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Benign Solitary Solid Cold Thyroid Nodules: US-guided Interstitial Laser Photocoagulation—Initial Experience[1]

PURPOSE: To evaluate the effects of ultrasonography (US)-guided interstitial laser photocoagulation (ILP) on the volume of benign solitary solid cold thyroid nodules and any nodule-related symptoms.

MATERIALS AND METHODS: ILP was performed in 16 patients with normal thyroid function and a solid benign thyroid nodule. None of the patients had uptake on a radionuclide scan. Patients underwent one ILP session. A needle was positioned in the thyroid nodule with US guidance, and the laser fiber was placed in the lumen of the needle. Patients were treated for 287–1,200 seconds with an output power of 1–3 W. ILP was performed with continuous US guidance and terminated when the echogenic changes were stationary. Thyroid nodule volume and thyroid function were evaluated before and 1, 3, and 6 months after treatment. During the same period, 15 untreated patients (control group) were followed up to evaluate the size of the untreated thyroid nodule.

RESULTS: In the 16 patients treated with ILP, the mean thyroid nodule volume decreased from 10 to 5.4 mL ($P < .001$) after 6 months. The median energy given was 761 J. There was no relationship between the dose of thermal energy given and nodule reduction. Pressure symptoms were significantly reduced ($P = .0002$) after 6 months. The treatment was well-tolerated in all patients. No significant change in thyroid nodule volume was seen in the control group.

CONCLUSION: US-guided ILP could become a useful nonsurgical alternative in the treatment of the benign solitary solid cold thyroid nodule in patients who cannot or will not undergo surgery.

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The therapeutic strategy for patients with normal thyroid function and a benign solitary thyroid nodule that appears cold on a radionuclide scan is still a matter of debate. Surgery is regarded to be the standard therapy for thyroid nodules causing symptoms of compression and/or cosmetic complaints. Because nodular goiter is common in the general population (4%–7% have palpable nodules) (1,2) and thyroid carcinoma is rare in the absence of clinical suspicion (<5% of patients in Denmark who undergo surgery for solitary thyroid nodules have cancer [3]), a nonsurgical approach is often recommended. This is supported by results of questionnaire surveys in both Europe and North America (4,5) and by clinical practice guidelines (1). Thorough clinical and biochemical evaluation and ultrasonography (US)-guided fine-needle aspiration biopsy of solitary thyroid nodules have reduced the risk of overlooking malignancy in less than 1%–2% of cases (1,4,5).

Treatment with L-thyroxine in thyroid-stimulating hormone (TSH)–suppressive doses, although frequently used (1,4,5), has little or no effect on nodule size and symptoms, whereas nodules left untreated seem to have a slight growth potential in borderline

iodine-deficient areas (6). US-guided percutaneous ethanol injection (PEI) therapy induces coagulative necrosis and a median reduction in nodule volume of 47% that can be achieved with a dose of 20% of the pretreatment nodule volume (6,7). However, pain and side effects (eg, paranodular fibrosis) that impede subsequent surgery—if treatment is unsuccessful and surgery is needed—clearly limit the use of PEI and accounts for the reluctance to introduce this treatment for routine use (7).

Interstitial laser photocoagulation (ILP) has become useful for tumor palliation in patients with different kinds of advanced cancers (8–10). ILP is a minimally invasive interventional procedure that has also been used in the ablation of benign tumors (11). In addition, the technique was introduced in an in vitro study of the human thyroid (12). The purpose of our study was to evaluate the effect of US-guided ILP on the volume of benign solitary solid cold thyroid nodules and nodule-related symptoms.

MATERIALS AND METHODS

Study Protocol and Patient Population

The study protocol was approved by the ethics committee of the county of Funen. Patients gave signed informed consent before participating in the study.

In this prospective study, patients with a palpable nodule were referred by their primary care physicians. All treated patients had pressure symptoms, and 10 of 16 (63%) had cosmetic complaints. Other patients with the same disease as the treatment group who declined laser treatment or surgery because of a lack of pressure symptoms were recruited during the same period; they served as a nonrandomized control group. They were not treated and were reexamined once after a median of 12 months (range, 6–18 months).

