Laser Ablation and 131-Iodine: A 24-Month Pilot Study of Combined Treatment for Large Toxic Nodular Goiter

M. Chianelli, G. Bizzarri, V. Todino, I. Misischi, A. Bianchini, F. Graziano, R. Guglielmi, C. M. Pacella, H. Gharib, and E. Papini

Endocrinology Unit (M.C., I.M., F.G., R.G., E.P.), Nuclear Medicine Unit (V.T.), and Interventional Radiology, Department Of Diagnostic Imaging (G.B., A.B., C.M.P.), Regina Apostolorum Hospital, 00041 Albano Laziale, Rome, Italy; and Endocrinology Division (H.G.), Mayo Clinic College of Medicine, Rochester, Minnesota 55905

Context: It is normally recognized that the preferred treatment in large toxic thyroid nodules should be thyroidectomy.

Objective: The aim of the study was to assess the efficacy of combined laser ablation treatment (LAT) and radioiodine 131 (131I) treatment of large thyroid toxic nodules with respect to rapidity of control of local symptoms, of hyperthyroidism, and of reduction of administered 131I activity in patients at refusal or with contraindications to surgery.

Design and Setting: We conducted a pilot study at a single center specializing in thyroid care.

Patients: Fifteen patients were treated with LAT, followed by 131I (group A), and a series of matched consecutive patients were treated by 131I only (group B).

Intervention(s): Laser energy was delivered with an output power of 3 W (1800 J per fiber per treatment) through two 75-mm, 21-gauge spinal needles. Radioiodine activity was calculated to deliver 200 Gy to the hyperfunctioning nodule.

Main Outcome Measure(s): Thyroid function, thyroid peroxidase antibody, thyroglobulin antibody, ultrasound, and local symptoms were measured at baseline and up to 24 months.

Results: Nodule volume reduction at 24 months was: 71.3 ± 13.4 vs 47.4 ± 5.5%, group A (LAT+131I) vs group B (131I), respectively; $P < .001$). In group A (LAT+131I), a reduction in radioiodine-administered activity was obtained (−21.1 ± 8.1%). Local symptom score demonstrated a more rapid reduction in group A (LAT+131I). In three cases, no 131I treatment was needed after LAT.

Conclusions: In this pilot study, combined LAT/131I treatment induced faster and greater improvement of local and systemic symptoms compared to 131I only. This approach seems a possible alternative to thyroidectomy in patients at refusal of surgery. (***J Clin Endocrinol Metab*** **99: E1283–E1286, 2014)**

Conventional treatment modalities of toxic thyroid nodules (TTNs) include thyroidectomy and radioiodine ablation (1). Even in the absence of unequivocal criteria (1, 2), a surgical approach is frequently preferred for patients with TTNs larger than 5 cm (1–3) because, in large nodules, radioiodine 131 (131I) therapy is less effective and side effects are more frequent (4, 5). Thermal ablation procedures are reported as rapid and effective for

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received July 25, 2013. Accepted March 14, 2014.
First Published Online March 31, 2014

Abbreviations: 131I, radioiodine 131; LAT, laser ablation treatment; MMI, methimazole; SPET, single photon emission tomography; SYS, symptom score; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TTN, toxic thyroid nodule; US, ultrasound.

nodule volume reduction (6–9). In large TTNs, however, laser ablation treatment (LAT) would require several sessions with increasing cost and discomfort (10, 11).

In this pilot study, we assessed the efficacy of combined LAT and 131I radionuclide treatment of large TTNs with respect to rapidity of control of local symptoms, of hyperthyroidism, and of reduction of administered 131I activity.

Patients and Methods

Entry criteria were: 1) a single or dominant hyperfunctioning nodule, either solid or with a fluid component <20% at ultrasound (US); 2) volume >10 mL with at least one diameter >30 mm; 3) hyperactive appearance of the lesion at 99mTc thyroid scintiscan; 4) suppressed levels of TSH or methimazole (MMI) treatment for hyperthyroidism; 5) normal levels of thyroid autoantibodies; and 6) refusal or contraindication to surgery for physical status 3 or higher as defined by the American Society of Anesthesiologists (presence of comorbidities such as renal failure, heart failure, or worse).

