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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

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Objective: Laser ablation is a therapeutic modality used to reduce the volume of large benign thyroid nodules. Unsatisfactory reduction and regrowth are observed in some treated nodules. The aim of the study was to evaluate the long-term outcomes of laser treatment for solid nodules during a 5-year follow-up period, the regrowth rate, and the predictive risk factors of nodule regrowth.

Materials and Methods: We retrospectively evaluated patients with benign, solid, cold thyroid nodules who underwent laser ablation and were followed-up for 5 years. According to the selection criteria, 104 patients were included (median baseline nodule volume, 12.5 mL [25.0–75.0%, 8–18 mL]; median energy delivered, 481.5 J/mL [25.0–75.0%, 370–620 J/mL]). Nodule volume, thyroid function test results, and ultrasound were evaluated at baseline and then annually after the procedure.

Results: Of 104 patients, 31 patients (29.8%) had a 12-month volume reduction ratio (VRR) < 50.0% and 39 (37.5%) experienced nodule regrowth. Of these 39 patients, 17 (43.6%) underwent surgery and 14 (35.9%) underwent a second laser treatment. The rate of nodule regrowth was inversely related to the 12-month VRR, i.e., the lower the 12-month VRR, the higher the risk of regrowth ($p < 0.001$). The mean time for nodule regrowth was 33.5 ± 16.6 months. The 12-month VRR was directly related to time to regrowth, i.e., the lower the 12-month VRR, the shorter the time to regrowth ($p < 0.001$; $R^2 = 0.3516$). Non-spongiform composition increased the risk of regrowth with an odds ratio of 4.3 (95% confidence interval [CI] 1.8–10.2; $p < 0.001$); 12-month VRR < 50.0% increased the risk of regrowth with an odds ratio of 11.7 (95% CI 4.2–32.2; $p < 0.001$).

Conclusion: The VRR of thyroid nodules subjected to similar amounts of laser energy varies widely and depends on the nodule composition; non-spongiform nodules are reduced to a lesser extent and regrow more frequently than spongiform nodules. A 12-month VRR < 50.0% is a predictive risk factor for regrowth and correlates with the time to regrowth.

Keywords: *Thyroid; Laser; Thermal ablation; Nodule; Ultrasound*

INTRODUCTION

Image-guided thyroid ablation (I-GTA), such as radiofrequency (RF) and laser ablation, is mainly used to treat benign nonfunctioning thyroid nodules that show progressive growth over time, become symptomatic, or show cosmetic concerns (1, 2). In the last decade, several studies confirmed that laser ablation and RF are effective for cystic and hot thyroid nodules and are considered safe and cost-effective (3-6). Several studies demonstrated a significant benefit in the volume reduction ratio (VRR), usually by 50.0–80.0% over a follow-up period of up to 5 years (7-9). A recent metanalysis

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showed that significant nodule shrinkage is achieved after RF and laser ablation at 6–12 months and that the mean VRR remains stable for up to 3 years (10). Concerns have been raised regarding the long-term effects of I-GTA on the chance of unsatisfactory nodule volume reduction and putative risk factors for regrowth (11, 12).

The aim of this study was to retrospectively evaluate the long-term outcomes of laser treatment in solid nodules during a 5-year follow-up period, with a particular focus on the 12-month post-treatment VRR, regrowth rate, and predictive risk factors of nodule regrowth.

MATERIALS AND METHODS

The research presented in the manuscript was ethically conducted in accordance with the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies as well as according to animal welfare regulations, including the Animal Research. This study was approved by the Institutional Review Board (IRB). Informed consent from patients was exempted by the IRB because of the retrospective nature of this study.

Institutional Management for Laser Ablation of Thyroid Nodules

Laser ablation has been used at the "V. Fazzi" Hospital of Lecce, Italy since 2009 to treat benign thyroid nodules. According to our institutional guidelines, thyroid nodules are eligible for laser ablation if they cause local compressive symptoms and/or cosmetic concerns, are diagnosed as benign after two cytological assessments, and if they show a solid ultrasound pattern (≤ 10.0% fluid component; nodules with a larger fluid component are aspirated and submitted to ethanol injection when necessary). Since 2009, the same two operators have treated the patient population with laser ablation.

