CLINICAL STUDY

Randomized prospective study comparing a single radioiodine dose and a single laser therapy session in autonomously functioning thyroid nodules

Helle Døssing, Finn Noe Bennedbæk¹, Steen Joop Bonnema², Peter Grupe³ and Laszlo Hegedüs²

Department of Oto-Rhino-Laryngology and Neck Surgery, Odense University Hospital, DK-5000 Odense C, Denmark, ¹Department of Endocrinology and Metabolism, Herlev University Hospital, DK-2730 Herlev, Denmark, Departments of ²Endocrinology and Metabolism and ³Nuclear Medicine, Odense University Hospital, DK-5000 Odense, Denmark

(Correspondence should be addressed to H Døssing; Email: helle.doessing@ouh.fjns-amt.dk)

Abstract

Objective: To compare the efficacy of interstitial laser photocoagulation (ILP) with radioiodine in hot thyroid nodules.

Design: Thirty consecutive outpatients with subclinical or mild hyperthyroidism and a scintigraphically solitary hot nodule with extraglandular suppression were randomized to either one ILP session or one radioiodine (¹³¹I) dose.

Methods: ILP was performed under continuous ultrasound-guidance and with an output power of 2.5–3.5 W. ¹³¹I was given as a single dose based on thyroid volume and a 24-h thyroid ¹³¹I uptake. Thyroid function and nodule volume were evaluated at inclusion and at 1, 3 and 6 months after treatment.

Results: Normalization of serum TSH was achieved in 7 out of 14 patients in the ILP group and in all 15 patients in the ¹³¹I group ($P=0.0025$). In the ILP group, mean thyroid nodule volume reduction was $44 \pm 5\%$ (S.E.M.; $P<0.001$), and in the ¹³¹I group $47 \pm 8\%$ ($P<0.001$), within 6 months, without between-group difference ($P=0.73$). The mean reduction of total thyroid volume was $7 \pm 5\%$ in the ILP group ($P=0.20$) and $26 \pm 8\%$ ($P=0.006$) in the ¹³¹I group ($P=0.06$ between-group). Two patients in the ¹³¹I group developed hypothyroidism but no major side effects were seen.

Conclusions: This first randomized study, comparing ILP with standard therapy, demonstrates that ILP and ¹³¹I therapy approximately halves thyroid nodule volume within 6 months; but in contrast to ¹³¹I, extranodular thyroid volume is unaffected by ILP and no patient developed hypothyroidism. Using the present design, ILP seems inferior to ¹³¹I therapy in normalization of serum TSH. The potential value of ILP as a non-surgical alternative to ¹³¹I needs further investigation.

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Introduction

Approximately 10% of solitary nodules are scintigraphically hot, half of which are autonomously functioning (1, 2). Biochemical hyperthyroidism, often subclinical with suppressed serum thyroid-stimulating hormone (TSH) and normal peripheral thyroid hormones, is present in ~75% of the patients with an autonomously functioning thyroid nodules (AFTN; (2)).

Radioiodine and surgery are both effective in the treatment of pretoxic as well as toxic thyroid nodules (3). The reluctance to use radioactive iodine, especially in southern Europe, has led to the introduction of ultrasound (US)-guided percutaneous ethanol injection (PEI) of AFTN. Results have been promising, but the limitations of PEI are related to the difficulty in predicting the diffusion of the ethanol which can cause pronounced

pain, and side effects such as extraglandular fibrosis impeding subsequent surgery, needed in case of treatment failure. The need of repeated injections to achieve euthyroidism and nodule shrinkage may increase the risk of side effects. This, in addition to the lack of randomized trials testing PEI against standard therapy (surgery or ¹³¹I), has clearly limited the routine use of PEI (1, 4–7).

US-guided percutaneous interstitial laser photocoagulation (ILP) has been introduced in solid cold thyroid nodules (8–11). ILP is a minimally invasive interventional procedure and the necrosis induced by the thermic energy can be delivered in a controlled fashion with no or minimal damage to the surrounding tissue (12, 13). The procedure is performed on an outpatient basis and is well tolerated. The nodule volume reduction is comparable to that obtained following one PEI treatment (4, 14), and

the only reported side effects have been slight discomfort and moderate pain for up to a few days (8, 9).

