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ORIGINAL ARTICLE

Laser photocoagulation therapy for thyroid nodules: long-term outcome and predictors of efficacy

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Abstract

Purpose The aim of the present study was to retrospectively evaluate the efficacy of interstitial laser photocoagulation (ILP) ablation of thyroid nodules during a 6-year follow-up period and to identify possible predictors of the final outcome.

Methods Forty-three outpatients (38 women) were assigned to ILP therapy. The study group included euthyroid patients with benign thyroid nodules. Thyroid size, nodule volume and features, and autoimmune test were collected at baseline. Patients underwent US control after the ILP procedure and 1 month, 6 months, 12 months later and then annually.

Results During the follow-up, two distinct groups of patients emerged: the responders ($N=33$) and the non-responder ($N=10$) ones to ILP. In the responder group, the nodule volume significantly decreased during the follow-up, but a trend toward a slight increase in nodule volume was recorded up to the end of follow-up. No significant decrease in nodule volume was observed in the non-responder group. Neither baseline clinical nor demographic features were significantly different between responders and non-responders groups. In the whole group of patients, the energy delivered per mL of nodule tissue was significantly correlated with the percent volume decrease at the end of follow-up.

Conclusions Interstitial laser photocoagulation is a safe technique able to reduce byabout 50% the volume of benign thyroid nodules in the majority of treated patients. However, due to the great variability of results, an active follow-up is required. The only independent predictor of ILP outcome is the energy delivered per mL of nodule tissue.

Keywords Thyroid nodule · Interstitial laser photocoagulation · Ultrasound · Therapeutic outcome

Introduction

Thyroid nodules are common in the general population, mainly in areas of iodine deficiency, and their prevalence increases with age. Due to the high sensitivity of thyroid ultrasound, the detection rate of these nodules has increased over the time, reaching an estimated prevalence of 19–68% in different countries [1, 2]. The majority of thyroid nodules are benign, so they often do not require invasive treatment, but only clinical and ultrasound follow-up. However, some of them grow over the time, thus causing pressure symptoms, such as dysphagia and dyspnea, or cosmetic complaints. Large symptomatic thyroid nodules usually require surgery, which however carries the risk of permanent complications including hypoparathyroidism, laryngeal nerve injury, bleedings or skin scarring. Moreover, surgery may not be suitable for all patients, because of critical health conditions or refuse to undergo surgery.

During the last decades, a few minimally invasive procedures were developed, searching for a valid alternative to traditional surgery for the treatment of symptomatic benign nodules: ethanol injection for cystic nodules, radiofrequency or laser ablation for solid or spongiform nodules. Laser ablation is currently used in several clinical settings. Due to its low invasiveness and high precision, it was used in the treatment of benign and hyperfunctioning thyroid nodules, while limited data are available on the role of laser ablation in malignant thyroid lesions [3–6]. Specific adverse events, such as subcapsular hematoma, skin burn, fever, pain, and

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laryngeal nerve damage are rarely reported [7–9]. Although long-term data on the clinical outcome of laser-treated thyroid nodules are limited, some retrospective and prospective studies, with a maximal follow-up period of 5 years, reported a stable volume reduction over the time [3, 10–13]. However, failure to shrink or later regrowth of laser-treated nodules was also reported [14]. In the few studies addressing the outcome issue, the US characteristics of the nodule, its size, and position within the thyroid gland were taken into account, but results were controversial [3, 10, 12, 13].

Aim of the present study was to retrospectively evaluate the efficacy of percutaneous laser ablation of thyroid nodules during a 6-year follow-up period and to identify possible predictors of the final outcome.

Subjects and methods

From January 2010 to January 2013, 43 euthyroid patients (38 women; mean ± SD age = 55.89 ± 12.75 years and 5 men; mean ± SD age = 57.4 ± 10.4 years) were treated with interstitial laser photocoagulation (ILP) therapy. The study group included euthyroid patients with a solitary nodule or a dominant nodule within a multinodular goiter causing pressure symptoms and/or cosmetic complaints. The coexistence of thyroid autoimmunity was assessed by searching for serum anti-thyroglobulin (TG) and/or anti-thyroid peroxidase (TPO) autoantibodies.