All treated and untreated patients had a solitary solid benign thyroid nodule that was evaluated clinically and with US-guided fine-needle aspiration biopsy. Clinically, there was no suspicion or family history of thyroid cancer. None of the patients had previously undergone radiation therapy of the neck. Patients ranged in age from 20 to 70 years. None had uptake on a radionuclide scan. All patients had normal serum calcitonin levels. All patients had normal thyroid function, as determined with serum thyroid-stimulating hormone levels (Delfia;

Wallac, Turku, Finland) (normal range, 0.30–4.0 mIU/L), and none had anti–thyroid peroxidase antibodies (Ria Dyno test; Brahms Diagnostica, Berlin, Germany) (normal range, <60 U/mL). At enrollment and at the 6-month follow-up, the patients were asked to rate pressure symptoms and cosmetic complaints by using a visual analogue scale (scale, 0–10 [0 = no complaints, 10 = the worst complaints imaginable]), and they were blinded to clinical data. In patients treated with ILP, indirect laryngoscopy was performed immediately before and at 6 months after treatment by specialists in otorhinolaryngology to evaluate the motility of the vocal cords. ILP was performed on an outpatient basis after the administration of local anesthesia (lidocaine). The ILP procedure was performed by one of the authors (in most cases by H.D.). Immediately after termination of the ILP procedure, patients were asked whether they would undergo the treatment again, as a surrogate marker of tolerability. Although patients were asked to report the degree of pain and/or discomfort, this was not registered on a visual analogue scale. The patients were evaluated a 1, 3, and 6 months after the treatment by one of the authors (in most cases by H.D.). At follow-up, nodule volume and serum thyroid-stimulating hormone levels were obtained. Anti–thyroid peroxidase antibodies were measured at 6-month follow-up.

US was performed in a nonblinded fashion with regard to group but without knowledge of previous results. We used a Logiq 500 scanner (GE Medical Systems, Milwaukee, Wis) with a 12-MHz linear transducer (model 739L) mounted with a needle-steering device for precise US-guided punctures. Under sterile conditions and with US guidance, an 18-gauge (1.2-mm) needle was positioned centrally in the thyroid nodule and the laser fiber (0.4 mm in diameter) placed in the lumen of the needle. The needle was withdrawn 20 mm, leaving the end of the fiber in direct contact with the tissue. In all cases, the distance from the neurovascular bundle was at least 1.5 cm to avoid injury to these structures as a result of the thermal effect of ILP. Patients were then treated with an output power of 1–3 W—dependent on pretreatment nodule volume—for a median of 490 seconds (range, 287–1,200 seconds). The entire procedure was performed under continuous US guidance with an infrared diode (model 15; Diomed, Cambridge, England) laser power source. During laser treatment, the main feature was an irregular echogenic area enlarging over time

(Fig 1), and the procedure was terminated when this area was unchanged in size. The energy delivered during photocoagulation was recorded. Thyroid nodule volume was calculated on the basis of US by recording cross sections through the gland with a 5.5-MHz static compound scanner (model 1846; B-K Medical, Gentofte, Denmark), as previously described (5,6). The intra- and interobserver variation was in the range of 5%–7% (5).

Statistical Analysis

Continuous data are given as medians, ranges, SDs, or means and SDs, when appropriate. Nodule volume change in the treatment and control groups was tested with the Wilcoxon signed rank test. Comparison of the initial thyroid nodule volume between the two groups was performed with a Mann-Whitney test.

Correlation between energy deposition and reduction in nodule volume at 6-month follow-up was measured with the Spearman rank correlation coefficient. Pressure and cosmetic symptoms in the treatment group were rated on a visual analogue scale of 0 to 10 before and 6 months after treatment, and changes were evaluated by using a sign test (13).

RESULTS

ILP was performed in 16 patients with normal thyroid function (13 women, three men) and a median age of 47 years (SD, 11; range, 24–67 years). The median energy given was 761 J (SD, 607; range, 555–2388 J) and was dependent on the time exposure.