The feasibility and the efficacy of US-guided ILP in AFTN has previously been reported only in few patients (15, 16), but never in a randomized study comparing it with standard therapy. Therefore, the aim of our study was to evaluate the effect of ILP in a prospective randomized study where ILP was compared with ^{131}I therapy.

Patients and methods

Thirty consecutive patients with a median thyroid nodule volume of 9.8 ml (range 3.0–43.0 ml) and a median total thyroid volume of 25.0 ml (11.0–50.0 ml), referred due to subclinical or mild hyperthyroidism or a thyroid nodule, were included. All patients had a solitary hot thyroid nodule, evaluated clinically, scintigraphically and by US. The latter demonstrated increased vascularization by colour Doppler. None had prior radiation to the neck or symptoms or findings suggestive of thyroid malignancy (rapidly growing, firm or adherent nodules, compression symptoms or regional lymphadenopathy). Blood tests included serum thyrotrophin (TSH; normal range 0.3–4.0 mU/ml) determined by DELFIA (Wallac OY, Turku, Finland), serum total thyroxine (T_4 ; normal range 65–135 mmol/l) determined by RIA (Diagnostic Products Corp., Los Angeles, CA, USA) and serum total triiodothyronine (T_3 ; normal range 1.00–2.10 mmol/l) determined by RIA (Johnson & Johnson, Clinical Diagnostics Ltd, Amersham). Free T_4 (FT_4) and free T_3 (FT_3) indices were calculated multiplying serum T_4 and T_3 levels respectively, with the percentage T_3 resin uptake. Serum anti-thyroid peroxidase antibodies (anti-TPOAb) were determined by RIA DYNO test (Brahms diagnostica GMBH, Berlin, Germany; normal range < 60 U/ml).

Randomization was achieved using a random number generator on a computer. The protocol was approved by the ethics committee of the county of Funen (journal no. 20 000 240) and registered at www.clinicaltrials.gov (registration number: NCT00150150). Prior to participation, all the patients gave signed informed consent. Patients were randomized to one treatment session of US-guided ILP or one dose of ^{131}I . Both ILP and ^{131}I -therapy were carried out on an outpatient basis. One patient in the ILP group was excluded from the study since she was lost to follow-up immediately after treatment, leaving 29 patients for the final analysis. These individuals were investigated with assessment of the thyroid function and nodule volume at 1, 3 and 6 months after the treatment. Thyroid function was additionally investigated 2 months after treatment. Furthermore, anti-TPOAb was determined and a scintigraphy performed 6 months after treatment. Thyroid nodule volume was calculated on the basis of an ultrasonic scanning procedure, by recording cross-sections through the

gland, using a 5.5 MHz static compound scanner (type 1846, B&K Medical, Gentofte, Denmark) as previously described (17).

In the ILP group, a Logiq 500 US scanner (GE Medical Systems, Milwaukee, WI, USA) with a 12 MHz linear transducer (type 739L) mounted with a needle steering device for precise US-guided punctures was used. Under sterile conditions and guided by US, the laser fibre (0.4 mm in diameter) was positioned in the thyroid nodule through the lumen of an 18 gauge (1.2 mm) needle and preceded by local anaesthesia with lidocaine (10 mg/ml). The needle was withdrawn at least 20 mm leaving the end of the fibre in direct contact with the tissue. Patients were then treated with an output power of 2.5–3.5 W, depending on pretreatment nodule volume and the position of the nodule. The entire procedure was performed with an infrared diode (model 15; Diomed, Cambridge, England) laser power source and under continuous US-guidance. During laser treatment, the vapour from the tissue was clearly visible on US as an irregular echogenic area enlarging over time. Based on previous experience, at present, we suggest a safety distance from the neurovascular bundle of at least 1.5 cm to avoid injury to these structures as a result of the thermal effect of ILP (8, 12). Typically, three or four areas were treated and the absence of flow signs in the treated areas, evaluated by colour flow Doppler, was used as a surrogate marker of immediate treatment success, to determine when the procedure should be terminated. The energy delivered during photocoagulation was recorded.