Thyroid echography was performed using a real-time ultrasound (US) device equipped with a linear transducer operating at 7.5 MHz (Mylab 70XVG). The following US features of thyroid nodules were taken into account: nature (solid, cystic or mixed); echogenicity (hyperechoic, isoechoic or hypoechoic compared with normal parenchyma and with neck muscles); volume; micro-calcifications; presence of regular or irregular margins; halo sign; color flow Doppler pattern. Nodule volume was estimated by the elliptical shape formula (length × width × depth × 0.479). All thyroid US scans were performed by the same operator (S.C.), with more than 5-year experience of thyroid imaging. Fine needle aspiration cytology (FNAC) was performed according to the current guidelines [15] under US guidance by a skilled endocrinologist using a 23-gauge needle attached to a 2.5 mL syringe. All nodules were diagnosed as benign lesions (TIR2) at cytological examination.

Exclusion criteria included: small nodules (less than 3 mL), a family history of thyroid cancer, previous neck radiation therapy, nodules with a > 50% cystic component, and nodules with suspicious US features (micro-calcifications, irregular margins).

All patients included in the study were investigated by neck US immediately after the ILP procedure and then at 1 day, 1 month, 6 months, 12 months, and yearly after the procedure. US features of the nodule and its estimated volume were assessed. All patients completed the first year of follow-up. Thereafter, ten patients with persistent cosmetic and/or compressive complains, underwent thyroid surgery. The total follow-up period was 6 years. For each patient, the percent decrease of thyroid nodule from the baseline volume was calculated at each follow-up visit.

All patients gave their written informed consent for treatment with ILP. The study was conducted in accordance with the Helsinki Declaration and was approved by the Local Ethical Committee.

Ablation technique

Interstitial laser photocoagulation was performed under real-time US guidance. Before the procedure, 2 mL of 1% lidocaine was injected locally and 2.5 mg of midazolam was administered i.v. Under US guidance, the introducer needle (90-mm-long 22-gauge Yale spinal needle, Becton–Dickinson, Rutherford, NJ, USA) was inserted into the thyroid nodule along its longest axis, placing the tip in the deepest part of the nodule and keeping a safety distance of at least 15 mm from the inferior margin of the lesion and the surrounding cervical structures. Subsequently, a 400 µm plane-cut quartz optical fiber was introduced and then withdrawn to expose the fiber tip by at least 5 mm. Optic fibers were then connected with a continuous wave diode laser operating at 1064 nm (Quanta D-Plus, Quanta-System Solbiate-Olona-VA, Italy) with an optical beam-splitting device. The number of treatments during a single session of ILP depended on the nodule size and position. When the nodule was small or oval-shaped, the needle tip was placed in the center of the nodule and one treatment was performed. In the case of big or round-shaped nodule, the needle tip was placed in the center of the superior and inferior hemi-nodule (two treatments). The exact position of the fiber tip was measured by a centimeter scale on the needle. Each treatment was performed with an output power of 2–3 W. The ILP sessions lasted from 5 to 10 min.

Side effects, and in particular pain, need for analgesics after treatment, local hemorrhage, burning, damage to the surrounding cervical structures, and dysphonia were carefully registered.

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSS, Inc., Evanston, IL, USA). The effect of ILP treatment on thyroid nodule volume (evaluated as percent decrease compared with pre-treatment value) was assessed by analysis of variance (ANOVA) and post hoc analysis was performed by Bonferroni correction. All comparisons between different groups were performed by Mann–Whitney *U* test.

Correlation between two variables was ascertained by Spearman's correlation test. A p value < 0.05 was considered statistically significant.

Results

Table 1 summarizes the clinical and demographic data of patients at baseline, before ILP treatment. Associated thyroid autoimmunity, as assessed by circulating thyroid antibodies, was detected in 10 out of 43 patients (23.2%). The mean (± SD) pre-treatment volume of thyroid nodules was 21.1 ± 19.9 mL. The mean (± SD) energy delivered was 5084.84 ± 2043.79 J corresponding to 336.46 ± 190.59 J/mL nodule tissue. The serum levels of the TSH and FT4 recorded at each visit did not present significant changes during the follow-up period.

