.0 mL), VRR = 59%; and 6.4 mL (range, 4.1-34.0 mL), VRR = 59%, respectively. At each of these timepoints the

nodule volume was significantly lower compared with pretreatment ($P < 0.001$).

The noncumulative incidence of nodule regrowth is shown in Fig. 2. At the 1-year follow-up assessment, there were no cases of regrowth, even when regrowth was defined as < 25% increase in nodule volume. For all definitions of regrowth, cases of regrowth were more common at 4 years and 7 years compared with year 1; at 4 years, there were 3 cases (1.7%) of regrowth > 50%, 2 cases (1.2%) with regrowth 25% to 50%, and 1 case (0.6%) with regrowth < 25%. At 7 years, the corresponding values were 8 cases (4.7%), 7 cases (4.1%), and 4 (2.3%). There were no additional cases of regrowth detected at the 10-year follow-up. At 4 years, 5 patients (2.9%) went to surgery due to regrowth, and 16 patients (9.4%) went to surgery for regrowth at 7 years.

Table 2 summarizes data on the therapeutic response when patients were stratified according to pretreatment nodule volume. In patients with an initial nodule volume < 15 mL, the VRR of 74% that was achieved at
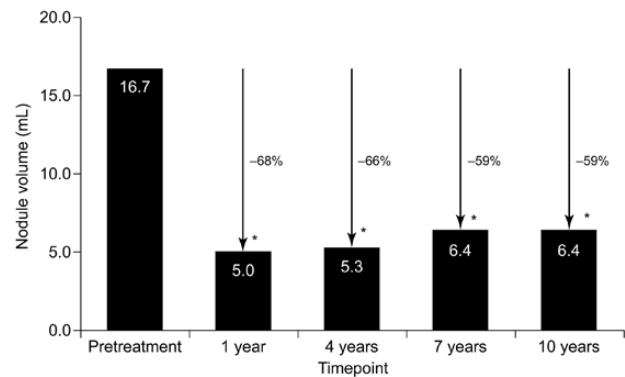

Figure 1. Median nodule volume in the overall study population over 10 years of follow-up. *$P < 0.001$ vs pretreatment nodule volume. Percentage values indicate the VRRs at each timepoint. The number of patients who underwent nodule-volume assessment at the different timepoints was as follows: pretreatment and 1 year, 171; 4 years, 166; 7 years, 150; 10 years, 150.

Table 1. Baseline characteristics of the population studied

Variable	
Sex (male/female)	72/99
Age (years)	61 (28-87)
Nodule volume (mL)	16.7 (11-97)
< 15 mL/15-25 mL/> 25 mL	21/67/83
Energy administered per mL of nodular tissue (J)	510 (424-680)
TSH (μIU/mL)	1.7 ± 0.7
FT4 (pg/mL)	10.4 ± 2.2
Tg (ng/mL)	125 ± 312

Data for age, nodule volume, and energy administered are expressed as median and range; thyroid function parameters are expressed as mean ± SD.
Abbreviations: FT4, free thyroxine; Tg, thyroglobulin; TSH, thyroid-stimulating hormone.
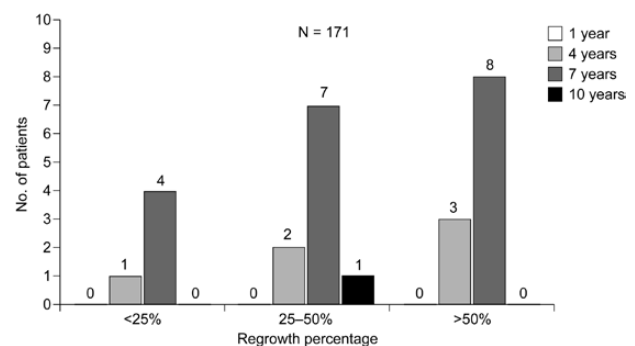

Figure 2. Noncumulative regrowth according to different regrowth categories. The number of patients who underwent nodule-volume assessment at the different timepoints was as follows: 1 year, 171; 4 years, 166; 7 years, 150; 10 years, 150.

