

## Treatment of hyperfunctioning thyroid nodules with ultrasound guided percutaneous ethanol injection - 30 months experience

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**Background.** Our technique of performing percutaneous ethanol injection (PEI) and results after 30 months are presented and compared with results from the literature.

**Material and methods.** PEI was performed in 40 patients (37 female, 3 male, age range 28-76 years); in 35 cases, there was a solitary, scintigraphically "hot" nodule, and in 5 cases a toxic nodular goiter was found. The volume of treated nodules was in the range from 2.5 to 38 ccm (mean volume  $20.7 \pm 14.1$  ccm). Ethanol was injected with the "free-hand" technique, usually in multiple sessions, with the color and power Doppler ultrasound guidance. The total injected volume of ethanol was 1.5 times the volume of the treated nodule.

**Results.** The procedure was technically successful in 37 patients (92.5%). Pain during injection was observed in all cases, subcutaneous hematoma in 6 cases, and transitory dysphonia in one patient. There were no long-term complications. In 36 patients, the successfulness of the treatment was evaluated after 3-4 months on the basis of scintigraphy, hormonal status and ultrasonographic findings. A complete and partial cure was achieved in 22 (61.1%) and in 10 patients (27.8%) of patients, respectively, whereas in 4 patients (11.1%) the result was unsatisfactory, since only a moderate hormonal remission was observed after the completion of the procedure. A satisfactory result was observed in 32/36 patients (88.9%). Significant reduction of nodular volume was noted in all cases. A better result was observed in smaller nodules and in cases of autonomous adenomas. No cases of recurrent hyperthyreosis were detected.

**Conclusions.** Percutaneous ethanol injection under ultrasound guidance is an efficient and safe method in the treatment of autonomous thyroid nodules, that enables inactivation of nodules with minimal and/or transitory complications, without permanent or serious complications that can be observed after radioiodine or surgical therapy.

**Key words:** thyroid nodule - drug therapy; ethanol; thyroid neoplasms - ultrasonography; autonomous adenoma

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## Introduction

Thyroid toxic adenomas and toxic nodular goiters have until recently been exclusively treated with radioiodine therapy or surgical resection.<sup>1,2</sup> According to the numerous reports in the literature, both of these methods are known to have potentially serious and/or permanent and relatively frequent complications.<sup>2-6</sup> Ethanol is percutaneously being instilled in hepatocellular carcinomas using ultrasound guidance,<sup>7</sup> and, in the region of the neck, Solbiati started to use ethanol for parathyroid glands sclerosations in cases of the secondary hyperparathyroidism.<sup>8</sup> In 1990, Livraghi started with the ultrasound-guided percutaneous ethanol injections (PEI) for sclerosation of autonomous and toxic thyroid adenomas.<sup>9</sup> Reported results were promising and the method spread fast throughout Italy.<sup>10-16</sup> Surprisingly, the method is not frequently used in other countries; there are only two published articles about its utilization outside Italy - one from Turkey<sup>17</sup> and one from Germany.<sup>18</sup>

Our two institutions (University Hospitals "Mercur" and "Dubrava") started jointly with the percutaneous ethanol injection of thyroid autonomous and toxic nodules under the ultrasound color and power Doppler guidance in August of 1996. In this paper, our technique of performing PEI and results after 30 months are presented and compared with the results from the literature.

## Patients and methods

Percutaneous ethanol injection is performed under the ultrasound guidance, using linear electronic high-frequency probes with a frequency range between 7.5 and 10 MHz. Color and power Doppler are used to evaluate increased vascularisation which can be observed in the vast majority of autonomous (scintigraphically "hot") thyroid nodules. All

PEI procedures were performed by the first author (BB), using US scanner Acuson 128 XP4 with a linear 7.5 MHz probe (from August 1996 until September 1997) and Acuson 128 XP10 with a linear multifrequency probe 7.5-10 MHz (from September 1997 onwards). Both scanners are equipped with color and power Doppler capabilities and provide high-quality visualization of thyroid nodules in B-mode and visualization of intra and perinodular vascularisation. PEI under color and power Doppler guidance was especially valuable in cases of multinodular thyroids, when only one (or some) of nodules was autonomous; in these cases, such nodules can be differentiated from adjacent non-functioning nodules that are less vascularized.