Patient Selection and Follow-Up

In July 2019, we retrospectively searched our database for patients followed-up for at least 5 years after treatment (between July 2009 and July 2014). Patients were included in the study if they were > 18 years of age, had normal thyroid function and normal calcitonin levels, had not previously received thyroid treatment (i.e., thermal ablation, radioiodine, external radiotherapy, LT4/LT3, or iodine supplements), had received no drugs interfering with thyroid function, showed hypofunctioning on the ^{99m}Tc thyroid scintiscan, and had solid nodules (absent or minimal, i.e., < 10.0%, cystic component). Of all patients treated with laser ablation at our institution, 127 were followed-up for at least 5 years. Of these, 23 (18.1%) were excluded according to the above selection criteria and 104 were finally included. The group of excluded patients was similar to our cohort of patients in terms of age (median age, 55 years; 25.0–75.0%, 38–70 years), sex (four men/19 women), nodule volume at baseline (median, 14 mL; 25.0–75.0%, 11–24 mL), energy delivered (median, 7521 J; 25.0–75.0%, 6056–9006 J), and energy delivered/mL (median, 431 J/mL; 25.0–75.0%, 337–601 mL). After laser treatment, patients were monitored at least annually. Monitoring consisted of thyroid ultrasound and determination of free T4 (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibodies (TgAb), peroxidase antibodies (TPOAb), thyroglobulin (Tg), and calcitonin levels. All thyroid ultrasound images were stored. Cosmetic score (scale from 1 to 4) and symptom score (scale from 0 to 10) were evaluated at baseline and then annually (13).

Laboratory Evaluation

Serum TSH, FT4, Tg, TPOAb, TgAb, and calcitonin were assessed as per the scheduled protocol (before treatment and then annually). Serum TSH, FT4, and Tg were measured using a third-generation electrochemiluminescence immunoassay (Roche Diagnostics, Monza, Italy). Reference values were 0.3–4.2 mIU/L for TSH, 0.8–1.7 ng/dL for FT4, and 0.2–70 ng/mL for Tg. TPOAb and TgAb were determined using a radioimmunoassay kit (DiaSorin, Saluggia, Italy); the reference range was 0–16 IU/mL for TPOAb and 5–100 for TgAb. Calcitonin was determined using commercially available immunoradiometric assay kits (normal value < 10 ng/mL).

Ultrasound Evaluation

Thyroid ultrasound (US) evaluation was conducted at baseline and then at least annually using a commercially available US scanner (MyLab25Gold, Esaote S.p.A., Genoa, Italy) equipped with a 7.5–13.0-MHz linear transducer. Nodule volume was reported in mL using the ellipsoid volume formula: (length x width x depth) x 0.524. Changes in nodule volume were expressed as the VRR calculated using the following formula: (initial volume - final nodule volume) x 100/initial volume (1).

Nodule regrowth was defined as a nodule volume increase ≥ 50.0% compared to the minimum recorded volume

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measured at a given follow-up time point (14). "Technical failure" was defined as 12-month reduction < 50.0% (14).

Two medical doctors (endocrinologist and radiologist) evaluated nodule composition by mutual consent at the patient's enrolment. For the purposes of the study, we only evaluated solid nodules, i.e., those with an absent or minimal (< 10.0%) cystic component. Nodules were classified as "spongiform" if the nodule composition was characterized by the presence of intervening multiple, diffuse microcystic lacunae and "non-spongiform" if the nodule composition was characterized by the absence of intervening multiple, diffuse microcystic lacunae. Nodules with a volume ≤ 10 mL were considered "small," those with a volume 11–30 mL were considered "medium," and those with a volume > 30 mL were considered "large" (14).

Laser Ablation Procedure

Light conscious sedation was obtained using intravenous midazolam (2–5 mg) in fractioned boli. After US examination of the neck and the definition of the entry point of the needles, local anesthesia was administered with an injection of 2% xylocaine from the skin deep to the thyroid capsule. Laser ablation was performed by inserting 21-gauge spinal needles into the target thyroid lesion under US monitoring. After freehand positioning of the needle tips, under ultrasound monitoring, a 300-µm-diameter plane-cut quartz optical fiber was introduced through the sheath of the needle and the fiber tip was placed in direct contact with the tissue. Optic fibers were connected to the laser source, a continuous-wave Nd-YAG laser operating at 1064 µm with an optical beam splitting device (EchoLaser, Elesta, Florence, Italy) and an output power of 3–5 W. One to three needles were placed manually along the longitudinal, cranio-caudal, and major nodule axis, at a distance of 10 mm each, fitting as best as possible to the shape of the nodule. The procedure was started with a deposition energy of 1200–1800 J per fiber in the caudal part of the nodule, 10 mm from the lower margin, trachea, and carotid. By upward needle/fiber pullbacks of 10 mm, additional energy was administered until a distance of 5–10 mm from the upper part of the nodule was reached. During ultrasound monitoring, the treatment area was visualized as a transient hyperechoic zone, which became enlarged over the time due to the formation of gas microbubbles within the coagulated tissue. After treatment, patients were given an intravenous injection of ketoprofen (15).