The mean initial nodule volume measured with US was 10.0 mL (SD, 7.9; range, 1.5–25.9 mL), and this decreased significantly ($P < .001$, Wilcoxon signed rank test) (Fig 2) within 6 months to 5.4 mL (SD, 5.1; range, 1.2–20.9 mL). The largest decrease was seen at the 1-month evaluation. Overall, nodule volume was reduced 46%. There was no correlation between energy deposited and reduction in nodule volume ($r = 0.26$, $P = .4$, Spearman rank correlation coefficient) (Fig 3). Even after correction for the pretreatment nodule volume, there was no statistically significant correlation with energy load ($r = 0.27$, $P = .32$, Spearman rank correlation coefficient). Pressure symptoms were significantly reduced ($P = .0002$, sign test) after 6 months (median, 5.0; SD, 2.40–2.25; SD, 1.5) (Fig 4). Initially, patients reported only slight cosmetic symptoms (median, 1.0; SD,
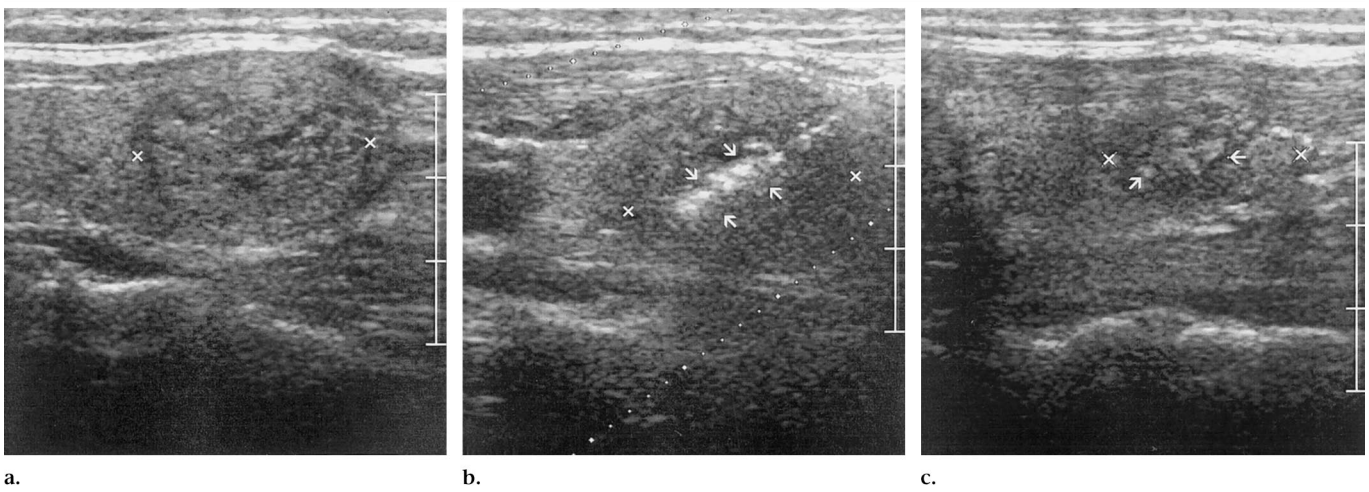
a. b. c.

Figure 1. Longitudinal US scans of the neck of a 47-year-old treated female patient show a solid nodule in the left thyroid lobe **(a)** before, **(b)** during, and **(c)** at 1 month after ILP. Cursors indicate the outer margins of the nodule. In **b**, which was obtained 60 seconds after ILP had been initiated, a cylindrical echogenic area is seen centrally (arrows). In **c**, a hyperechogenic area representing scar tissue is seen in the center of the nodule (arrows). A small rim was untreated in the proximal and caudal part of the nodule (area between arrow and cursor). The scale is in centimeters.
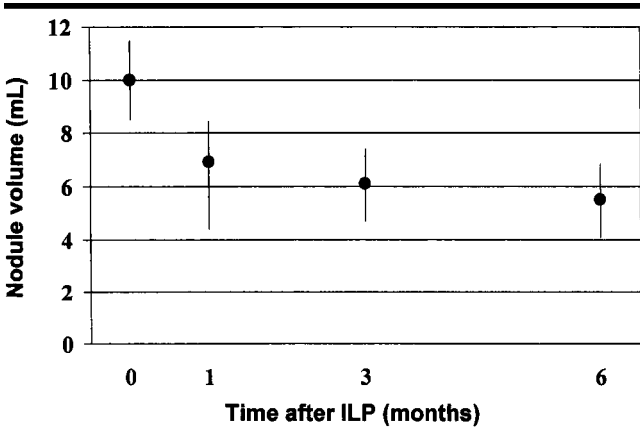

