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Ultrasound-Guided Laser Thermal Ablation in the Treatment of Autonomous Hyperfunctioning Thyroid Nodules and Compressive Nontoxic Nodular Goiter

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Objective: Percutaneous laser thermal ablation (LTA) has been applied in several tumors. In this study we evaluated the safety and long-term efficacy of LTA in the treatment of benign thyroid nodules. *Design and patients*: Seven patients with autonomous hyperfunctioning thyroid nodule (group A) and five patients with compressive nodular goiter (group B) were treated with LTA. Up to three needles were positioned centrally in the thyroid nodule and laser fiber was placed in the lumen of the needle. Laser illumination was performed reaching a maximal energy deposition of 1800 J per fiber. *Measurements*: Thyroid nodule volume, endocrinologic, and clinical evaluation were performed at baseline, 3, and 12 months after the treatment. Scintigraphy was performed at diagnosis and 12 months after the first session in group A. *Results*: In group A, mean thyroid volume decreased from 3.15 ± 1.26 mL to 0.83 ± 0.49 mL ($p < 0.001$) after 12 months. The treatment induced disappearance of clinical signs and symptoms related to hyperthyroidism; normalization of free triiodothyronine (FT_3), free thyroxine (FT_4), and thyrotropin (TSH) serum levels and recovery of extranodular uptake at scintiscan. In group B, mean thyroid volume decreased from 11.14 ± 4.99 mL to 3.73 ± 1.47 mL ($p < 0.01$) after 12 months. Pressure symptoms in the neck, difficulty in swallowing and tracheal displacement improved in all patients. The treatment was well tolerated in both groups of patients. *Conclusions*: LTA appears to be a valid and safe alternative approach in the treatment of benign thyroid nodules.

Introduction

THYROID NODULE is a common disorder with a prevalence ranging from 5%–50%. This wide range depends on the population studied as well as the sensitivity of detection methods (1,2). Most thyroid nodules are benign lesions. The therapeutic strategy for treatment benign nodules includes several options. Surgery is usually advised in toxic or if malignant nodular goiter is suspected, in large nodules (> 3 cm in diameter) with pressure symptoms, or in nodular goiter for cosmetic concerns (3,4). Radioiodine is a simple, cost-effective, and safe procedure in the treatment of autonomously hyperfunctioning thyroid nodule (5,6). In addition, radioiodine may be recommended to treat large, nontoxic multinodular goiters in patients who decline surgery or who are at high surgical risk (7). Medical therapy includes levothyroxine therapy at thyrotropin (TSH)-suppressive doses and thionamides. Levothyroxine-suppressive therapy is indicated in young patients with small solid cold nodules and normal thyroid function (8,9). Thionamides can normalize free triiodothyronine (FT_3), free thyroxine (FT_4), and TSH concentrations in toxic nodules. These agents are used to induce euthyroidism before definitive therapy is performed (10). Percutaneous intranodular ethanol injection (PEI) has been described by several authors as alternative treatment of toxic thyroid nodules, cysts, and large nontoxic thyroid nodules (11–28).

Several authors have recently proposed interstitial laser thermal ablation (LTA) as a new therapeutic method for thyroid nodules (29,30). It is a minimally invasive interventional procedure able to induce thyroid tissue ablation.

We herein report the results of a preliminary study undertaken to assess safety and usefulness of LTA treatment in patients affected by single autonomous hyperfunctioning thyroid nodule and in euthyroid patients with compressive nodular goiter, evaluating the effects of this therapy on nodule volume, biochemical and clinical benefit.

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Patients and Methods

Patient selection

The present study was carried out in two groups of patients.