The needle is introduced into the nodule using the "free-hand" technique, without the local anesthesia. We used 22-gauge needles with the end-hole and a 96% sterile ethanol (prepared in the State Institute of Transfusiology). The total volume of ethanol instilled was 1.5 times of the nodular volume, with a maximum of 10 ml of ethanol that could be injected in a single session (personal communication by Livraghi to the first author). The nodular volume (in ccm) was calculated in a usual fashion ( $a \times b \times c \times 0.5$ ;  $a$ =length,  $b$ =width,  $c$ =depth in centimeters). The number of injections (sessions) was calculated according to the nodular size and varied from 1 to 8 injections per therapy cycle. The volume of ethanol being injected per session was determined depending on the individual patient's compliance with the procedure; in larger nodules, it was at most 30% of the nodular volume, while in small nodules, the total ethanol volume required could be injected either in one or two sessions.

In each session, the ethanol was injected once or twice, with the needle being directed to different areas of the nodule to insure an equal distribution of the ethanol. The utilization of the side-hole needles simplifies the procedure and ensures an equal ethanol dis-

tribution with no need to move the needle within the nodule. The procedure was repeated twice per week until the total planned volume of ethanol was injected into the nodule. The injection and distribution of ethanol within the nodule were clearly visible in real-time under the ultrasound guidance, as tiny brightly echogenic dots within the nodule. Occasionally, a rapid wash-out of ethanol in a highly vascularized nodule could be observed; in these cases, a larger volume of ethanol could be injected, until its distribution within the nodule was observed. During the ethanol injection to the posteriorly located nodules, special care should be taken in order to avoid possible impairment of the recurrent laryngeal nerve with the ethanol.

The thyreostatic medication was not applied routinely prior to PEI; the therapy being taken was not altered because of the procedure. In all patients T3, T4, FT3, FT4, TSH and thyroid antibodies in the serum were determined using standard laboratory methods. In all patients the thyroid scintigraphy with Tc-99m pertechnetate was performed and scintigraphic and US/color Doppler findings compared prior to the commencement of the PEI, so that the ethanol could be injected into the right nodule, which proved to be particularly beneficial in cases of multinodular thyroids.

PEI was performed in the period from August 1996 to January 1999 in 40 patients (37 women and 3 men) with the age range of 28-76 (mean  $54.2 \pm 12.8$ ) years. Thirty-five patients had the solitary "hot" nodule, and five patients the toxic nodular goiter, with 2 scintigraphically "hot" nodules which were both sclerosed with ethanol. All the procedures were performed on the out-patient basis.

All the patients, who were referred for the PEI by endocrinologists, and who had multinodular thyroids with scintigraphically visible multiple "hot" nodules, and in whom particular nodules could not be ultrasonographically

reliably differentiated from cold nodules, were refused from the PEI and referred for the radioiodine therapy. Thirty-four patients were hyperthyroid, with elevated FT3 and FT4 levels and suppressed TSH level, and scintigraphically suppressed extranodular tissue. Six patients had only minimal extranodular uptake of the Technetium on scintigraphy (developing autonomous adenomas); three of them had normal TSH level, and three had suppressed TSH and thyroid hormones within the normal range.

The smallest treated nodule had a volume of 2.5 ccm, and the largest of 38 ccm (mean  $20.7 \pm 14.1$  ccm). The injected volume varied from 4 ml to 57 ml of ethanol, with the maximum volume of 1.5 times the nodular volume. Maximum number of injections in one cycle was 10. The largest single volume of ethanol injected in one session was 10 ml. It was injected exclusively to the patients living far away for whom frequent travels to our Institution for the injection, would present a problem. Usually single volumes of up to 5-6 ml per session were administered. PEI procedure was as a rule performed in two sessions per week, with 3 or 4 days between each session.