1 year was maintained throughout 10 years of follow-up. In patients with an initial nodule volume between 15 and 25 mL, the VRR at 1 year was 70.5%, which reduced slightly at 7 years to 67.9% but remained stable at 10 years. For nodule volumes > 25 mL, VRR was 67.1% at 1 year, reducing to 59.5% at 7 years, and remaining stable at 10 years. The incidence of nodule regrowth increased with increasing nodule volume. There was one case of regrowth (< 25%) in patients with an initial nodule volume < 15 mL, compared with a total of 8 cases in the 15 to 25 mL category and 17 cases in the > 25 mL category.

Compared with pretreatment values, serum TSH and free thyroxine levels showed little change during follow-up, whereas serum Tg levels were reduced at 1 year and remained stable thereafter (Table 3).

After treatment, compressive symptoms improved in 152 patients (89%), and cosmetic effect improved in 139 patients (81%). The procedure was defined as well tolerated by 168/171 (98%) of patients, who scored the pain as lower than 4/10, and declared themselves ready to accept possible subsequent treatment, if needed. The other 3 patients rated the periprocedural pain as moderate-to-severe (visual analog score of 4 to 7). None of the patients treated with ultrasound-guided laser ablation had major complications. An association was found between amounts of energy and the development of minor complications; there were, in particular, cases of fever (14/171, 8.2%) and local pain (13/171, 7.6%). The most common side effect was fever (range, 37.2-37.6 °C) limited to the first 24 hours after treatment. Only 9 cases required medical therapy (acetaminophen and/or nonsteroidal anti-inflammatory drugs were given for up to 5 days).

Discussion

The use of laser ablation in benign thyroid pathology achieves nodule reduction through the process of laser-induced cytoreduction (LICR). In this procedure, a part of the nodule is treated and during the weeks after the treatment necrotic tissue is removed by macrophage activity, with a resulting reduction in nodule volume. In the present study, technique efficacy was achieved in 92% of patients at 1 year. A median VRR of 68% was observed at 1 year, which was essentially stable over the first 4 years of follow-up and largely retained at the end of follow-up; at 10 years the VRR was 59%.

Nodule regrowth may occur after LA, and regrowth is a key metric used to assess clinical outcome [18]. Using a cutoff of 50% to define regrowth, no cases were observed at 1 year, and while 3 cases (1.7%) and 8 cases (4.7%) were observed at 4 years and 7 years, respectively, there were no further cases seen beyond this timepoint. Further cases of regrowth were recorded when lower cutoff values were used.

The effectiveness and durability of LA depends on the amount of energy that is delivered to the nodule volume, expressed as Joules per mL of tissue [12]. Previous publications have concluded that in general, a dose exceeding 500 J per mL is required to produce good results [5, 12, 19, 20]. In the present study, the median energy delivered was 510 J (range, 424-680) per mL of tissue.

In our cohort, 5 patients (2.9%) went to surgery due to regrowth at 4 years, and 16 patients (9.4%) went to surgery for regrowth at 7 years. It should be considered that at the time this series of patients received their single session of LA (2009-2010), failure of treatment was declared in case of nodule regrowth, and patients were sent to surgery. Over time, ablation techniques have evolved and we now know that laser treatment can and should eventually be repeated over time in order to achieve optimal cytoreduction

Table 2. Analysis of therapeutic response according to the initial volume of the nodule

Timepoint	Nodule volume (mL)		
	< 15 mL	15-25 mL	> 25 mL
	(N = 21)	(N = 67)	(N = 83)
Pretreatment	14.1 (11-14.9)	22.4 (15-24.9)	48.9 (25-97)
1 year	3.7 (2.1-4.1)	6.6 (3.5-7.9)	16.1 (7.9-36.1)
4 years	3.7 (2.2-4)	6.9 (3.5-9.2)	16.9 (7.9-37.9)
7 years	3.7 (2.1-4.3)	7.2 (3.5-9.6)	19.8 (7.9-49.6)
10 years	3.7 (2.2-4.3)	7.2 (3.5-9.6)	19.8 (25-97)
Volume reduction ≥ 50% at 1 year	21/21 (100%)	61/67 (91.0%)	76/83 (91.6%)
Regrowth			
< 25%	1 (4.7%)	1 (1.5%)	3 (3.6%)
25-50%	0	4 (6.0%)	6 (7.2%)
> 50%	0	3 (4.5%)	8 (9.6%)

Data for nodule volume are expressed as median and range. Data for regrowth are at 10-year follow-up. The number of patients who underwent nodule volume assessment at the different time points was as follows: pretreatment and 1 year, 171; 4 years, 166; 7 years, 150; 10 years, 150.