Figure 2. Graph shows thyroid nodule volume before and at 1, 3, and 6 months after treatment. Data are given as means and standard errors of the means. There was a significant reduction in thyroid nodule volume from 0 to 6 months ($P < .001$).
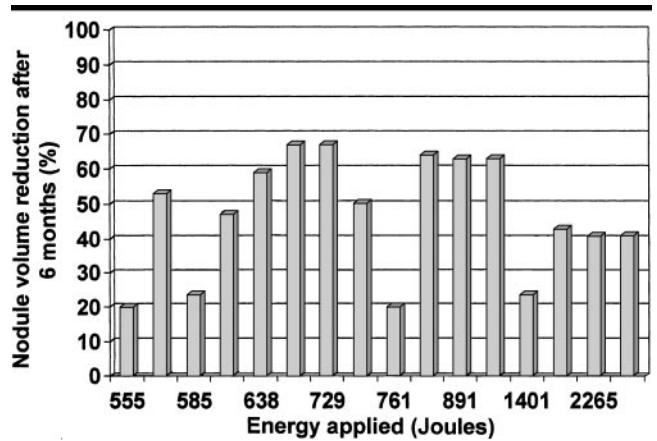

Figure 3. Graph shows the relationship between energy deposition and reduction in thyroid nodule volume at 6-month follow-up in 16 patients treated with ILP. No correlation between the energy deposition and reduction in thyroid nodule volume is seen.
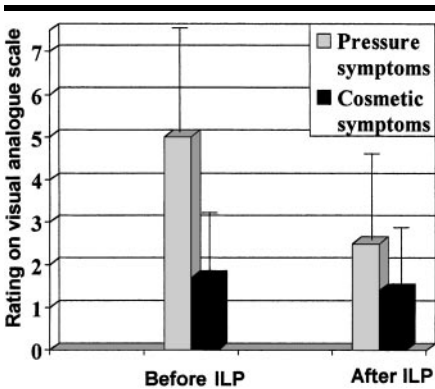

Figure 4. Graph shows the pressure symptom and cosmetic complaint ratings—determined with the visual analogue scale—before and at 6 months after ILP. Data are given as medians and SDs. A significant reduction in pressure symptoms is evident ($P < .0002$).

1.6), and only a modest reduction was seen after 6 months (median, 0.8; SD, 1.5; $P = .1$, sign test) (Fig 4).

Fifteen patients (women) with a median age of 40 years (SD, 12 years; range, 19–69 years) who declined treatment and had no pressure symptoms were used as our control group and followed up for a median of 12 months (SD, 3 months; range, 7–18 months). Initially, nodules in this group were smaller (median, 2.8 mL; SD, 3.6; range, 0.8–13.4 mL) than those in the treatment group ($P = .005$, Wilcoxon signed rank test). Nevertheless, spontaneous nodule growth was seen in eight (53%) of the 15 patients (median, 20%; SD, 26; range, −15% to 60%), although this change did not reach statistical significance ($P = .2$, Mann-Whitney test). The only purpose of follow-up in this control group was to rule out the possibility of spontaneous nodule shrinkage and, thereby, provide evidence that the effect in the laser-treated patients is a result of treatment and not the consequence of the natural history of the benign nodule. There was no statistically significant difference between the median age of the two groups ($P = .33$, Wilcoxon signed rank test).