Thirty-two patients with TTNs matching the entry criteria were recruited for the study. No patient had previously undergone surgery or radioiodine therapy. Treatment selection was chosen by patients who were then allocated to either group A (LAT+131I) or group B (131I). Fifteen patients were treated with combined LAT and radionuclide treatment (group A); a second group of 17 patients with matched clinical, demographic, and instrumental findings was treated with 131I according to the guidelines of the Italian Association of Nuclear Medicine (group B). The study was conducted in compliance with the Helsinki Declaration.

Group A: LAT and 131I treatment

Fifteen patients (10 females and 5 males; mean age, 62 ± 16 y) with large autonomous nodules (mean ± SD, 27.7 ± 17.0 mL) were recruited. Eleven patients were treated with antithyroid drugs, and four had suppressed TSH levels with normal thyroid hormones. One LAT session was performed for diameters between 3 and 5 cm and two sessions for diameters between 5.1 and 7 cm. In six patients, the second LAT was given 1 month after the first session. Patients were treated with 131I 1 month after the last LAT. Serum free T_4, free T_3, TSH, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were assessed at baseline, 1 month after LAT, and 1, 3, 6, 12, and 24 months after radioiodine. Radioiodine uptake and single photon emission tomography (SPET) thyroid scans with 99mTc-pertechnetate were performed before LAT, 1 month after LAT, and 1 year after LAT. Thyroid US was performed before and 1 month, 1 and 2 years after initial LAT.

Group B: 131I treatment

Seventeen patients (11 females and 6 males; mean age, 59 ± 15 y) with large autonomous nodules (mean ± SD, 29.4 ± 10.6 mL) were treated with 131I only. Thirteen patients were treated with MMI, and four had suppressed TSH. Serum free T_4, free T_3, TSH, TPOAb, and TgAb were assessed at baseline and 1, 3, 6, 12, and 24 months after radioiodine. Radioiodine uptake and SPET thyroid scans with 99mTc-pertechnetate were performed before and 1 year after 131I treatment. Thyroid US was performed before, 1 and 2 months, and 1 and 2 years after initial treatment with 131I.

Nodule volume assessment

US evaluation was conducted at baseline and 1, 12, and 24 months after LAT or 131I with a commercially available US scanner (Mylab 70; Esaote) equipped with a 7.5- to 13.0-Mhz linear transducer. Volume was calculated with the ellipsoid formula as the mean of two measurements. Internal values for intra- and interobserver coefficients of variation for US volume assessment were 3.9 and 5.6%, respectively (6). In patients with coexistent cold nodules, malignancy was ruled out by US-guided fine-needle aspiration.

Assessment of local symptoms

Evaluation of local symptoms was made using a visual analog arbitrary scale (symptom score [SYS]) developed on occasion of a previous study in cold nodules by our group (6). SYS ranged between 1 and 5 (1, absent; 5, constant cervical symptoms and dysphagia). The SYS was calculated at entry and 1, 12, and 24 months after LAT or 131I.

Laser ablation treatment

After local anesthesia with xylocaine 2%, two 75-mm, 21-gauge spinal needles (Becton-Dickinson) were inserted into thyroid lesions under US guidance (6). Energy was delivered with an Nd:YAG laser (Echolaser; Elesta) with output power of 3 W and an illumination period of 10 minutes, reaching a total energy delivery of 1800 J per fiber per treatment, calculated on the basis of our previous experience in cold nodules (6). The total amount of energy delivered to the nodules ranged from 1800 to 3600 J. Patients were monitored for 60 minutes in the outpatient clinic and had a subsequent US control. Before LAT, patients were given an im injection of betamethasone (Bentelan 4 mg; Biofutura) to limit edema and possible pain (6).

Radioiodine uptake and thyroid SPET

At the time of treatment with LAT or 131I and during follow-up, patients underwent thyroid SPET 20 minutes after iv injection of 185 MBq of 99mtechenetium-O4-. SPET studies were performed with a dual-head gamma camera system equipped with low-energy, high-resolution, parallel-hole collimators (Forte; Philips). Radioiodine uptake was measured using a gamma probe (**I**'ACN) 6 and 24 hours after the oral administration of 370 kBq of 131I.