The follow-up of patients after PEI was performed under the following protocol: serum thyroid hormones were assessed after 1, 3, 6 and 12 months; the control ultrasound examinations were performed in the same intervals. Thyroid scintigraphy was performed for the first time 3-4 months after the completion of PEI, which proved to be a sufficient period in the majority of cases to evaluate the treatment successfulness.

After the successful PEI, the hormonal status was normalized, as well as scintigraphic finding. The majority of patients did not take thyreostatic medications after the therapy and the evaluation of the successfulness of PEI could be performed on the basis of hormonal status. However, we always analyzed scintigraphic findings to evaluate definitely

the successfulness of the procedure. Color and power Doppler US played important role in the follow-up, since the successfully sclerosed nodules exhibited considerably less or even no vascularization, as compared to the pre-procedure findings. B-mode US showed, as a rule, the shrinking of nodules and changing of echogenicity: the nodules became hyperechogenic (due to the ethanol-induced coagulation necrosis<sup>9</sup>) as compared to the pre-procedure echogenicity. If residual hypervascularisation was observed with color and power Doppler, the additional ethanol was injected into the region. If the procedure was not successful upon the completion of the first cycle of injections, the ethanol could be injected again; the volume of ethanol needed in the second or the third cycle was determined arbitrarily according to the size of the nodule, degree of hypervascularization and hormonal status. In the presented group of patients we performed at most two cycles of PEI (one patient with unsuccessful outcome after the second cycle refused the proposed third cycle).

## Results

### *Technical successfulness of the procedure and complications*

Six patients developed subcutaneous neck hematomas after the procedure; two of these patients were hospitalized, one for two days and the other for five days. In both patients

hematomas resolved completely without therapy, and without permanent sequels. In one of the latter two patients, hematoma developed after the last session in the second PEI cycle, and the final result of the procedure was complete cure of the toxic adenoma. In the other patient, hematoma occurred after the second of the four planned sessions. She refused further treatment. Another patient refused the treatment after the first session; she had a minimal subcutaneous hematoma, but could not tolerate the pain during and after the injection. The latter two patients were included in the group of patients, where the procedure was considered as technically unsuccessful. The third patient in this "technical failure" group could not tolerate the pain during the injection, and she immediately refused further treatment.

All patients complained of the pain of varying degree during the injection. The pain was projected toward the jaw, ear or sternum, and lasted several minutes after the procedure. Many patients experienced some pain also 1-2 days after the session (as a rule, the pain was stronger when more ethanol was injected). Nevertheless, significant complications were not noted, and patients tolerated the procedure well. One patient had a transient dysphonia, which passed after 7 days. Transient dysphonia occurred due to the unilateral vocal cord paresis, most probably caused by the ethanol when injected in nodules adjacent to the posterior contour of the thyroid lobe and coming in contact with the recurrent laryngeal nerve. It is assumed that a chemically or compression induced lesion of

**Table 1.** Technical successfulness of the PEI procedure

No. of pts in whom PEI was performed	40
No. of pts where PEI was technically successful	37 (92.5%)
No. of pts where PEI was technically unsuccessful	3 (7.5%)
Reasons for the failure of the procedure	(1) refusing after 1st session due to pain; (2) minimal subcut. hematoma and pain after 1st injection; (3) major subcutaneous hematoma after 2nd injection

the nerve occurs.<sup>19</sup> This was a reversible paresis without anatomical break of the nerve, as opposed to surgical impairment in which transection of the nerve causes permanent nerve damage.<sup>2,19</sup>

There were no cases of thyreotoxicosis or hyperthyreosis observed after the procedure. In all 37 patients, ultrasonography showed a satisfactory and even distribution of ethanol within the nodule.