ILP was well tolerated by all patients, as evidenced by all accepting additional

treatment if offered and reports of only slight discomfort or short-lasting tenderness. No cases of hemorrhage or local infections were encountered. Six patients received mild analgesics (salicylic acid or acetaminophen) for pain for up to 1 day. Serum thyroid-stimulating hormone levels were unaltered throughout the study. In all patients, normal motility of the vocal cords was seen at indirect laryngoscopy before and after ILP. None of the patients developed thyroid autoantibodies during follow-up.

DISCUSSION

US-guided PEI has been introduced as an alternative to surgery for patients with symptomatic benign cold thyroid nodules and has proved superior to thyroxine in inducing volume reduction in these nodules (6,14,15). The results of several studies have confirmed that PEI is effective for inducing necrosis and subsequent nodule shrinkage—even up to 1 year after the treatment. It appears that more than three PEI sessions are required to achieve a reduction in nodule volume of more than 50% (7,14–16). This may increase the risk of side effects. With PEI, a number of side effects are related to the leakage of ethanol outside the capsule of the nodule. These side effects include extraglandular fibrosis that may impede subsequent surgery, paralysis of the vocal cords, edema of the prethyroid region, mild to moderate pain, and mild fever (7,15). Development of thyroid autoantibodies has been noted in 5% of patients (7,16). The side effects of PEI seem to be related to the number of treatment sessions (7,16).

The fact that PEI has a number of side effects related to ethanol leakage outside the nodule and thyroid gland tempted us to perform laser therapy in these patients. ILP is a minimally invasive technique for focal tissue ablation. The technique has become useful in the palliation of different kinds of advanced cancers and seems to be better tolerated by patients than PEI administered in one treatment session (10). In the ablation of carcinoma in the liver, ILP appears to be as effective as PEI and is considered to be a safe and relatively simple procedure (17,18). Unlike with ethanol, the laser-induced destruction zone and necrotic area can be controlled, resulting in no or only minimal damage to the surrounding tissue (18,19). ILP has proved to be an effective, minimally invasive, and well-tol-

erated technique for tissue ablation, and the applicability has made it widely used in many medical specialties (11,12). Results of histologic tissue examination after ILP helped confirm the presence of a well-defined necrotic area, which demonstrates the ability of this technique to cause coagulative necrosis in a controlled fashion. A substantial area of controlled tissue destruction can be produced with an accurate correlation between the treated area seen at imaging (US or magnetic resonance imaging) and histologic examination (11,19). It is well known, however, that a one-to-one correlation between the area of hyperechogenicity and the area of coagulation does not exist (12,20). Results of a recent in vitro study (12) demonstrated a correlation between energy applied and the size of the histologic lesion but a poor correlation between sonographic changes and histologic findings. Whether this is also valid for the in vivo situation is not clarified. With US-guided ILP, it is important to state how long the energy is applied because thermal necrosis at low energy occurs after 4–6 minutes. That is, hyperechogenicity per se is not evidence of coagulation and tissue death. The lesion created by the laser is more elongated than round, as evident in Figure 1. The use of another method to cut the fiber may create a rounder lesion.

In our study, nodule volume was reduced 46% or equal to that obtained with one PEI session (6,7). As with PEI, most of this effect was evident within the 1st month. Eleven of the 16 patients (69%) had a reduction in pressure symptoms after ILP, which indicates that the performance of ILP is similar to that of PEI (15). There is no correlation between dose and/or energy given and the reduction of the nodule volume with either PEI or ILP. There are no discriminating features at US or pathologic examination that can be used to predict the outcome of either PEI or ILP. Most likely, the composition of each nodule, especially the amount of colloid or fluid collection and preexisting fibrosis, may account for the difference in outcome (7). Other biologic characteristics, such as the vascularization of the tissue, can alter the thermal deposition of the laser energy. As seen in the liver, the reaction to coagulation necrosis varies widely from patient to patient (18). The end point of nodule volume reduction is probably a two-step development after therapy. First,

the thermal energy or the ethanol must destruct the tissue. Then, the lesion will shrink. Unlike PEI (6,7), ILP was well-tolerated by all patients and only slight discomfort or short-lasting tenderness was reported. Because no other side effects were encountered, further studies about possible applications in nodular thyroid diseases are warranted.