Statistical Analysis

Nonparametric continuous variables are expressed as the median with interquartile range. Statistical differences in continuous variables were evaluated using the Wilcoxon test for coupled samples and using the ANOVA test for group comparisons. Categorical variables were compared using the Pearson chi-squared test and Pearson's *r* correlation was used to measure the relationship between linearly related variables. Multivariate logistic regression analysis was used to evaluate the relative weight of independent variables (baseline volume, energy delivered/mL of tissue, VRR, and nodule composition) to predict the dependent variable (nodule regrowth). A p value < 0.05 was considered significant. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the characteristics of the study group. At the final follow-up, 2/104 patients (1.9%) were TPOAb- and TgAb-positive, seven patients (6.7%) were TPOAb-positive, and 10 patients (9.6%) were TgAb-positive. The overall prevalence of thyroid autoimmunity, as well as thyroid function and Tg values (except for two patients who developed hypothyroidism) did not change over time.

When we considered the nodule volume reduction results 12 months after laser ablation, we found that 73 (70.2%) nodules had VRR ≥ 50.0% and the remaining 31 (29.8%) had VRR < 50.0%. These two subgroups showed

Table 1. Baseline Characteristics of Patients

Number of patients	104
Sex (male/female)	21/83
Age (years) (median; 25.0–75.0%)	54 (45–66)
TSH (mIU/L) (median; 25.0–75.0%)	1.2 (0.9–2)
Non-spongiform/spongiform	46/58
Energy delivered (J) (Median; 25.0–75.0%)	6179.5 (4057–8044)
Energy delivered/mL (Median; 25.0–75.0%)	481.5 (370–620)
Nodule volume at baseline (mL) (Median; 25.0–75.0%)	12.5 (8–18)
Small nodules (≤ 10 mL) (%)	41 (39.4)
Medium nodules (11–30 mL) (%)	57 (54.8)
Large nodules (> 30 mL) (%)	6 (5.8)
VRR at 12-month follow-up (%) (median; 25.0–75.0%)	60.5 (47–71)

TSH = thyroid-stimulating hormone, VRR = volume reduction ratio

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no significant differences in sex, age, TSH level, volume at baseline, or the energy delivered; however, there was a significant difference in terms of composition, as non-spongiform nodules were more prevalent in the "< 50.0% group" than in the "≥ 50.0% group" (Table 2). After the initial 12-month follow-up ultrasound monitoring, we observed that 39/104 (37.5%) experienced nodule regrowth; of these, 17/39 (43.6%) underwent surgery and 14/39 (35.9%) underwent a second laser procedure. One patient who underwent surgery had a final diagnosis of follicular cancer. Once the 17 patients who underwent further surgery were excluded, the remaining group composed of 14 patients who underwent a second laser treatment, and the 73 patients who underwent only one laser session showed a significant and stable 65.0% (median) nodule volume reduction at the 5-year follow-up; furthermore, a significant and stable amelioration of cosmetic and symptom scores was observed (Table 3). When stratifying the VRR throughout the 5-year follow-up based on baseline volume (small, ≤ 10 mL; medium, 11–30 mL; large, > 30 mL), no significant difference was observed (Fig. 1). Among the 41 small nodules, 14 had regrowth (34.1%); of these, surgery was performed on 5/41 (12.2%) and a second laser treatment was performed on 4/41 (9.8%). Among the 57 medium nodules, 23 had regrowth (40.3%); of these, surgery was performed on 11/57 (19.3%) and a second laser treatment was performed on 9/57 (15.8%). Among the six large nodules, two had regrowth (33.3%); of these, surgery was performed on one (16.7%) and a second laser treatment was performed on one (16.7%).