**Table 2.** Complications in 37 patients where PEI was technically successful

Pain during injection	37/37
Pain 1-2 days after the injection	15/37
Subcutaneous hematoma, hospitalization	1/37
Minor subcutaneous hematoma	3/37
Transient dysphonia	1/37

### Results (outcome) of the PEI procedure

The outcome of the PEI in our patients could be categorized into three groups, according to the literature<sup>8-18</sup>:

- 1.) *Complete cure* with the normalization of serum thyroid hormones and TSH levels, normalization of clinical status and reappearance of extranodular uptake on scintigraphy, while the node is either "cold", or non-visible on the scan;
- 2.) *Partial recovery* with the remission of clinical symptoms, normalization of serum thyroid hormones and TSH levels, reappearance of extranodular uptake on scintigraphy, with the node (or part of the node) still "hot" on the scan;

3.) *Hormonal remission* - clinical status improved, serum thyroid hormone levels normal, TSH still suppressed; scintigraphically "hot" nodule, with suppressed extranodular uptake.

Our results include 40 patients in whom procedure was started during the last 30 months, and was technically successfully completed in 37 (92.5%). In 36 patients, the definite successfulness of the procedure could be evaluated 3-4 months after the completion of the procedure. In these 36 patients, the successfulness of the PEI was assessed on the basis of scintigraphic and ultrasonographic findings and of hormonal status. In 32 patients, a solitary nodule was observed (6 autonomous adenomas and 26 toxic adenomas), and 4 patients had toxic nodular goiter. The results of the procedure in these 36 patients are presented in the Table 3.

A complete cure was achieved in 22 patients, and partial recovery in 10 patients; both outcomes are considered favourable result of the PEI. Therefore, the overall success of the procedure was achieved in 32/36 patients (88.9%). A complete cure was obtained in all 6 patients who developed autonomous adenomas. The initial nodule volume in patients in whom complete cure (I), partial cure (II) and hormonal remission (III) was obtained, was  $18.2 \pm 12.7$  ccm,  $22.4 \pm 13.9$  ccm, and  $30.1 \pm 21.1$  ccm, respectively. One cycle of therapy was applied in 19/22 patients with complete cure and 7/10 patients with partial recovery and in one patient with hormonal remission. In the remaining nine patients, two cycles of PEI were performed.

**Table 3.** Outcome of PEI in 36 patients

Outcome	No. of patients	%	Solitary nodules	TNG
I	22/36	61.1	22/22	0/22
II	10/36	27.8	8/10	2/10
III	4/36	11.1	2/4	2/4

I-complete cure, II- partial recovery, III-hormonal remission

In four patients, the procedure was not successful. One patient with toxic nodular goiter was referred for radioiodine therapy after the completion of the first cycle, and the procedure was not repeated; in three patients PEI was repeated with the new cycle of treatment and was not successful. In two cases of toxic nodular goiters, a partial recovery was achieved after the second cycle, and, in one case, the procedure was unsuccessful after the second cycle.

Overall, out of 36 patients with solitary "hot" nodules the PEI was successful in 32 (88.9%), while in 4 patients with toxic nodular goiter, the procedure was successful in two patients (50%).

The longest follow-up after the procedure was 26 months. The largest observed reduction in the volume of the nodule after the procedure was observed in the patient with the largest treated nodule; the initial volume of 38 ccm was reduced to 6 ccm (15.8% of the initial volume) 6 months after PEI. During the follow-up of 3-26 months, the initial nodular volume was reduced more than 50% in 34 of 36 patients. In the follow-up period, no recurrence was noted in the cases of complete or partial recovery after PEI.

In all patients with the successful outcome of the procedure, a considerable reduction of flow or even disappearance of intranodular flow was observed with color and power Doppler ultrasound. Moreover, B-mode ultrasonography showed a markedly increased echogenicity of the treated nodules in these patients.

## Discussion

There are three published studies in the literature, comprising larger number of treated patients, with longer follow-up and evaluation of the successfulness of the therapy.