Table 3. Assessment of thyroid function during follow-up

Variable	Timepoint			
	Pretreatment	1 year	5 years	10 years
TSH (µUI/mL)	1.7 ± 0.7	1.5 ± 0.5	1.6 ± 0.7	1.8 ± 0.8
FT4 (pg/mL)	10.4 ± 2.2	11.2 ± 2.1	10.8 ± 1.9	10.9 ± 2.5
Tg (ng/mL)	125 ± 312	76 ± 214	71 ± 209	72 ± 202

Abbreviations: FT4, free thyroxine; Tg, thyroglobulin; TSH, thyroid-stimulating hormone.

and relief of compressive symptoms, should the first session not suffice to produce expected results [2]. Repeatability is indeed one of the key benefits of this micro-invasive approach: based on our more recent experience, it is only advisable to pursue other surgical treatment options after at least one re-do procedure. In agreement with recent clinical practice guidelines [3], we recommend that patients should have their thyroid nodules evaluated by ultrasound at 3, 6, and 12 months after a single session of LA, with long-term follow-up performed every 12 months thereafter, to check for nodule regrowth.

In a subgroup analysis that categorized patients according to pretreatment nodule volume, the best results were seen in patients with a baseline nodule volume < 15 mL. Compared with this group, patients with initial nodule volumes of 15 to 25 mL and > 25 mL exhibited numerically smaller, slightly less durable VRRs, and more cases of regrowth, regardless of the definition of regrowth that was used.

The treatment was well tolerated, with only minor, transient complications of fever and local pain reported, and 98% of patients stating that they would be willing to recommend the treatment. These findings are consistent with our previous experience [12, 21, 22] and the results reported by other groups who have used this technique [10, 15]. Subcutaneous hematoma and transient dysphonia are occasionally a side effect of treatment, although no cases were recorded in the present study.

The efficacy results of our study are in marked contrast to those of a retrospective comparison of imaged-guided LA in a small cohort of patients with solid nodules vs those with spongiform thyroid nodules [23]. In that study, an unfavorable outcome was recorded in 19 of 29 (65.5%) patients with solid nodules compared with 5 of 33 (15.1%) patients with spongiform nodules. However, in the subset of LA patients who had favorable outcomes, the 5-year VRR was 59.7%, which is broadly similar to the VRR of 59.0% that we observed at 7 years. The reason for the subset of patients who had unfavorable outcomes after LA in this study is not explained in the publication; hence, it can be speculated that energy doses delivered were too low to reach optimal efficacy.

Prospective, direct studies comparing image-guided LA vs RFA are limited. Cesareo et al [10] have compared these 2 modalities in a randomized, open-label comparison in 60 patients with benign nonfunctioning thyroid nodules characterized as solid or predominantly solid. The 2 treatments had comparable success rates at 6 months, and improvements in compressive symptoms and cosmetic scores were significantly improved in both treatment groups. Longer-term follow-up was not available from this study, and so data for the VRR at 1 year are unavailable. However, initial

clinical outcome and safety profile of the treatments were comparable.

In a retrospective, multicenter study, Bernardi et al [16] compared the 2 ablation techniques in 406 patients with benign thyroid nodules (75% solid, median baseline volume 14.3 mL for RFA and 12.2 mL for LA), reporting 5-year follow-up for these patients. In the overall study population, RFA and LA significantly reduced nodule volume (VRR at 1 year = 72% for RFA; 55% for LA), with reduction generally maintained over the 5-year follow-up. Technique efficacy at 1 year was achieved in 85% of the RFA group and 63% of the LA group, and regrowth at 4 years occurred in 16.7% vs 33% of patients, respectively. At 4 years, 8 patients (3.7%) had been sent to surgery in the RFA group, compared with 21 patients (11.1%) in the LA group. These data were confirmed by propensity score matching. Therefore, across a range of outcomes, the results of our study are markedly better than those reported for LA in the retrospective study of Bernardi et al [16]: 1-year technique efficacy (92% vs 63%); VRR at 1 year (68% vs 55%), percentage of patients sent to surgery at 4 years (2.9% vs 11.1%), and regrowth at 4 years (1.7% vs 33%).