Group A (Table 1) included seven patients (six women and one man, age ranging between 23 and 57 years, mean ± standard deviation [SD]: 42.57 ± 11.5 years) with single autonomous hyperfunctioning thyroid nodule. Inclusion criteria were: high levels of FT_3 and/or FT_4 and suppressed TSH values; normal circulating levels of thyroglobulin, calcitonin, antithyroglobulin antibodies and antimicrosomal antibodies; evidence of a single hot nodule at scintigraphy, with suppression of extranodular thyroid tissue uptake by ^{99m}Tc; benign cytologic examination performed by ultrasound-guided fine-needle aspiration; clinical evidence of the disease (tachycardia, weight loss, asthenia, fatigue, emotional lability, tremor, increased sweating); high surgical risk or refusal of surgical or other conventional treatments (radioiodine therapy, PEI); no history of neck irradiation and surgery. All patients were pretreated with methimazole for 1 month before and 1 week after the LTA procedure to avoid thyrotoxic crisis.

Group B included five female euthyroid patients (age ranging between 63 and 81 years, mean ± SD: 69.4 ± 7.3 years) with compressive nodular goiter. Inclusion criteria were: normal serum levels of FT_3, FT_4, TSH, calcitonin, thyroglobulin, antithyroglobulin and antimicrosomal antibodies; evidence of cold nodules at scintigraphy with a solid pattern at ultrasound; cytology negative for malignancy by ultrasound-guided fine-needle aspiration; presence of local mass-associated symptoms (neck discomfort and dysphagia) and tracheal displacement; free from treatment in the 6 months before starting the trial; high surgical risk or refusal of surgery or other conventional treatments (TSH-suppressive therapy with levothyroxine, PEI); no previous history of neck irradiation, and surgery.

This study was approved by the local Bioethics Committee. Before starting treatment with LTA all patients gave informed consent.

LTA procedure

Before each LTA session all patients underwent ultrasound examination to determine the site of the nodule. An ultrasound scanner (AU5 Harmonic, Esaote, Genoa, Italy) equipped with a 7.5–10 MHz linear probe for morphologic study working at 4.7 MHz for color and power Doppler was used for all procedures.

After careful cleansing, 1.0–1.5 mL of 2% lidocaine (Xilocaine 2%; AstraZeneca, Basiglio, Italy) was slowly injected into superficial cervical tissue. Under sterile conditions and with ultrasound guidance, up to three 21-gauge 70-mm Ecojekt spinal needles (Hospital Service, Rome, Italy) were implanted into core of thyroid nodule, along the greatest axis of the nodule, in each treatment. The needle tip was placed in the area to be treated at least 15 mm below the margin of the lesion and at least 15 mm from surrounding cervical structures. After the needle has been fixed in the correct site, a sterile 300-μm quartz fiber optic (Medical Energy Inc., Pensacola, FL) was inserted through the sheath of the needle. The optical fiber was advanced until at least 5 mm of the bare fiber tip was inserted, leaving the fiber tip in direct contact with the deepest part of the nodule. The laser source, a continuous-wave neodymium yttrium-aluminium-garnet (Nd:YAG) operating at 1.064 μm (D.E.K.A.-M.E.L.A., Florence, Italy) was used with an optical beam-splitting device (SMART 1064 HCC; D.E.K.A.-M.E.L.A.) with up to three fibers that were illuminated simultaneously (31–33). Laser illumination was performed setting the output power at 4–5 W reaching a maximal energy deposition of 1800 J per fiber, by using appropriate exposure times. The simultaneous use of several optical fibers has been performed in order to obtain a large tissue ablation. During LTA, correctness of needle tip positions and characteristics and diameters of laser-induced lesions were assessed by ultrasound. After laser irradiation the optical fiber was slowly pulled out with the laser kept off. Once the needles were pulled out and 24 hours after the procedure, neck ultrasound scans were performed to assess intraglandular and/or extraglandular complications. The patients were watched for 30 minutes without any medication. These procedures have been performed in an outpatient setting. In the subsequent sessions the needle and fiber tips were positioned in the untreated contiguous area at least 20 mm from a previous LTA lesion. The side effects of all treatments were recorded.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH SINGLE AUTONOMOUS HYPERFUNCTIONING THYROID NODULE AND EFFECTS OF LTA TREATMENT ON NODULE SHRINKAGE