In patients with a 12-month VRR > 75.0%, no regrowth was seen; in those with 50.0 < VRR ≤ 75.0%, the regrowth rate was 29.6%; in those with 25.0 ≤ VRR ≤ 50.0%, the regrowth rate was 60.0%; and in those with VRR < 25.0%, the regrowth rate was 88.9%. There was a significant difference in regrowth rate between nodules with a 12-month VRR < 50.0% and those with a 12-month VRR ≥ 50.0% ($p < 0.001$) (Fig. 2). The rate of nodule regrowth was inversely related to the 12-month VRR; the lower the 12-month VRR, the higher the risk of regrowth.

Compared to nodules that reduced ≥ 50.0% in volume, those that reduced < 50.0% in volume had an odds ratio for regrowth of 8.96 (95% confidence interval [CI] 3.5–22.8); those that reduced < 25.0% had an odds ratio for regrowth of 29.9 (95% CI 3.5–257.8).

The mean time for detection of nodule regrowth was 33.5 ± 16.6 months. Of the 17 patients who underwent

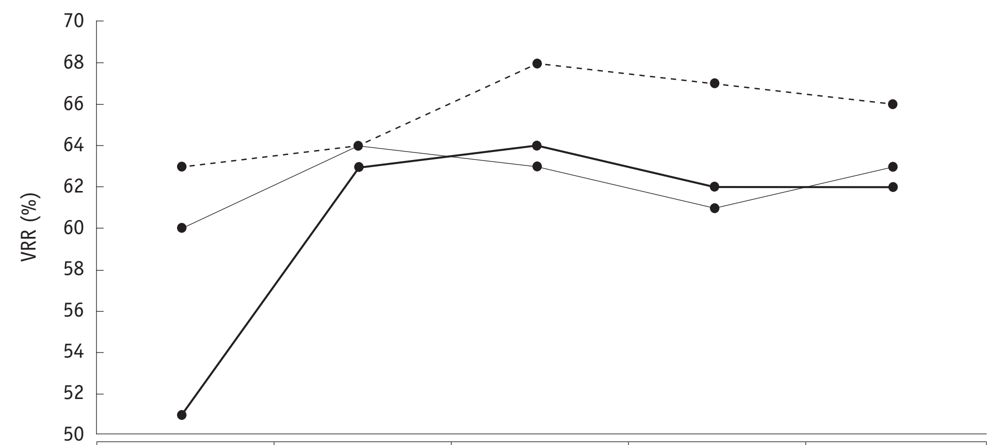
Table 2. Characteristics of Patients, with Nodules Stratified by VRR < 50.0% and ≥ 50.0%

	Patients with Nodules VRR < 50% at 12-Month Follow-Up	Patients with Nodules VRR ≥ 50% at 12-Month Follow-Up	*P*
Number of patients	31	73	-
Sex (male/female)	6/25	12/61	0.779
Age (years) (median; 25.0–75.0%)	54 (41–65)	54 (46–66)	0.887
TSH (mIU/L) (median; 25.0–75.0%)	1.1 (0.8–1.6)	1.3 (0.9–2)	0.780
Non-spongiform/spongiform	20/11	28/45	0.018
Energy delivered (J) (median; 25.0–75.0%)	6006 (3617–9008)	6200 (4057–7920)	0.451
Energy delivered/mL (median; 25.0–75.0%)	521 (415–667)	477 (333–603)	0.642
Nodule volume nodule at baseline (mL) (median; 25.0–75.0%)	12 (7–17)	13 (8–19)	0.821
VRR at 12-month follow-up (%) (median; 25.0–75.0%)	36 (21–45)	66 (59–74)	< 0.001

Table 3. VRR Expressed as Percentage in 5-Year Follow-Up

	Baseline	1-Year	2-Year	3-Year	4-Year	5-Year	*P*
Number of patients*	104	104	99	92	90	88	-
Number of patients surgery	-	5	7	2	2	1	-
Number of patients second laser	-	2	2	4	1	5	-
VRR (median; 25–75%)	-	60 (47–71)†	63 (46–72)†	64 (54–74)†	64 (53–73)†	65 (51–74)†	< 0.001
Cosmetic score (1–4)	3.0 ± 0.8	1.2 ± 0.6†	1.2 ± 0.5†	1.2 ± 0.5†	1.2 ± 0.4†	1.2 ± 0.4†	< 0.001
Symptom score (0–10)	3.5 ± 1.5	1.5 ± 0.8†	1.4 ± 0.7†	1.4 ± 0.7†	1.4 ± 0.7†	1.4 ± 0.7†	< 0.001

*17 patients underwent surgery; 14 patients underwent second laser treatment, †vs. baseline.