In considering the findings of the multicenter study, several points should be noted. First, the data for patients treated with RFA came from 6 centers, whereas only 2 centers provided data on LA patients, meaning that the results for LA were more influenced by data from each of the 2 centers, thus potentially skewing the results. In addition, the retrospective study design means that there was potential for confounding factors to have influenced the results, even though propensity analyses were conducted. Most importantly, despite propensity score matching, the median energy delivered per mL was significantly higher in the RFA group vs the LA group (1397.9 vs 348.1 J/mL; *P* < 0.001) [16]. The latter value is considerably lower than the energy delivery in our present study and other previous studies [5, 12, 20]. Therefore, considering these differences, it is evident that the different efficacies between the 2 treatment groups in the multicenter study, and between the LA group in the multicenter study and our findings can be attributed to suboptimal energy dosage.

Pacella et al [24] compared the performance of LA with RFA using a propensity score matching analysis of a multicenter cohort of 601 patients with benign thyroid nodules. Propensity matching generated a cohort of 276 patients who had similar baseline characteristics in the 2 treatment groups. In the overall cohort, the proportion of patients with technical success was numerically higher in the LA group vs the RFA group (75% vs 69%; *P* = 0.197). In the propensity score matched cohort, mean nodule reduction at 1 year was significantly higher for LA vs RFA

$(70 \pm 19\%$ vs $62 \pm 22\%$; $P = 0.001)$. This study demonstrated the contribution of operator skill to the clinical result, with operators with interventional training (surgeons or interventional radiologists) having a higher rate of technical success.

Certain strengths and limitations of the present study deserve mention. To our knowledge, our study is the first to report 10-year follow-up of patients who underwent a single session of image-guided LA for benign solid thyroid nodules. Our data double the previous reported duration of follow-up, and were obtained in a relatively large cohort of patients (n = 171). On the other hand, the study was retrospective in nature and lacked a control group.

In conclusion, in this longest reported follow-up of patients with benign thyroid nodules, treatment with percutaneous ultrasound-guided LA showed long-term benefits and was well tolerated.

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Additional Information

Correspondence: Giovanni Gambelunghe, MD, PhD, Endocrine Unit, Clinica Liotti, Via Serafino Siepi, 11, 06123 Perugia, Italy. Email: giovanni.gambelunghe@me.com.

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Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

References

1. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and managements of thyroid modules - 2016 update. Appendix. *Endocrin Pract.* 2016;**22**(Suppl 1):1-60.

2. Papini E, Pacella CM, Solbiati LA, et al. 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.* 2019;**36**(1):376-382.

3. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European thyroid association clinical practice guideline for the use of image-guided ablation in benign thyroid nodules. *Eur Thyroid J.* 2020;**9**(4):172-185.

4. Pacella CM, Bizzarri G, Guglielmi R, et al. Thyroid tissue: US-guided percutaneous interstitial laser ablation-a feasibility study. *Radiology.* 2000;**217**(3):673-677.

5. Pacella CM, Bizzarri G, Spiezia S, et al. Thyroid tissue: US-guided percutaneous laser thermal ablation. *Radiology.* 2004;**232**(1):272-280.

6. Gambelunghe G, Fatone C, Ranchelli A, et al. A randomized controlled trial to evaluate the efficacy of ultrasound-guided laser photocoagulation for treatment of benign thyroid nodules. *J Endocrinol Invest.* 2006;**29**(9):RC23-RC26.

7. Papini E, Rago T, Gambelunghe G, et al. Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial. *J Clin Endocrinol Metab.* 2014;**99**(10):3653-3659.