Livraghi was the first to commence with PEI; in 1994 he published his results on a

group of 101 patients, with the mean age of  $50.8 \pm 12.4$  years.<sup>19</sup>

In ten patients with developing autonomous adenomas, PEI was successful in all cases. Out of 91 patients with suppressed TSH, a complete cure was observed in 49 (53.9%); the initial nodular volume in this group was  $16.8 \pm 10.3$  ccm, and after PEI it was reduced to  $2.8 \pm 1.6$  ccm (16.7% of the initial volume). Color Doppler showed complete lack of nodular hypervascularization. In 42 patients PEI was performed in a single cycle, and in 7 patients in two cycles. A partial recovery, also considered as successful outcome, was observed in 34 (37.4%) patients. The nodular volume was reduced to 24.5% of initial volume (from  $20.8 \pm 12.2$  ccm to  $5.1 \pm 4.0$  ccm). In this group, one, two and three cycles of PEI were performed in 23, 9 and 2 patients, respectively. A hormonal remission, considered as failure of PEI, was noted in 9 patients (9.9%); the nodules in this group were mainly large, with an average volume of  $30.4 \pm 19.9$  ccm, that was reduced to 26.6% of the initial volume after PEI ( $8.1 \pm 7.9$  ccm). Three patients had 3 PEI cycles, four had two cycles, and one had one cycle. As a rule, the results are more favorable in small nodules as compared to large ones. The satisfactory response can be expected in the nodules below 40 ccm. TSH in serum is detectable usually 1-3 months after the therapy is finished. Livraghi's results are excellent, and even in 9 patients with unsuccessful procedure a significant decrease of serum FT3 and FT4 levels was observed. A significant reduction of the nodular volume was observed in all cases. In the follow-up period of 6 months to 4 years, no recurrence was noted in cases of complete or partial recovery after PEI.

In 1997, a group from Pisa published their results of five-year follow up of 111 patients after PEI.<sup>20</sup> Seventy-seven had a toxic adenoma, and 40 developing autonomous adenomas. The results are similar to Livraghi's, with all autonomous adenoma patients being

successfully treated. In 77 patients with TA, a complete cure was noted in 60 (78%), partial recovery in 7 (9%), and PEI was unsuccessful in 10 patients (13%). PEI was equally successful in the case of solitary "hot" nodule or two "hot" nodules. A significant reduction of nodular volume was observed in all cases, and no recurrences of hyperthyreosis occurred during the follow-up period. Only one patient developed subclinical hypothyreosis after five years; however, that patient had considerably elevated thyroid antibodies serum levels prior to the therapy. Unlike Livraghi, these authors did not observe any differences in the outcome related to the volume of the nodules.

The results of Italian multicentric study were published in 1996.<sup>21</sup> It comprised 429 patients with PEI performed in solitary autonomous nodules (242 toxic adenomas, 187 autonomous adenomas). Complete cure was observed in 2/3 of patients with toxic adenoma, and 83.4% of patients with autonomous adenomas. In remaining patients, where no changes on scintigraphy were observed and/or TSH remained suppressed, the procedure was considered as a failure. In all treated patients, a significant reduction of nodular volume was noted, and there was no recurrence of hyperthyreosis or occurrence of hypothyreosis. Almost all successful results were obtained in nodules with a volume of < 15 ccms. Somewhat inferior results of this study as compared to previous two studies may be due to the recruitment of patients from a large number of centers, and one can assume that the procedure was not technically optimally performed in all institutions.

Although our group of patients is relatively small, the initial results are comparable with those reported by Livraghi, and other larger studies.<sup>19-21</sup> Complications are rare and acceptable. Pain during the injection is the inevitable component of the procedure, and should not be considered as complication.

Transient dysphonia is not a major complication either. We had relatively high number of clinically significant subcutaneous hematomas (6/40, 15%), higher than in other studies. It can be attributed to the utilization of an end-hole needles in our patients; the usage of side-hole needles probably reduces hematoma and enables equal distribution of ethanol within the nodule. All patients should keep the injection site compressed for 1-2 hours after the procedure, and avoid physical activity for at least 24 hrs to prevent bleeding. Early physical activity can increase the number of hematomas. Initial good results increased the interest of endocrinologists for the procedure, and the number of patients referred for the procedure has been lately increasing.