	1 yr	2 yr	3 yr	4 yr	5 yr
41 small nodules	60 (45–73)	63 (42–73)	63 (52–73)	61 (50–73)	63 (37–74)
57 medium nodules	63 (49–71)	64 (45–74)	68 (54–75)	67 (53–78)	66 (50–80)
6 large nodules	51 (36–59)	63 (31–87)	64 (31–89)	62 (32–90)	62 (37–90)

Fig. 1. VRR stratified by baseline volume. Data are expressed as (%) (median; 25.0–75.0%). VRR was not significantly different at each time point between three groups. VRR = volume reduction ratio

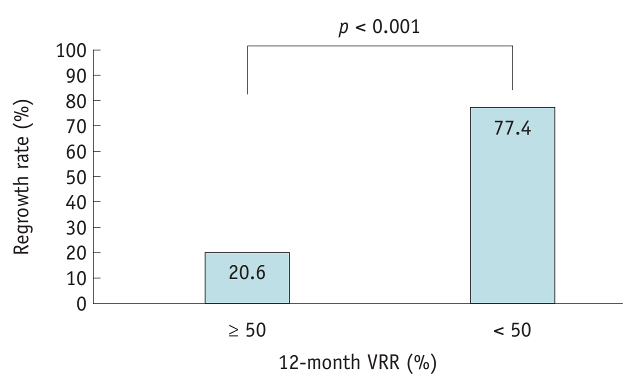


Fig. 2. Regrowth rate stratified by 12-month VRR. Nodules with 12-month VRR ≥ 50% had regrowth rate of 20.6%; nodules with 12-month VRR > 50% had regrowth rate of 77.4% ($p < 0.001$).

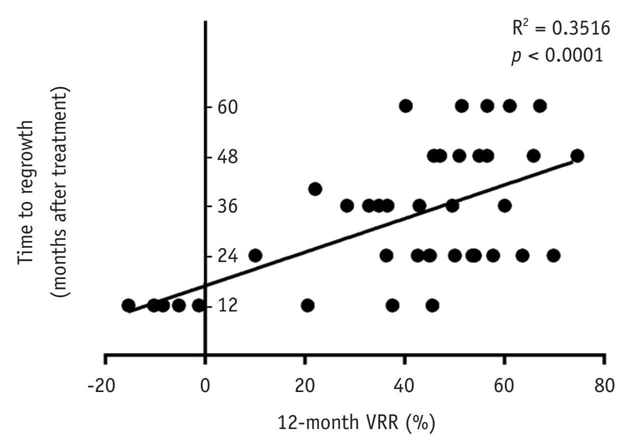


Fig. 3. Correlation between 12-month VRR and time to regrowth ($p < 0.0001$; $R^2 = 0.3516$).

surgery, in 12 cases (70.6%), the surgical option was decided after the one- or two-year evaluation. Of the 14 patients who underwent a second laser treatment, in 10 (71.4%) this option was decided after the four- or five-year evaluation. Twelve-month VRR was directly related to time for regrowth ($p < 0.001$; $R^2 = 0.3516$). As shown in Figure 3, the smaller the 12-month VRR, the shorter the time to regrowth.

The characteristics of patients with or without nodule regrowth were similar, except for composition (non-spongiform nodules were more prevalent in the "regrowth" group) and VRR at the 12-month follow-up (which was smaller in the "regrowth" group) (Table 4). Non-spongiform nodules vs. spongiform nodules had an odds ratio of 3.8 (95% CI 1.6–8.9; $p = 0.028$) for a 12-month VRR ≤ 50.0%.

Multivariate binary logistic regression analysis demonstrated that non-spongiform composition and 12-month VRR < 50.0% were independently associated with nodule regrowth. Non-spongiform composition increased the risk of regrowth with an odds ratio of 4.3 (95% CI 1.8–10.2; $p < 0.001$); 12-month VRR < 50.0% increased the risk of regrowth with an odds ratio of 11.7 (95% CI 4.2–32.2; $p < 0.001$).

All the following adverse events occurred transiently: 5.8% (6/104) of patients had periprocedural pain; 4.8% (5/104), transient vocal cord paresis; and 2.9% (3/104), fever during the days after the procedure.