8. Døssing H, Bennedbaek FN, Bonnema SJ, Grupe P, Hegedüs L. Randomized prospective study comparing a single radioiodine dose and a single laser therapy session in autonomously functioning thyroid nodules. *Eur J Endocrinol.* 2007;**157**(1):95-100.

9. Papini E, Guglielmi R, Bizzarri G, et al. Treatment of benign cold thyroid nodules: a randomized clinical trial of percutaneous laser ablation versus levothyroxine therapy or follow-up. *Thyroid.* 2007;**17**(3):229-235.

10. Cesareo R, Pacella CM, Pasqualini V, et al. Laser ablation versus radiofrequency ablation for benign non-functioning thyroid nodules: six-month results of a randomized, parallel, open-label, trial (LARA trial). *Thyroid.* 2020;**30**(6):847-856.

11. Døssing H, Bennedbaek FN, Hegedüs L. Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. *Eur J Endocrinol.* 2011;**165**(1):123-128.

12. Gambelunghe G, Fede R, Bini V, et al. Ultrasound-guided interstitial laser ablation for thyroid nodules is effective only at high total amounts of energy: results from a three-year pilot study. *Surg Innov.* 2013;**20**(4):345-350.

13. Pacella CM, Mauri G, Achille G, et al. Outcomes and risk factors for complications of laser ablation for thyroid nodules: a multicenter study on 1531 patients. *J Clin Endocrinol Metab.* 2015;**100**(10):3903-3910.

14. Valcavi R, Riganti F, Bertani A, Formisano D, Pacella CM. Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. *Thyroid.* 2010;**20**(11):1253-1261.

15. Negro R, Greco G, Deandrea M, Rucco M, Trimboli P. Twelve-month volume reduction ratio predicts regrowth and time to regrowth in thyroid nodules submitted to laser ablation: a 5-year follow-up retrospective study. *Korean J Radiol.* 2020;**21**(6):764-772.

16. Bernardi S, Giudici F, Cesareo R, et al. Five-year results of radiofrequency and laser ablation of benign thyroid nodules: a multicenter study from the Italian minimally invasive treatments of the thyroid group. *Thyroid.* 2020;**30**(12):1759-1770.

17. Na DG, Lee JH, Jung SL, et al. Radiofrequency ablation of benign thyroid nodules: consensus statement and recommendations. *Korean J Radiol.* 2012;**13**(2):117-125.

18. Mauri G, Pacella CM, Papini E, et al. Image-guided thyroid ablation: proposal for standardization of terminology and reporting criteria. *Thyroid*. 2019;**29**(5):611-618.

19. Gambelunghe G, Bini V, Monacelli M, et al. The administration of anesthetic in the thyroid pericapsular region increases the possibility of side effects during percutaneous laser photocoagulation of thyroid nodules. *Lasers Surg Med*. 2013;**45**(1):34-37.

20. de Freitas RMC, Miazaki AP, Tsunemi MH, et al. Laser ablation of benign thyroid nodules: a prospective pilot study with a preliminary analysis of the employed energy. *Lasers Surg Med*. 2020;**52**(4):323-332.

21. Gambelunghe G, Bini V, Stefanetti E, et al. Thyroid nodule morphology affects the efficacy of ultrasound-guided interstitial laser ablation: a nested case-control study. *Int J Hyperthermia*. 2014;**30**(7):486-489.

22. Gambelunghe G, Stefanetti E, Colella R, Monacelli M, Avenia N, De Feo P. A single session of laser ablation for toxic thyroid nodules: three-year follow-up results. *Int J Hyperthermia*. 2018;**34**(5):631-635.

23. Negro R, Greco G. Unfavorable outcomes in solid and spongiform thyroid nodules treated with laser ablation. A 5-year follow-up retrospective study. *Endocr Metab Immune Disorder Drug Targets*. 2019;**19**(7):1041-1045.

24. Pacella CM, Mauri G, Cesareo R, et al. A comparison of laser with radiofrequency ablation for the treatment of benign thyroid nodules: a propensity score matching analysis. *Int J Hyperthermia*. 2017;**33**(8):911-919.