Patient	Gender	Age (yrs)	Ultrasound pattern of nodule	No. of sessions	No. of needles	W	Delivered energy (J)	Volume (mL) Baseline	3 months	12 months	% reduction	Side effects
1A	F	23	Hypoechoic, CDIII, solid	1	1	5	1800	1.31	0.45	0.17	88	Pain
2A	F	32	Hypoechoic, CDIII, solid	1	1	4	1800	1.75	0.74	0.40	67	Pain
3A	F	43	Hypoechoic, CDIII, solid with colliquative areas	1	1	5	1600	2.84	1.12	0.68	76	—
4A	F	48	Hypoechoic, CDIII, solid	1	1	5	1800	3.31	1.08	0.66	80	—
5A	F	50	Hypoechoic, CDIII, solid	1	1	5	1800	4.07	1.93	1.26	69	—
6A	F	57	Hypoechoic, CDIII, solid	1	2	5	3200	4.28	1.97	1.11	74	—
7A	M	45	Hypoechoic, CDIII, solid with colliquative areas	1	2	5	3600	4.52	2.13	1.54	66	—

LTA, laser thermal ablation.

Follow-up

The ultrasonographic and color/power Doppler examination of the thyroid, clinical examination, and serum levels of FT_3, FT_4, TSH, thyroglobulin, antithyroglobulin and antithyroperoxidase antibodies were evaluated at study entry, at first LTA session (baseline), 24 hours, 3, and 12 months after the first session. During ultrasonographic examination a careful evaluation of the echogenecity (hyperechoic, isoisoechoic with hypoechoic, halo, hypoechoic, or mixed), echo structure (solid, mixed, or cystic), margins (well-defined, irregular, or blurred), the presence of hyperechoic spots (coarse calcifications or microcalcifications), the presence and the extension of perinodular and intranodular arterial flow (34,35) (Fig. 1) and volume of thyroid nodules (according the ellipsoid formula: length $\times$ width $\times$ depth $\times$ 0.525) were assessed in all patients (36). During this examination, tracheal displacement was evaluated by performing transversal scans at different levels of thyroid lobes: tracheal longitudinal axis variation of more than 1 cm was considered as positive. To exclude lumen reduction, tracheal displacement at ultrasound was confirmed by an upper mediastinum x-ray. The clinical exam included thyroid palpation and evaluation of local mass-associated symptoms (in group B patients) by an arbitrary score (0 = absent; 1 = moderate; 2 = severe), attributed to each symptom. The sum of these two single scores was indicated as the symptom score. Scintigraphy was performed at the time of the admission and at 12 months in group A.

Statistical analysis

The statistical analysis was carried out by analysis of variance (ANOVA) followed by the Newman-Keuls test for the intergroup comparisons and the paired t test for the intragroup comparisons where appropriate. Data were considered statistically significant when $p < 0.05$.

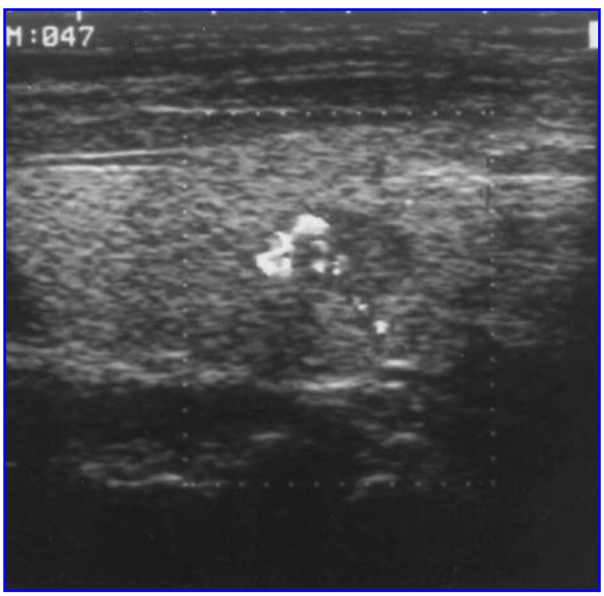

FIG. 1. Doppler scan, vascular signal of the autonomous thyroid nodule before laser thermal ablation (LTA) treatment is shown.