In conclusion, our preliminary results suggest that US-guided ILP is a feasible, minimally invasive technique for focal thyroid nodule ablation and could become a useful nonsurgical alternative for treating cytologically benign solid nodules in the thyroid gland. The procedure can be performed on an outpatient basis, and the only side effect related to the treatment is mild transient discomfort. Further randomized studies must address the optimum energy deposition, efficacy of repeat treatment, long-term efficacy, and side effects of ILP. In addition, the possibility of placing the fiber in different locations within the nodule and the use of more than one fiber simultaneously should be explored.

References
1. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch Intern Med 1996; 156: 2165–2172.
2. Shaha AR. Controversies in the management of thyroid nodule. Laryngoscope 2000; 110:183–193.
3. Al-Suliman NN, Ryttov NF, Qvist N, Blichert-Toft M, Graversen HP. Experience in a specialist thyroid surgery unit: a demographic study, surgical complications, and outcome. Eur J Surg 1997; 163:13–20.
4. Bennedbæk FN, Perrild H, Hegedüs L. Diagnosis and treatment of the solitary thyroid nodule: results of a European survey. Clin Endocrinol 1999; 50:357–363.
5. Bennedbæk FN, Hegedüs L. Management of the solitary thyroid nodule: results of a North American survey. J Clin Endocrinol Metab 2000; 85:2493–2498.
6. Bennedbæk FN, Nielsen LK, Hegedüs L. Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. J Clin Endocrinol Metab 1998; 83:830–835.
7. Bennedbæk FN, Hegedüs L. Percutaneous ethanol injection therapy in benign solitary solid cold thyroid nodules: a randomized trial comparing one injection with three injections. Thyroid 1999; 9:225–233.
8. Guglielmi R, Pacella CM, Dottorini ME, et al. Severe thyrotoxicosis due to hyperfunctioning liver metastasis from follicular carcinoma: treatment with 131I and

interstitial laser ablation. Thyroid 1999; 2:173–176.

9. Brookes JAS, Leeds WR, Bown SG. Photocoagulation for the treatment of lung cancer. AJR Am J Roentgenol 1997; 168: 357–358.

10. Amin Z, Harries SA, Lees WR, Bown SG. Interstitial photocoagulation. End Surg 1993; 1:224–229.

11. Law P, Gedroyc WMW, Regan L. Magnetic resonance–guided percutaneous laser ablation of uterine fibroids. Lancet 1999; 453:2049–2050.

12. Pacella CM, Bizarri G, Guglielmi R, et al. Thyroid tissue: US-guided percutaneous interstitial laser ablation—a feasibility study. Radiology 2000; 217:673–677.

13. Altman DG. Practical statistics for medical research. London, England: Chapman & Hall, 1995; 186–187.

14. Goletti O, Monzani F, Lenziardi M, et al. Cold thyroid nodules: a new application of percutaneous ethanol injection treatment. J Clin Ultrasound 1994; 22:175–178.

15. Caraccio N, Goletti O, Lippolis PV, et al. Is percutaneous ethanol injection a useful alternative for treatment of the cold benign thyroid nodule? five years experience. Thyroid 1997; 7:699–704.

16. Zingrillo M, Collura D, Ghriggi MR, Nirchio V, Trischitta V. Treatment of large cold benign thyroid nodules not eligible for surgery with percutaneous ethanol injection. J Clin Endocrinol Metab 1998; 83:3905–3907.

17. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati F, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 1999; 210:655–661.

18. Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. Radiology 2000; 214:761–768.

19. Nolsøe CP, Torp-Pedersen S, Holm HH, et al. Ultrasonically guided interstitial Nd-YAG laser diffuser tip hyperthermia: an in vitro study. Scand J Urol Nephrol Suppl 1991; 137:119–124.

20. Goldberg SN, Walovitch RC, Straub JA, et al. Radio-frequency–induced coagulation necrosis in rabbits: immediate detection at US with synthetic microsphere contrast agent. Radiology 1999; 213:438–444.