^{131}I was given as a single dose calculated as 3.7 MBq/g total thyroid mass (estimated by planimetric ultrasonography), corrected to a 100% thyroid uptake of ^{131}I after 24 h. The maximum therapeutic ^{131}I activity was limited to 600 MBq (16.2 mCi) according to the official Danish health authority regulations.

If severe hyperthyroid symptoms developed after the treatment, β -blockade (propranolol) was offered. Myxoedema, defined as serum TSH above normal levels and free thyroid hormones below normal levels, was treated with levo- T_4 (L-T_4).

Treatment outcome was evaluated in relation to complete cure, defined as normalization or elevation of serum TSH at the 6-month evaluation. Transient hypothyroidism was ruled out by reducing the L-T_4 dose before final classification.

Statistical analysis

Results for continuous data are given as median and ranges or mean and s.e.m. Fisher's exact test, one- and two-way ANOVA, Wilcoxon's-signed ranks test and the Mann-Whitney test were used to compare baseline characteristics and analyse differences in outcome. A P value of <0.05 was considered significant.

Results

Baseline characteristics

Clinical data of the patients randomized to ^{131}I therapy or ILP treatment are given in Table 1. Baseline characteristics were not significantly different in the two groups. Five patients in each group had mild hyperthyroidism but none needed anti-thyroid medication before therapy. In the five hyperthyroid patients, randomized to laser therapy, median serum TSH was 0.01 mU/ml (range <0.001–0.03), median FT_4I was 145 mmol/l (range 81–177) and median FT_3I was 2.7 mmol/l (range 1.9–4.4). In the five hyperthyroid patients, randomized to ^{131}I therapy, median serum TSH was <0.01 mU/ml (range <0.001–0.03), FT_4I was 174 mmol/l (range 143–217) and FT_3I was 3.8 mmol/l (range 2.5–4.3). There was no statistically significant difference in serum TSH ($P=0.31$), FT_4I ($P=0.51$) and FT_3I ($P=0.42$) between these two subgroups with mild hyperthyroidism (Table 1).

Outcome: nodule and thyroid volume

In the ILP group, median total energy given was 1726 J (range 796–2700), corresponding to a median energy of 217 J (range 19–553) per millilitre initial nodule volume. The median duration of the ILP treatment was 600 s (range 411–900). In the ILP group, the mean nodule volume reduction was $44 \pm 5\%$ (S.E.M.) at 6 months follow-up ($P<0.001$) with most of the effect evident during the first 3 months (Fig. 1). Scintigraphy was normalized (homogeneous uptake without any sign of the nodule) in 2 out of 14 patients. The mean reduction in total thyroid volume was $7 \pm 5\%$ (S.E.M.; $P=0.20$) after 6 months (Table 1). In the ^{131}I group, the median activity of ^{131}I was 327 MBq (range 200–600). In this group, the overall

nodule volume reduction was $47 \pm 8\%$ after 6 months. Most of the effect was evident during the first 3 months (Fig. 1). After ^{131}I therapy, the thyroid scintigraphy was normalized in 8 out of 15 patients ($P=0.0025$ compared with ILP). The overall mean reduction in thyroid volume was $26 \pm 8\%$ ($P=0.006$) during follow-up. There was no significant between-group difference in the nodule volume reduction ($P=0.73$), while the difference in the reduction of the total thyroid volume was borderline significant ($P=0.06$ between-groups; Table 1).