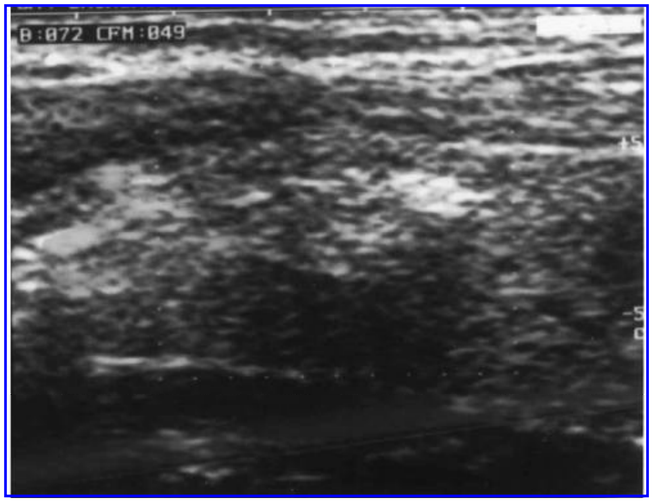

FIG. 2. Ultrasound (US) B-Mode scan, a hyperechoic area with acoustic shadowing during laser thermal ablation (LTA) treatment.

Results

Ultrasonographic evaluation

The effects of LTA on thyroid nodules were monitored online by ultrasound during laser irradiation. An irregular echogenic area was observed gradually and slowly enlarging over time around the fiber tip (Fig. 2). The vapor was clearly visible on ultrasound as small, highly echogenic foci close to the laser-induced lesion. At the end of the procedure a large, ill-defined hyperechoic area with associated acoustic shadowing was detected in all patients. Color and power Doppler ultrasonography showed the loss of peripheral and/or intranodular vascular signals, as a consequence of necrosis induced by laser (Fig. 3). Twenty-four hours after laser application ultrasound images showed a "target" lesion (Fig. 4) characterized by a central hypoechoic area (zone

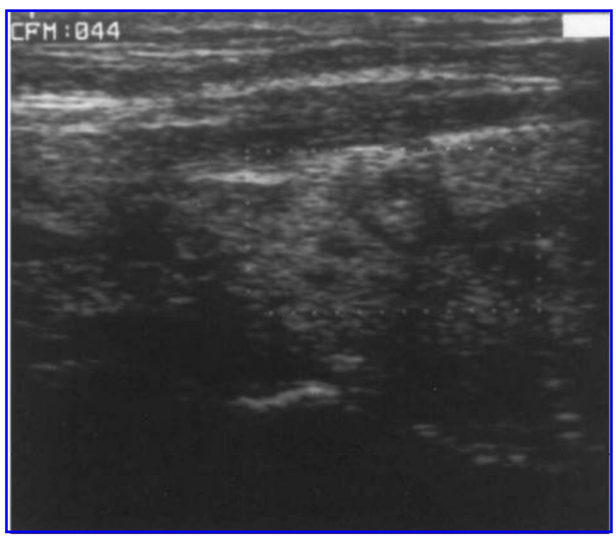

FIG. 3. Doppler scan, absence of vascular flow at the end of the laser thermal ablation (LTA) treatment.