Radioiodine therapy

In patients treated with MMI, this was discontinued to obtain suppressed levels of TSH at the time of 131I administration. In group A (LAT+131I), after LAT, only four patients were still receiving MMI. 131I therapeutic activity was aimed at delivering 200 Gy to the hyperfunctioning nodule. Group A (LAT+131I) patients underwent 131I treatment 1 month after LAT. Group B (131I) patients received radioiodine after preliminary evaluation with the same modalities. No patient was given MMI after 131I therapy.

Table 1. Hormonal, Clinical, and Sonographic Changes in Group A (LAT+131I) at Baseline, at 1 Month (1 Month After LAT), 2 Months (2 Months After LAT and 1 Month After 131I) at 12 and 24 Months (12 Months After LAT and 11 Months After 131I) and in Group B (131I) at Baseline and 1, 2, 12, and 24 Months After 131I

Months	0		1		2		12		24	
Group	A	B	A	B	A	B	A	B	A	B
Treatment	No	No	LAT	131I	LAT + 131I	131I	LAT + 131I	131I	LAT + 131I	131I
SYS	2.7 ± 1.3	2.8 ± 1.3	2.1 ± 1.0	2.7 ± 1.4	1.7 ± 0.8[a]	2.4 ± 1.2	1.2 ± 0.4	1.4 ± 0.6	1.1 ± 0.4	1.3 ± 0.5
Volume, mL (US)	27.7. ± 17.0	29.4 ± 10.6	23.5 ± 14.9	27.5 ± 10.5	20.6 ± 13.5	25.3 ± 9.8	10.1 ± 9.3	15.4 ± 5.3	9.6 ± 8.9[a]	15.3 ± 5.1
Volume reduction, %			16.6 ± 6.2[b]	7.5 ± 3.6	27.8 ± 9.1[b]	15.0 ± 3.7	67.8 ± 13.2[b]	46.9 ± 5.3	71.3 ± 13.4[b]	47.4 ± 5.5
Free T_3, pg/mL	4.06 ± 0.66	4.12 ± 0.78	3.73 ± 0.72	4.01 ± 0.56	3.17 ± 1.18	3.52 ± 0.83	3.13 ± 0.45	3.29 ± 0.78	3.38 ± 0.80	3.31 ± 0.72
Free T_4, pg/mL	14.78 ± 4.64	15.02 ± 5.01	13.36 ± 3.99	13.96 ± 4.67	12.6 ± 5.12	13.43 ± 4.63	12.54 ± 5.43	12.37 ± 6.02	12.19 ± 4.84	12.38 ± 6.23
TSH, mIU/mL	0.04 ± 0.04	0.06 ± 0.06	0.66 ± 0.70	0.33 ± 0.21	0.87 ± 0.61[a]	0.40 ± 0.28	1.66 ± 1.02	1.48 ± 1.02	1.71 ± 1.12	1.57 ± 1.07

Normal range, TSH, 0.2–4.0 mIU/mL; free T_3, 2.2–5.0 pg/mL; free T_4, 8.0–18.5 pg/mL.

[a] $P < .05$; [b] $P < .01$, group A vs group B.

Laboratory evaluation

Serum TSH (normal range, 0.2–4.0 mIU/mL), free T_3 (range, 2.2–5.0 pg/mL), free T_4 (range, 8.0–18.5 pg/mL), TgAb (range, 0.0–70.0 IU/mL), and TPOAb (range, 0.0–70.0 IU/mL) were determined with commercially available radioimmunological assay kits (Radim).

Statistical analysis

Results are expressed as mean ± SD. Student's *t* test for paired data was used to compare data within the same group; Student's *t* test for unpaired data was used to compare data between groups.

Results

Baseline characteristics were not significantly different in the two groups (Table 1). No complications occurred, as assessed by post-procedure neck US, and discomfort was minimal: mild cervical pain, self-resolving or controlled with ketoprofen.