Table 1 Clinical and demographic features of all patients before laser ablation treatment

Sex, male/female (total)	5/38 (43)
Age (years) (mean ± SD)	56.06 ± 12.40
Presence of thyroid autoimmunity (yes–no) (total)	10–33 (43)
Thyroid volume (mL, mean ± SD)	35.3 ± 19.3
Thyroid nodule volume (mL, mean ± SD))	21.1 ± 19.9
Thyroid nodule hypo-echogenicity (yes–no) (total)	13–30 (43)
Thyroid nodule vascularization (intra-peripheral or absent) (total)	19–24 (43)
Total joules (mean ± SD)	5084.84 ± 2043.79
J/mL (mean ± SD)	336.46 ± 190.59
Number of fibers (1–2) (total)	18–25 (43)
Number of applications (1–2)	34–9

Change of thyroid nodule volume during follow-up

During the follow-up, two distinct groups of patients emerged: the responders (N = 33) and the non-responder (N = 10) ones to ILP. Patients in the latter group eventually underwent surgery. Table 2 shows percent changes of mean thyroid nodule volume in patients who did not underwent thyroid surgery after ILP and in those who were treated with thyroidectomy.

In the responder group, the nodule volume significantly decreased during the follow-up (ANOVA p < 0.001). A nodule volume decrease was recorded in the first 3 years of follow-up. Thereafter, a trend toward a slight increase of nodule volume was observed up to the end of follow-up. No significant decrease of nodule volume was observed in the non-responder group. As a consequence, the percent decrease of nodule volume significantly differed in the responder as compared with the non-responder group at 6 months, 1 year, and 2 years of follow-up (Table 2).

To further evaluate the potential effect of ILP procedure in reducing thyroid nodule volume, the maximum percent decrease of nodule volume during follow-up, was calculated in individual patients. As expected, the mean maximum percent decrease was significantly greater in responder patients as compared with the non-responder ones (46.9 ± 18.2 vs. 25.0 ± 21.4, respectively, p = 0.02) (Fig. 1). Table 3 reports the clinical and demographic features of patients before ILP. No significant difference was observed in responder patients as compared with the non-responder ones. Thyroid nodule volume was larger in the non-responder group, but

Table 2 Mean (± SD) percent decrease of nodule volume during the follow-up in responders and non-responders to ILP (mean ± SD)

	1 month	6 months	1 year	2 years	3 years	4 years	5 years	6 years
ILP responders (N = 33)* Baseline nodule volume (mean ± SD) 19.3 ± 16.4	16.3 ± 21.2	38.0 ± 20.8	41.3 ± 23.7	36.7 ± 20.4	33.4 ± 27.4	27.8 ± 32.0	26.6 ± 29.9	25.1 ± 29.3
ILP non-responders (N = 10) Baseline nodule volume (mean ± SD) 27.2 ± 21.9	11.1 ± 21.1 (N = 10)	13.5 ± 19.0 (N = 10)	− 5.29 ± 21.3 (N = 10)	9.5 ± 25.7 (N = 7)	− 21.8 ± 34.3 (N = 3)			
p		**0.006**	**0.001**	**0.015**				

Bold values indicate statistical significance (p < 0.05)

Data are the mean of the individual percent volume decrease from the baseline

*ANOVA p < 0.001

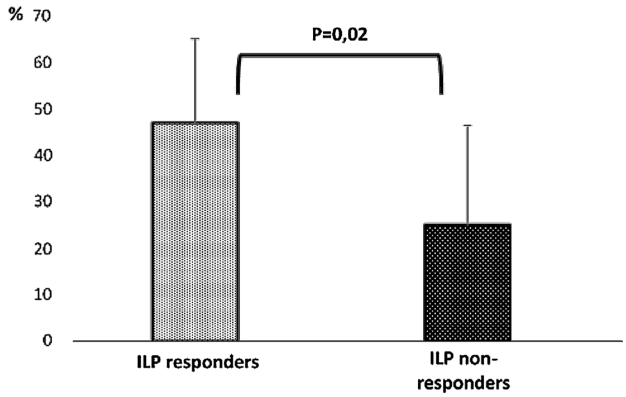

Fig. 1 Maximum percent decrease of nodule volume in responders and non-responders to ILP (mean ± SD)

the difference did not reach statistical significance, while intra-nodular vascularization was significantly more frequent in ILP non-responders when compared to ILP responders.