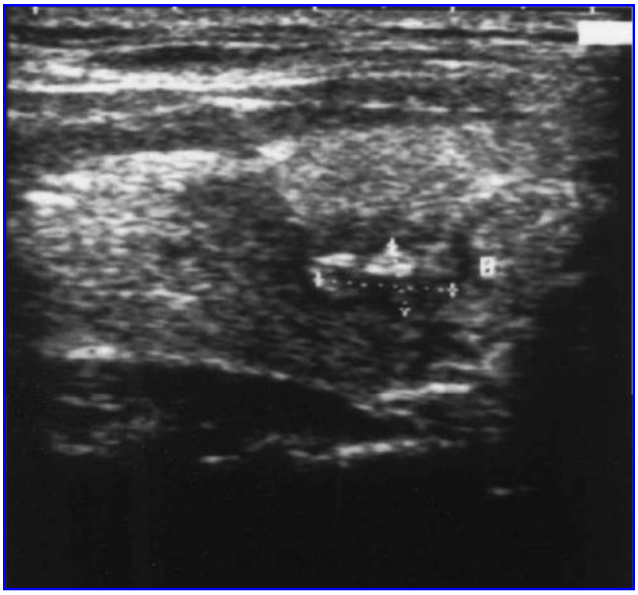

FIG. 4. Ultrasound (US) B-Mode scan, the "target aspect" of the necrotic area at 24 hours after laser thermal ablation (LTA) treatment is shown.

of vaporization), surrounded by a hyperechoic rim (zone of carbonization), and an outer hypoechoic layer (zone of coagulative necrosis). This appearance was nearly identical to that on 3-month follow-up images, apart from a decrease in size of both central cavity and entire heated area. After three and twelve months these characteristic images were not more visible and ultrasound scans showed an ill-defined hyperechoic area with associated acoustic shadowing (Fig. 5).

Group A. Mean initial nodule volume was 3.15 ± 1.26 mL (range, 1.31–4.52 mL). A significant decrease of nodule volume was observed after 3 months ($p < 0.005$) and 1 year ($p < 0.001$) (Table 1). At the end of the follow-up, the mean nodule volume and percentage of nodule volume reduction were 0.83 ± 0.49 mL (range, 0.17–1.54 mL) and 74.29% ± 7.89% (range, 66%–88%), respectively. It is noteworthy that all patients received only one LTA session and a nodule shrinkage greater than 50% was detected already after 3 months from the treatment.

Group B. Mean initial nodule volume was 11.14 ± 4.99 mL (range, 4.13–17.20 mL). Thyroid nodule volume significantly decreased after 3 months ($p < 0.05$) and 1 year ($p < 0.01$) (Table 2). At the end of the follow-up, the mean nodule volume and percentage of nodule volume reduction were 3.73 ± 1.47 mL (range, 2.52–6.07 mL) and 60.8% ± 16.68% (range, 39%–76%), respectively. The shrinkage of nodule volume greater than 50% was already detected in two of five cases at 3 months from the first treatment. Four of five and one of five patients received two and three LTA sessions, respectively. Tracheal displacement disappeared or significantly decreased (> 5 mm) during the follow-up in all patients.

Clinical, hormonal, and scintigraphic evaluation

Group A. Three months after the treatment with LTA the remission of clinical signs and symptoms related to hyperthyroidism and normalization of FT_3 (time of admission vs. 3 months: 6.90 ± 1.01 pg/mL vs. 2.73 ± 0.65 pg/mL, $p < 0.001$; baseline vs. 3 months: 4.31 ± 0.62 pg/mL vs. 2.73 ± 0.65 pg/mL, $p < 0.001$), FT_4 (time of admission vs. 3 months: 30.77 ± 6.24 pg/mL vs. 10.86 ± 1.83 pg/mL, $p < 0.001$; baseline vs. 3 months: 16.43 ± 2.30 pg/mL vs. 10.86 ± 1.83 pg/mL, $p < 0.001$) and TSH serum levels (time of admission vs. 3 months: 0.02 ± 0.03 mIU/L vs. 1.96 ± 0.82 mIU/L, $p < 0.001$; baseline vs. 3 months: 0.05 ± 0.05 mIU/L vs. 1.96 ± 0.82 mIU/L, $p < 0.001$) was observed in all patients with autonomous hyperfunctioning thyroid nodule. In these patients there was no recurrence of hyperthyroidism up to 12 months (FT_3: 2.61 ± 0.53 pg/mL; FT_4: 10.49 ± 1.31 pg/mL; TSH: 2.11 ± 0.47 mIU/L). In addition, appearance of extranodular tissue with the nodule no longer visible or cold (level of activity inferior to the one showed by the surrounding thyroid tissue) at scintiscan has been observed in all cases.