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Table 4. Characteristics of Patients Stratified by Nodule Regrowth

	Regrowing Nodules	Non-Regrowing Nodules	*P*
Number of patients	39	65	-
Sex (male/female)	7/32	13/65	1.000
Age (years) (median; 25.0–75.0%)	50 (42–67)	56 (46–66)	0.198
TSH (mIU/L) (median; 25.0–75.0%)	1.1 (0.9–1.7)	1.1 (1.0–2.2)	1.000
Non-spongiform/spongiform (number of patients)	26/13	20/45	< 0.001
Energy delivered (J) (median; 25.0–75.0%)	6159 (5205–9041)	6264 (3626–7726)	0.705
Energy delivered/mL (median; 25.0–75.0%)	477 (384–601)	482 (348–635)	0.520
Nodule volume at baseline (mL) (median; 25.0–75.0%)	14 (8–21)	12 (8–17)	0.221
VRR at 12-month follow-up (%) (median; 25.0–75.0%)	45 (33–56)	66 (58–75)	< 0.001
12-month VRR < 50.0% (number of patients; %)	24 (63.6)	7 (10.8)	< 0.001

DISCUSSION

The present investigation clearly indicates that solid thyroid nodules respond differently in terms of VRR, despite being subjected to the same amount of energy; moreover, the different extent of reduction correlates with the risk of regrowth and time to regrowth.

The short- and long-term success rate of I-GTA is of pivotal importance, especially when this procedure is compared with surgical treatment. Compared to surgery, I-GTA demonstrates several advantages: it is less expensive, has a reduced number of transient and permanent complications, requires a shorter hospital stay, is faster, entails a lower incidence of hypothyroidism, and does not leave a scar on the neck (16, 17). On the contrary, the evident advantage of surgery is that it guarantees a permanent resolution of the mass effect by removing the nodule and enables histological examination, which might reveal a false negative result or incidental thyroid cancer (18, 19). Considering this, the use of I-GTA should be properly addressed to represent a valid alternative to surgery. It is then relevant in clinical practice to understand the type of nodules that are candidates for treatment with I-GTA and to determine the optimal technique for magnifying benefits and minimizing failures. Studies published in the last decade observed a rate of nodule regrowth or referral to surgery or additional laser procedure for unsatisfactory results in up to 35.0% of cases (20-22). Some authors observed that after RF ablation (RFA) or microwaves procedures, a smaller than expected reduction rate and regrowth might be related to the baseline volume, with larger treated nodule size related to smaller volume reduction (23, 24). Unsatisfactory reduction rates and subsequent regrowth might be explained by the fact that the energy delivered/mL of tissue in large nodules is generally less than that in medium or small nodules, which may account for the presence of untreated parts of the nodule (vital volume) (25). In our group of patients, baseline volume was not related to the 12-month VRR; this was probably because large nodules represented only a minority of patient, subsequently having a small influence on determining the 12-month VRR and long-term outcomes. A recent study showed that when using laser ablation, higher energy deployment may be associated with improved results; between two groups of nodules undergoing different energy treatments, the one treated with a mean of 599.9 ± 136.5 J/mL obtained a VRR greater than the one treated with a mean of 240.2 ± 74.6 J/mL. The authors calculated that > 398.8 J/mL should be used to obtain better results (26). Though one might hypothesize that the regrowth rate we observed was influenced by the relatively low amount of energy supplied, the results undoubtedly showed that similar amounts of energy exerted different results in terms of VRR. The energy delivered (J/mL) was not significantly associated with VRR because 94.2% of nodules were small or medium, and in 2/3 of nodules, the median of energy delivered was greater than the "398.8 J/mL that should be deployed to obtain better results" (26). Other than the energy delivered, nodule volume and vital volume are structural characteristics that appear to have pivotal importance. Retrospective studies have shown that laser ablation performs better in spongiform nodules than in non-spongiform nodules, as the former exhibit major, progressive, and durable shrinkage, whereas the latter show a tendency toward regrowth (27, 28). A multicenter prospective study by Deandrea et al. (29) demonstrated that in nodules submitted to RF, spongiform composition and intranodular vascularity are associated with a greater reduction than nodules with a non-spongiform composition and peripheral vascularity, because in the former, heat spreads better than in the latter, inducing a more extensive ablation area (30). Experimental studies have explored the physical basis for understanding the extent of the RF effect, showing that different thermal and electrical conductivities significantly affect tissue ablation (31, 32). One study used spectral analysis to characterize nodules undergoing laser ablation (33). The images processed using spectral analysis exhibited different color distributions, which corresponded to different tissue densities. Each nodule belonging to the same group experienced, on average, a similar extent of necrosis, demonstrating that nodules with different configurations (colors) are ablated differently. This experimental example helps to understand that the extent of nodule volume reduction depends on the nodules composition and not only its baseline volume.