No differences were observed in baseline nodule volume between the two groups. Laser-induced nodule reduction depended on energy delivered with no relation to nodule volume. Volume reduction was faster in patients treated with laser treatment followed by 131I (group A). Volume reduction was observed 1 month after LAT (baseline volume, 27.7 ± 17.0 mL; vs 1-month volume, 23.5 ± 14.9 mL; volume reduction, 16.6 ± 6.2%), with further reduction 1 month after 131I. Two years after LAT, nodule volume showed a reduction of 71.3 ± 13.4% (10.1 ± 8.3 mL). In group B (131I), volume reduction at 2 years was 47.4 ± 5.5% (baseline vs 2-y volume, 29.4 ± 10.6%; 15.3 ± 5.1 mL) and was slower and smaller at all time points compared to group A (LAT+131I) ($P < .001$ at 1 y). Two months after initial treatment, local SYS demonstrated a more rapid reduction in group A (LAT+131I) (from 2.7 ± 1.3 to 1.7 ± 0.8, 1 month after 131I, 2 months after LAT) than in group B (131I) (from 2.8 ± 1.3 to 2.4 ± 1.2) ($P = .03$). Two years later, no difference was detectable.

TSH showed a progressive increase, reaching normal values after 12 months in all patients. In group A (LAT+131I), however, normalization of TSH occurred in nine of 15 patients (60%) already 1 month after LAT; in particular, in three of these patients radioiodine was not necessary (nodule size was 3.8, 4, and 5 cm, respectively). No relapse of hyperthyroidism was observed, and a second 131I activity was not needed; treated nodules showed slightly increased uptake at thyroid scintigraphy by the residual vital nodule without inhibition of surrounding normal tissue. No increase of TPOAb was registered. Late hypothyroidism was only observed in one patient of group A (LAT+131I).

In group A (LAT+131I), a reduction of about 6% in 131I 24-hour uptake and of 21.1 ± 8.1% in radioiodine-administered activity was obtained after LAT. All patients from group A (LAT+131I) were amenable to outpatient radionuclide treatment with activities lower than 600 MBq (maximum activity that can be administered on an outpatient basis in Italy) (average, 480.1 ± 119.6 MBq). In group B (131I), higher activities were required (622.8 ± 147.7 MBq; $P = .01$), and eight of 17 (47.1%) patients required hospitalization.

Discussion

131I is effective for the treatment of TTNs in the long term (1, 3, 12). Volume reduction, however, is a slow process that is wholly obtained 6 to 36 months after treatment. Large TTNs are frequently considered a relative contra-

indication to the use of 131I because the risk of local symptoms due to radioiodine therapies is increased, and the volume reduction is small and slow (12). In these patients, higher activities of 131I are usually required.

US-guided percutaneous ethanol injection (PEIT) (13, 14) combined with 131I treatment was reported to be effective in patients with large TTNs (15). Percutaneous ethanol injection, however, presents limitations in solid nodules and is currently recommended for cystic lesions only (16, 17).

Randomized trials demonstrated that LAT is safe and effective for debulking benign cold nodules (6), and successful LAT was recently reported in TTNs (7–9, 18). In large TTNs, however, repeated sessions are necessary with increased cost and discomfort (10).

We evaluated the combined use of LAT and 131I in large TTNs in an attempt to accelerate volume reduction and decrease 131I activity. We compared combined treatment to traditional 131I therapy.

Combined treatment determined faster volume reduction and relief of symptoms, and faster control of hyperthyroidism. Symptom improvement was faster in patients with greater discomfort, regardless of nodule volume, probably as a consequence of nodule position. At 1 month, normalization of TSH levels was observed in group A (LAT+131I) only. LAT resulted in a reduction in administered 131I activity, and patients were treated on an outpatient basis with activities lower than 600 MBq. Combined treatment was equally effective in nodules smaller or larger than 5 mL (12). In three patients with nodule size <5 cm, LAT induced normalization of TSH, and subsequent 131I therapy was not needed.

Conclusions

Combined LAT/131I treatment permitted lower activities of 131I, allowing outpatient treatment and reduced absorbed dose to patients and caregivers. This approach was well tolerated and induced faster improvement of local symptoms and of biochemical hyperthyroidism.

Acknowledgments

Address all correspondence and requests for reprints to: Marco Chianelli, MD, PhD, Department of Endocrinology, Regina Apostolorum Hospital, Via San Francesco 50, 00041 Albano, Rome, Italy. E-mail: marcochianelli@libero.it.

Disclosure Summary: The authors have nothing to disclose.

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