Group B. Pressure symptoms in the neck and difficulty in swallowing improved significantly in all patients. Symptoms score was significantly reduced after 3 months (2.2 ± 0.84 vs. 0.8 ± 0.83, $p < 0.05$) and at the end of the study (2.2 ± 0.84 vs. 0.6 ± 0.55, $p = 0.01$). We did not observe any significant change in FT_3, FT_4 and TSH levels during the follow-up.

Side effects and complications

The treatment was well tolerated in all patients. No major complications were observed. Four patients experienced a mild cervical burning pain lasting for few minutes during the treatment (pain medication was never required) and transient dysphonia lasting 24 hours in one patient, which spontaneously resolved (Tables 1 and 2). No antibiotic treatment was given before and after the procedure.

Discussion

PEI under ultrasonographic guidance is an effective and safe treatment of benign hot and cold thyroid nodules, causing shrinkage of thyroid nodules, normalization of thyroid function in hyperfunctioning nodules, and improvement of

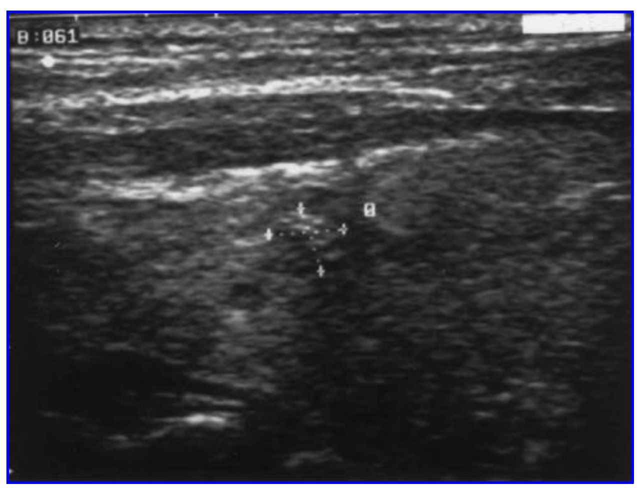

FIG. 5. Ultrasound (US) B-Mode scan, the ill-defined hyperechoic aspect of the necrotic area at 12 months after laser thermal ablation (LTA) treatment is shown.

Table 2. Characteristics of Patients with Euthyroid Nodular Goiter and Effects of LTA Treatment on Nodule Shrinkage

Patient	Gender	Age (yrs)	Ultrasound pattern of nodule	No. of sessions	No. of needles	W	Delivered energy (J)	Volume (mL) Baseline	3 months	12 months	% reduction	Side effects
1B	F	63	Hyperechoic, CDII	1	1	5	1800	4.13	3.14	2.52	39	Pain
				2	1	4	1500					
2B	F	65	Isoechoic, halo sign, CDII, macrocalcifications	1	2	5	3200	8.93	4.87	2.76	69	Pain
				2	2	5	3400					
3B	F	66	Hyperechoic, CDIII	1	2	5	3400	11.32	5.38	3.03	73	—
				2	2	5	3600					
4B	F	72	Hypoechoic, CDIII, macrocalcifications	1	3	5	4900	14.13	7.03	6.07	47	Dysphonia
				2	2	4	3200					
5B	F	81	Isoechoic, halo sign, CDII, macrocalcifications	1	3	5	5400	17.20	7.25	4.26	76	—
				2	2	5	3400					
				3	2	5	3400					

LTA, laser thermal ablation.

patient's compliance. Based on this, PEI has been proposed as an alternative therapy to surgery and radioactive iodine (18,27).