Outcome: thyroid function

At the 6-month investigation, the mean FT_3I was 2.2 ± 0.2 U/l (range 2.4–3.3) in the ILP group and 2.3 ± 0.3 U/l (range 1.30–5.13) in the ^{131}I group ($P=0.76$). The mean FT_4I in the ILP group was 109 ± 7 U/l (range 66–150) and in the ^{131}I group was 127 ± 14 U/l (range 57–270; $P=0.37$). Serum TSH was normalized in 7 out of 14 patients treated with ILP and in all 15 patients treated with ^{131}I therapy. In all cases with normalization of serum TSH, this was achieved within 3 months of therapy. Two patients receiving ^{131}I developed hypothyroidism 6 months after therapy (one of whom had positive anti-TPOAb initially).

Side effects

In one patient in the ILP group, the laser treatment induced pain, which disappeared momentarily when the energy was turned off. The only post-treatment side effect of ILP was slight to moderate pain in 5 out of 15 patients. Self-reported median duration of pain or tenderness was 2.5 days (range 0–5.0) and alleviation was obtained with mild analgesics.

Table 1 Baseline and treatment characteristics of the two groups with solitary autonomous thyroid nodules.

Variable	Laser therapy: baseline (n=14)	^{131}I therapy: baseline (n=15)	P values	Laser therapy: 6 months follow-up (n=14)	^{131}I therapy: 6 months follow-up (n=15)	P values
Age (years)	58 ± 3	54 ± 3	0.53			
Sex (M/F)	3/11	2/13	0.72			
Nodule volume (ml)	10.6 ± 2.5	11.2 ± 1.6	0.35	4.6 ± 0.6	6.3 ± 1.5	0.69
Nodule volume reduction				$44 \pm 5\%$	$47 \pm 8\%$	0.73
Thyroid volume (ml)	26.2 ± 3.0	24.6 ± 1.8	0.96	21.5 ± 2.0	18.4 ± 2.5	0.19
Thyroid volume reduction				$7 \pm 5\%$	$26 \pm 8\%$	0.06
Serum TSH (mU/ml) ^a	0.03 (<0.001–0.20)	0.02 (<0.001–0.27)	0.91	0.32 (<0.001–0.82)	1.21 (0.43–2.58) ^b	0.02
Normal/subnormal serum TSH (n)	0/14	0/15	0.98	7/7	15/0	<0.01
FT_4 index (U/l) ^c	113 ± 9	137 ± 11	0.17	109 ± 7	127 ± 14^b	0.37
FT_3 index (U/l) ^d	2.3 ± 0.2	2.6 ± 0.2	0.84	2.2 ± 0.2	2.3 ± 0.3^b	0.76
Anti-TPOAb (pos./neg.)	0/14	2/13	0.51	0/14	2/13	0.51

Values are number of cases, mean $\pm$ S.E.M. or median/range.

^aNormal value 0.3–4.0 mU/ml.

^bTwo patients who developed hypothyroidism are omitted.

^cNormal value 60–140 U/l.

^dNormal value 0.95–2.20 U/l.

Figure 1 Thyroid nodule volume reduction 1, 3 and 6 months after ILP treatment and ¹³¹I therapy (mean ± S.E.M). Laser vs. ¹³¹I at 6 months, $P=0.73$.

After ¹³¹I therapy, one patient had tenderness of the thyroid gland lasting for few days. Two developed hypothyroidism 6 months after therapy (one of whom had positive anti-TPOAb initially). Finally, hemithyroidectomy (benign histology) was performed in one patient receiving ¹³¹I because of persistent pressure symptoms during follow-up.

Discussion

The prevalence of AFTN ranges from 0.9% of unselected patients in regions with sufficient iodine supply, up to 9% in iodine-deficient regions (2, 3, 5). Treatment may be indicated either due to nodule size, compression of adjacent structures, cosmetic complaints, hyperthyroid symptoms, or in order to avoid progression of the hyperthyroidism (annual risk around 4%) (1, 18). Since subclinical hyperthyroidism has a detrimental effect on particularly the skeleton and the cardiovascular system (19, 20), treatment is often recommended, especially in elderly patients (21, 22). Current standard treatment options for AFTN include ¹³¹I-therapy and surgery. Many regard ¹³¹I as the therapy of choice for patients with AFTN. Treatment with low-dose ¹³¹I leads to a reduction of the nodule volume by ~45% within 2 years of therapy. The incidence of hypothyroidism after ¹³¹I therapy is reported to be ~10% within 5 years and increases in frequency over time (1, 5, 23).