One might speculate whether PEI should be used only in patients with toxic adenomas, because patients with autonomous adenomas seldom have clinical symptoms and autonomous adenomas can undergo spontaneous degeneration, involution and self-healing. According to Livraghi, PEI is indicated in developing autonomous adenomas, because it can prevent the development of overt hyperthyreosis in the future.<sup>19</sup> All studies previously discussed and our study have shown very favorable outcome of PEI in patients with autonomous adenomas. Since the procedure has no permanent or significant complications, we believe that treating patients with autonomous adenomas, even when they are euthyroid, is justifiable.

In addition to laboratory tests and scintigraphy, ultrasound itself proved useful in evaluating successfulness of the treatment. B-mod echogenicity increases in successfully sclerosed nodules due to the ethanol induced fibrosis after the coagulation necrosis.<sup>9</sup> We observed this phenomenon clearly in all cases. Ultrasound is indispensable as a guidance modality even in palpable solitary nodules, to insure the equal distribution of ethanol, which is clearly visible in real-time

during the injection. Color and power Doppler have also proved to be very useful in assessing the reduction of vascularization in sclerosed parts of the nodule. If we observed the area of residual intranodular hypervascularisation, we were able to inject ethanol in that particular area in subsequent sessions or cycles.

We observed favourable outcome only in 1/2 of patients (2/4) with toxic nodular goiter (TNG). Bearing in mind that we refused to start the procedure in several patients where it was hard to determine accurately scintigraphically "hot" nodules with ultrasound, we consider TNG to be inappropriate for the PEI treatment. These patients can be treated with radioiodine therapy. On the other hand, young female patients with solitary hyperfunctioning nodules seem to be ideal candidates for PEI procedure, especially those with autonomous adenomas. This is a group of patients where exposure to radioactive isotope therapy should be avoided because of long-lasting hypothyreosis that follows this kind of the therapy.

Hypothyreosis after PEI is extremely rare. In a study of 101 patients, only one case was noted,<sup>19</sup> as well as in a study of 111 patients.<sup>20</sup> Both patients had elevated thyroid antibodies prior to the treatment, which was most probably due to the progression of already existing autoimmune thyroiditis.

Unlike PEI, radioiodine therapy causes hypothyreosis in 5-30% of patients,<sup>3-5</sup> and it is also known to increase the risk of gastric carcinoma occurrence.<sup>6</sup> After the surgical resection of the thyroid gland, hypothyreosis can be observed in 11% of cases; other serious complications may occur, such as permanent damage of the recurrent laryngeal nerve and of the parathyroid glands.<sup>2</sup> Both radioiodine therapy and surgery are considerably more expensive as than PEI.

Only one case of thyreotoxicosis induced by PEI was described in the literature,<sup>14</sup> indicating very low rate of this complication.

Shortly after the PEI, one can observe only mild elevation of thyroid hormones and thyreoglobulin levels.<sup>9-19</sup>

We conclude that the percutaneous ethanol injection under ultrasound, color and power Doppler guidance is a safe and effective method for the treatment of autonomous and toxic thyroid nodules, in spite of the fact that all patients experience pain during the procedure. The best results are observed in the patients with small and solitary nodules. The recurrence (hyperthyreosis) does not occur in patients in whom complete cure or partial recovery are achieved. PEI is less efficient in the treatment of patients with toxic nodular goiters. The first choice of treatment of autonomous thyroid nodules in the most countries is still radioiodine therapy. However, we believe that PEI should become the treatment of choice for toxic and autonomous solitary nodules, specially in the younger age-groups of patients. The procedure enables permanent inactivation of autonomous nodules in up to 90% of patients, with minimal and transitory complications. Significant and/or permanent complications were not observed. Radioiodine therapy and surgery are the methods associated with higher proportion of serious and/or permanent complications. We believe that it should be reserved as the first-choice treatment modality for the patients with toxic nodular goiter. For the patients with solitary autonomous nodules, radioiodine therapy should be given only to the patients in whom PEI is not successful, to uncooperative patients, and patients with anxious reactions, intolerance of pain during injection of ethanol.

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