The mechanism of action of ethanol appears to be related to a direct coagulative necrosis and partial or complete small vessel thrombosis (21,37). However, the effects and extent of necrosis after PEI are influenced by several factors: nodule vascularization, the presence of capsule and intranodular fibrosis areas, histology of the nodule, and the experience and skill of the operator (25). These variables explain in part the varying success rate reported in the literature and the irregular pattern of tissue necrosis induced by PEI. Therefore, it is difficult to predict the area of the tissue damage after ethanol injection because of the uneven distribution of ethanol inside the tissue. PEI has other advantages and limits: side effects caused by alcohol seeping outside the lesion (extraglandular fibrosis, paralysis of vocal cords, edema of the prethyroid region, local pain, and mild fever) and need for repeated treatments in large nodules (22,26,27).

On the contrary, as reported by Pacella et al. (29), LTA appears to be precise in inducing necrosis secondary to an increase in temperature (> 100°C) within the treated lesion by using low-energy output (2–5 W per fiber). This results in vaporization of the thyroid lesion and coagulative necrosis of surrounding area. Therefore, the advantage of laser is the great precision, inducing well-defined areas of complete tissue ablation with a regular, homogeneous, and reproducible pattern. However, the effects of laser treatment depend on the involved tissue type. In fact, the presence of large cavitary areas, colloid or hemorragic collections prevents heat dispersion within the tissue. On these basis, the effectiveness of LTA in cystic or mixed nodules may be reduced. However, Pacella et al. (29) essentially related LTA treatment and tissue damage in 18 resected thyroid glands who had undergone total thyroidectomy because of Graves' disease or large goiter; therefore, the authors could not evaluate the safety and the long-term efficacy of this procedure.

Dossing et al. (30) have treated 16 patients affected by benign cold thyroid nodule with LTA. The mean baseline nodule volume was 10.0 ± 7.9 mL, while the mean percentage of nodule volume reduction was 46% after 6 months, using only one session and one optical fiber. In addition, the authors reported that the treatment was well-tolerated in all patients and pressure symptoms were significantly reduced (30).

The present study is the first evaluating the biochemical and long-term effects on thyroid volume after LTA treatment in hyperfunctioning thyroid nodules. LTA induced a significant nodule volume shrinkage (mean nodule volume reduction percentage, 74%), total cure (remission of clinical signs and symptoms, appearance of extranodular tissue with the nodule no longer visible or cold at scintiscan, normalization of thyroid hormones and TSH serum levels) and the disappearance of peripheral and intranodular vascularization in all hyperfunctioning thyroid nodules. The nodule vascularization has been evaluated with power-Doppler. This is a Doppler ultrasound technique able to detect even very small vessels, often invisible at color-Doppler (38,39). The complete loss of vascularization and the recovery of extranodular uptake with absence of uptake in the nodule at scintigraphy were suggestive of a complete necrosis of the lesion. In addition, LTA treatment significantly decreased volume of cold benign thyroid nodules (mean nodule volume reduction percentage, 61%), using up to three optical fibers simultaneously and up to three sessions. A relevant decrease of pressure symptoms and tracheal displacement has been observed after laser procedure in all patients with compressive nodular goiter. We have observed more significant shrinkage of thyroid nodule than was reported by Dossing et al (30). This discrepancy may be related to the use of concomitant optical fibers and multiple sessions in the present study.

Therefore, LTA under ultrasound guidance seems to be a valid tool in the treatment of autonomous hyperfunctioning thyroid nodules and compressive nontoxic nodular goiter. In addition, this technique appears to be safe and well tolerated, notwithstanding the use of multiple needles and sessions. These data are very encouraging. However, this is a preliminary study including a small series of patients with nodule volume less than 20 mL. Therefore, future prospectives and randomized clinical trials with large series of patients, larger nodule volume, and long follow-up, are needed to confirm these data and to establish the role of LTA in the therapeutic strategy of thyroid nodules.

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