In the non-responder group, four out of ten patients underwent lobectomy and six patients underwent total thyroidectomy. At histology, a colloid cystic nodule was diagnosed in eight patients, a follicular tumor of uncertain malignant potential (FT-UMP) in one, and a follicular carcinoma in another one. The mean percent volume change, as assessed before surgery, was 96.4% in benign nodules. The correspondent volume changes were 82.6% in the FT-UMP and 131.2% in the follicular carcinoma, the latter figure indicating a significant increase in size of the malignant lesion.

Predictors of ILP therapeutic outcome

As expected from the wide standard deviation interval, the response to ILP treatment was highly variable. To explain this heterogeneous behavior, the pre-treatment US features of thyroid nodules and the coexistence of thyroid autoimmunity were taken into account. No significant association was found between these parameters and the decrease of nodule volume. However, in the whole group of patients, the energy delivered per mL of nodule tissue was significantly correlated with the percent volume decrease at the end of follow-up (Fig. 2).

Tolerability and side effects

Mild self-limiting local pain was reported by almost all patients during the procedure. No major complication was reported.

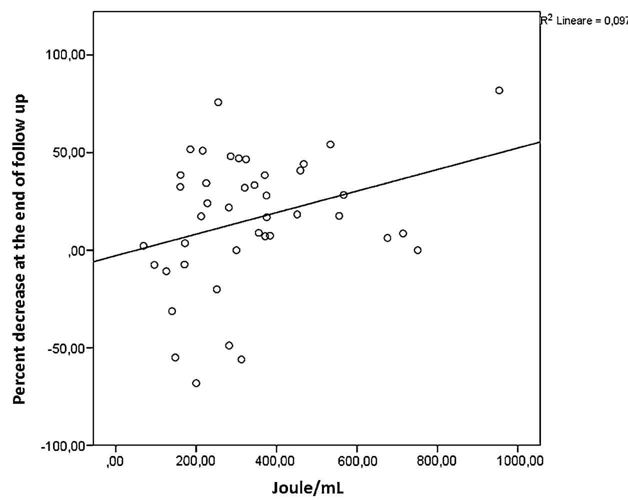

Fig. 2 Linear regression analysis between the energy delivered per mL of nodule tissue and the percent volume decrease at the end of individual follow-up (whole group of patients)

Table 3 Pre-treatment clinical and demographic features of responders and non-responders to ILP

	ILP responders (*N* = 33)	ILP non-responders (*N* = 10)	*p*
Sex, male/female (*N*)	29/4	9/1	0.67
Age (years) (mean ± SD)	56.4 ± 12.9	54.8 ± 10.8	0.72
Presence of thyroid autoimmunity (yes–no) (*N*)	7/26	3/7	0.42
Thyroid volume (mean ± SD)	32.5 ± 18.0	44.3 ± 21.8	0.66
Thyroid nodule volume (mean ± SD)	19.3 ± 16.4	27.2 ± 21.9	0.22
Thyroid nodule hypo-echogenicity (yes–no) (*N*)	8/25	5/5	0.12
Thyroid nodule vascularization (intra/peripheral or absent) (N)	11/22	8/2	0.01
Total Joules (mean ± SD)	5074.6 ± 1989.6	5117.3 ± 23321	0.94
J/mL (mean ± SD)	360.4 ± 193.7	259.8 ± 166.3	0.07
Number of fibers (1–2) (*N*)	15/18	3/7	0.80
Number of applications (1–2)	29/4	5/5	0.09

Discussion

Interstitial laser photocoagulation is a minimally invasive procedure used for the treatment of symptomatic and/or large benign thyroid nodules [16, 17]. ILP results in nodule shrinkage [3, 8, 18] through an irreversible cell damage due to coagulation necrosis produced by high temperature. Yet, data on its long-term efficacy are limited. The present study reports the results obtained in a series of patients who were followed-up for 6 years, the longest period recorded so far.

We experienced a great variability in the response to treatment, which is consistent with most of the previous ILP studies [10, 13]. In our series, there were ten non-responders who, due to persistent complains, underwent thyroid surgery. The poor response to ILP was already evident in the first year after treatment, thus allowing an early identification of non-responders and their shift to surgery. With the limit of a small sample size, no statistically significant difference was found in pre-treatment demographic and clinical features when comparing responder with non-responder patients. A non-significant trend toward a larger volume of the gland and of ILP-treated nodules was found in non-responders, while a significantly greater prevalence of nodules showing internal vascularization was found.