The observed data also suggest that at least for small and medium nodules, composition matters more than baseline volume, as the regrowth rate was similar among small, medium, and large nodules.

Our results confirmed that at a similar level of energy delivered/mL of tissue, different levels of nodule reduction were obtained. In our cohort of patients, about 30.0% of nodules reduced < 50.0% 12 months after treatment, which is considered a "technical failure" (14). In fact, our data showed for the first time that nodules that were reduced < 50.0% at 12 months after the initial laser ablation have a significantly higher risk for regrowth in the subsequent years compared with those that were reduced ≥ 50.0%. The convention of using a threshold of 50.0% for distinguishing successful from unsuccessful treatment is supported our data. One can object that debulking a nodule, for instance, by 40.0% might be considered a success anyway in terms of symptom or cosmetic concern relief. Our data demonstrate that a less than optimal reduction predicts subsequent regrowth. As a consequence, a VRR < 50.0% should be considered not only a "technical failure" but also a "clinical failure" as patients may need surgery or additional thermal treatment.

In our cohort of patients, we mostly opted for surgery to treat nodules showing earlier regrowth and a second laser treatment in those showing later regrowth; such a strategy was based on the clinical judgement that a second laser treatment would probably have been of little benefit in faster growing nodules. The consistency of our results is confirmed, for the first time, by evidence that VRR correlates with time to regrowth, similar to how earlier regrowth is related to a smaller reduction in volume. Although we are aware that our results should be limited to laser treatment, they suggest that an intrinsic risk of regrowth should be considered. This risk could be reduced through the careful selection of patients, considering age, expectancies, comorbidities, and nodule volume and composition. In cases of unsatisfactory 12-month VRR, the appropriate management strategy could be timely performance of further ablation, instead of waiting for inescapable nodule regrowth. In any case, the information that a "technical failure" will probably become a "clinical failure" in subsequent years must be considered by both the physician and patient in order to plan treatment strategies (surgery or second thermal treatment) and allow for shared decision making.

The limitations of the study are that data were collected retrospectively and came from a single center. During the 5-year follow-up period, patients showed a stable reduction of approximately 60.0% (median) for the first 2 years; thereafter, the observed reduction was approximately 65.0% (median), after excluding those who had been thyroidectomized. Most treated nodules were small or medium; thus, the rate of technical failure and regrowth should also be investigated for large nodules. It is reasonable that the results we observed might be extended to large size nodules; in other words, large nodules are likely to display a larger proportion that is untreated and that in such cases, more than one session should be preventively performed. Moreover, data of laser ablation cannot automatically be extended to other I-GTA techniques; for instance, it is possible that the use of the "moving shot" technique of RFA may be more effective than the "pull back" technique of laser ablating peripheral parts of the nodule in preventing or limiting the risk of regrowth (34). Marginal regrowth is used to describe the phenomenon of regrowth occurring from the undertreated peripheral areas. Most cases of regrowth occur as a result of marginal regrowth. In nodules treated with RFA, Lim et al. (35) described regrowth occurring from the incompletely treated peripheral regions and concluded that controlling the peripheral margin of the nodule with a moving shot technique is important to prevent marginal regrowth. The usefulness of timely retreatment of nodules with a 12-month unsatisfactory VRR confirm the concept that when the viable volume begins to increase, it is time to consider additional ablation (11). In RFA, vascular ablation and hydrodissection may represent technical advancements with goal of complete ablation of the nodule (36).

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It would be of importance to corroborate these results with multicenter prospective studies, using both laser ablation and RF, and pre-established amounts of energy to be delivered/mL of tissue.

In conclusion, the study showed that: 1) approximately one-third of laser-treated nodules exhibited technical failure at the 12-month follow-up and the risk to regrowth correlates with the 12-month VRR; 2) non-spongiform composition is associated with an increased risk of technical failure and nodule regrowth; and 3) a 12-month VRR < 50.0% would suggest timely performance of a second session to prevent nodule regrowth.

Prospective studies are needed to better understand the types of nodules that are the best candidates for thermal ablation and the best techniques to optimize the use of I-GTA and reduce the failure rate.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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