Chemical ablation with ethanol injected under US-guidance is not currently adopted by the majority of endocrinologists as repeated injections are needed (3, 24) and clear disadvantages and limitations, especially when treating solid nodules, are related to this technique (5, 25, 26). The immediate advantage of ILP-induced thermal destruction is that the spread of energy, and thus the extent of tissue destruction, can be controlled, in contrast to the tissue necrosis induced by ethanol (13, 27, 28). Under US-guidance, the laser fibre is clearly visualized as a hyperechoic spot, and during

treatment the areas treated are clearly visualized as hyperechoic areas enlarging over time. Therefore, the advantage of ILP is the superior precision in inducing a well-defined area of tissue necrosis with a reproducible pattern. So far, the only side effect seems to be slight to moderate pain for a few days (8–10).

Previously, we have demonstrated that the size of scintigraphically cold thyroid nodules was reduced by about 45% after one ILP treatment (8, 9). The technique has also successfully been applied in an 18-year-old woman with an AFTN (15). However, the experience with ILP in AFTN is limited (16, 29). Seven patients with an AFTN were treated successfully by Spiezia *et al.* (29), while Pacella *et al.* (16) concluded that ILP was not effective in the control of an AFTN. Evidently, both studies involved few patients and were non-randomized. Our study is the first to compare ILP and standard treatment. In order to standardize the comparison of ILP and ¹³¹I, the laser treatment was given as a single treatment session, but the fibre was relocated in typically three or four areas to affect as much as possible of the nodule tissue. After one ILP session, we achieved a mean nodule volume reduction of 44%, which is comparable with that obtained by ¹³¹I therapy. Since normalization of the scintigraphy was obtained to a lesser degree after ILP than after ¹³¹I, despite a similar nodule volume reduction, it seems that the AFTN reacts differently to thermic- and radioactive destruction. Unfortunately, absence of flow signs in the treated areas, as evaluated by colour flow Doppler, can only serve as a rough marker of immediate treatment success following ILP but cannot predict clinical cure. By increasing the energy (up to six ILP-treatment sessions), a mean reduction of up to 61–74% may be achieved (16, 29).

In the present study, thyroid function was normalized – defined as normalization of serum TSH – in 47% of the patients after ILP and in all patients after ¹³¹I, two of whom developed hypothyroidism. In the ILP group those with mild hyperthyroidism seemed less hyperthyroid (although not significantly so) when compared with the ¹³¹I group, but nonetheless treatment success was achieved in all in the ¹³¹I group, favouring the latter. Furthermore, long-term efficacy has been confirmed for ¹³¹I and relapse after 6 months in the ILP group cannot be excluded, as reported for PEI, 1–5 years after successful treatment (30). The scintigraphy was normalized in 2 out of 14 patients after ILP treatment and in 8 out of 15 patients after ¹³¹I therapy. However, the results of the scintigraphy cannot be used as an indicator of complete cure. Even in patients where euthyroidism is achieved after ¹³¹I therapy, a hot nodule suppressing the uptake in the extranodular tissue is found in 50% or more of the patients 1–16 years later (23, 31). Favouring ILP, only patients offered ¹³¹I developed hypothyroidism. This is most likely due to the perinodular uptake of ¹³¹I (23, 32), whereas ILP is specifically targeted against the nodule.

Our randomized study substantiates that US-guided ILP is a safe and minimally invasive technique. However, using the present design, ILP seems inferior to ^{131}I therapy for normalization of serum TSH in patients with an AFTN. The nodule volume reduction after ILP is similar to that obtained after ^{131}I therapy, whereas the extranodular thyroid tissue is unaffected after ILP. Further large-scale studies, including evaluation of patient satisfaction, should address the efficacy of repeat ILP treatment, before ILP may be considered as a useful alternative for patients who are not candidates for surgery or ^{131}I therapy.

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