In the responder group, the maximum percent decrease of thyroid nodule volume was 46.9%. This finding is in line with other data in the literature. In another series with a long follow-up period (median 5.5 years), which, however, included smaller nodules (mean starting volume 8.2 mL), the median reduction was 51% [10]. In other studies, with variable follow-up (from 3 to 4 years), the mean volume reduction ranged from 47.8 to 57% [3, 10, 13]. In our study, the responder group experienced a progressive decrease of thyroid nodule volume during the first 2 years after ILP, thereafter, up to the end of follow-up, we observed a trend toward a slight increase of nodule volume. This phenomenon was previously reported in other series. In a prospective multicenter study including 101 patients [3], the reduction of thyroid nodule volume was progressive up to 12 months after ILP, and remained stable during a 3-year follow up. However, 5% of laser-treated nodules showed a partial regrowth. Similarly, in a large prospective series [11], the ILP-induced reduction of thyroid nodule volume persisted for 3 years after the procedure. Afterward, a trend toward volume increase was observed in 9% of them.

In previous studies, several pre-treatment parameters were blamed as predictors of a poor response to ILP. Differences in heat dispersion, due to peculiarities in thyroid histology, are the main determinants of the variable effect of laser treatment [19, 20]. However, both an intense nodule vascularization, resulting in a cooling effect, and the presence of fibrosis could influence energy transmission to the tissue [10, 21]. In the present study, we also evaluated echogenicity, vascularization, and amount of liquid component of the nodule as possible predictors of ILP outcome, but none of them results with the degree of post-ILP shrinkage. This finding is in agreement with the results of other authors [3, 10, 12, 21]. The coexistence of autoimmune thyroiditis was also taken into account, but no association was found between its presence and nodule volume reduction after ILP. In the current study, only the energy delivered per mL of tissue was significantly associated with the degree of nodule shrinkage. This relationship was also analyzed in previous studies, but contradictory results were reported [10, 21, 22]. Some studies found that the greater was the energy delivered, the larger was the coagulative necrosis of the nodule [19, 20]. However, other studies demonstrated that for very high values of delivered energy, the curve describing its relationship with ILP-induced necrosis reaches a plateau, thus suggesting a logarithmic correlation [19]. This plateau effect results from the carbonization of the fiber tip. In a previous study with a follow-up period of 3 years, Gambelunghe et al. [22] compared 2 groups of 20 patients each, equally subdivided according to low or high energy delivered by ILP. They found that, at variance with the high energy group, patients in the low energy more frequently experienced a nodule regrowth. Other studies did not find an association between energy delivered and nodule volume decrease [10, 21]. High energies delivered in old ILP studies and technical differences in ILP procedures could explain the heterogeneous results. In our study, the nodule showing the most important volume increase after ILP (131%) harbored a follicular carcinoma at post-surgical histology. The case of this patient emphasizes the need of a careful follow-up of nodules being submitted to ILP treatment. It is important to emphasize that in the latest consensus statement from the Italian minimally-invasive treatments of the thyroid group, it is strongly suggested that a double cytological confirmation of benignity should be obtained prior to image-guided thermal ablation of thyroid nodules [23]. In our retrospective study, data were obtained from patients treated with ILP therapy in the period ranging from 2010 to 2013. Therefore, fine-needle aspiration cytology was performed only once, according to the previous guidelines. Indeed this proved to be a pitfall because we had one false negative result in a patient that at surgery was found to have a follicular carcinoma.

The main limitations of the present study stem from its retrospective design and from the limited number of investigated patients. The long follow-up period and the inclusion of patients who eventually were switched to surgery represent the main strengths.

In conclusion, ILP is a safe technique, which, at a 6-year follow-up period, is able to reduce by about 50% the volume of benign thyroid nodules in the majority of treated patients. However, due to the great variability of results, an active follow-up is required. After 1 year of follow-up, non-responder patients can be identified and eventually shifted to different types of treatment. The only independent predictor of ILP outcome is the energy delivered per mL of nodule tissue.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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