

Percutaneous ethanol injection therapy for autonomously functioning thyroid nodule

Kunihiro NAKADA, Chietsugu KATOH, Kakuko KANEGAE, Eriko TSUKAMOTO,
Kazuo ITOH and Nagara TAMAKI

Department of Nuclear Medicine, Hokkaido University School of Medicine

Four patients with solitary autonomously functioning thyroid nodule (AFTN; 2 toxic and 2 subclinically toxic) received ultrasonography (US)—guided percutaneous ethanol injection therapy (PEIT). The pretreatment scintigraphic appearance of the nodule was hot, and radioactivity in the extranodular tissue was completely suppressed throughout. Ninety-nine percent ethanol was slowly injected under US guidance. As a rule, the injection was performed in fractionated sessions and the treatment was repeated until the total amount of ethanol exceeded the baseline nodular volume. The therapy was successful. Complete remission of hyperthyroidism was observed among the patients with toxic nodule. The basal level of TSH and its response to TRH injection was normalized in the patients with subclinically toxic nodule. Posttreatment scintigrams revealed that the extranodular tissue recovered and radioactivity in the hot nodule had noticeably decreased. The rate of reduction in the nodular volume was more than 80% in all. There was no recurrence or development of hypothyroidism during a follow up of 10 to 23 months. The main side effect was mild and transient pain and/or a burning sensation at injection. No severe or permanent complications occurred. Although the number of our cases was small, the results suggest that PEIT is a useful program in treating AFTN.

Key words: autonomously functioning thyroid nodule, hyperthyroidism, percutaneous ethanol injection therapy

INTRODUCTION

AUTONOMOUSLY FUNCTIONING THYROID NODULES (AFTN) are not under the control of the pituitary TSH. On scintigram, they concentrate more radionuclide than the surrounding normal thyroid in proportion to their function and secrete excessive amounts of thyroid hormones.^{1–3} Most of the patients with AFTN are euthyroid at diagnosis and remain so, but if once hyperthyroidism occurs, anti-thyroid drugs (ATD) are only palliative.^{1–3} Conventional therapy has been surgery or radioiodine,^{4–11} both of which have drawbacks or side effects. There were reports recently that percutaneous ethanol injection therapy (PEIT) could be an alternative to those therapies. Initial results, which were all from Italy, were good.^{12–17} We treated 4

Japanese patients with AFTN by PEIT to confirm the efficacy of the technique and compared our results with the previous reports.

MATERIALS AND METHODS

Patients

Four females with solitary AFTN who had previously refused surgery gave their informed consent to undergo PEIT as an alternative therapy. Two patients had toxic nodule with hyperthyroidism, one of whom (case 2) has had propylthiouracil for 4 years. The remaining two had subclinically toxic nodule without apparent signs of hyperthyroidism but had an undetectable TSH level and no response to TRH test (500 μ g i.v.). One patient (case 4) had suffered from ischemic heart disease. The clinical features of the subjects are listed in Table 1. AFTN was diagnosed by thyroid scintigraphy with ^{99m}Tc or ¹²³I, ultrasonography (US), and measurement of the serum levels of FT₃, FT₄, TSH, TSH receptor antibody (TRAb) and thyroglobulin (Tg). TRAb was undetectable, and the

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For reprint contact: Kunihiro Nakada, M.D., Department of Nuclear Medicine, Hokkaido University School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060, JAPAN.

Tg values were high in all. To rule out possible malignancy, patients underwent US-guided needle biopsy prior to PEIT. The histological diagnosis was follicular adenoma in one and adenomatous nodule in the others. To investigate the action of PEIT on parathyroid function, serum levels of intact PTH (PTH-I) were monitored in all. Thyroid scintigraphy was performed using a digital gamma camera GCA-602A (Toshiba, Japan) equipped with a low-energy parallel-hole collimator for thyroid scanning. Planar anterior image in 512 × 512 matrix was obtained. When ^{99m}Tc was used, 350 k counts were acquired 15 minutes after intravenous injection of 148 MBq of ^{99m}TcO₄⁻. In the case of ¹²³I, data were acquired for 15 minutes at 3 hours after oral intake of 3.7 MBq of Na¹²³I. Radioiodine uptake rate (RIU) was measured with a scintillation counter at 24 hours following administration.

An echo camera SSD-650 or SSD-1200 CV a with 7.5 MHz linear probe or a mechanical sector (Aloka, Japan) was used for sonographic studies. Serum levels of FT₃ and FT₄ were measured with an RIA kit. Tg, PTH-I, and TSH values were measured with an IRMA kit. TRAb was determined by radioreceptor assay. In our institute, normal values for the tests used are: FT₃ 2.7–5.5 (pg/ml), FT₄ 0.87–1.96 (ng/dl), TSH 0.3–4.0 (μU/ml), Tg < 35.0 (ng/ml), TRAb < 10(%), PTH-I 10–65 (pg/ml) and RIU at 24 hours 10–40(%)

Design of PEIT

PEIT was performed according to our protocol for recurrent thyroid carcinoma¹⁸ with minor modifications. The baseline nodular volume (V_b) was calculated with the formula; $V = 4/3\pi \times a \times b \times c$, where a, b, and c are the three orthogonal radii of the nodule measured by US. Patients with toxic nodule were given β blocker and inorganic iodine in preparation for PEIT, from 6–7 days before the treatment to 7–10 days after the treatment. As a rule, the patient was hospitalized for 1 or 2 days. Along with keeping a venous line, dripped infusion of physiological saline including vitamin B, antiemetics, and anastaltics was started just before PEIT. Sterile 99% ethanol (prepared by the pharmacological institute in Hokkaido University Hospital) was slowly injected under US guidance with a fine needle following local anesthesia. As a rule, treatment was done in fractionated sessions and was repeated until the total ethanol dose exceeded V_b at intervals of once or twice a week. Ethanol was never injected as a single bolus in any session. Punctures were repeated from different angles. The needle apex was at first set slightly ahead in the center of the nodule, and was moved to different angles little by little at each puncture. Injection was terminated when the intranodular distribution of the ethanol became diffused and homogeneous, or when the needle apex could not be distinguished. The ethanol dose for one session, which ranged from 2.5 ml to 17.3 ml, was varied according to V_b. It took at least 5–6 minutes to finish injection at each session. We used 2

Table 1 Patient characteristics

Case	Age/Sex	Nodular function	Longest diameter (cm)	Histological diagnosis
1	28/F	T*	5.5	AN***
2	58/F	T	4.7	AN
3	21/F	ST**	3.2	AN
4	62/F	ST	3.5	FA****

*: toxic, **: subclinically toxic, ***: adenomatous nodule, ****: follicular adenoma

kinds of needles; gauge 23 or 25 injection needles (Top, Japan), and gauge 21 or 22 BIOSUC C-7 needles (Hakko, Japan). The latter has an additional side hole near the apex of the needle. Therapeutic effects were evaluated at 3 to 4 month intervals after the final session by repeating scintigraphy, US and laboratory studies. The duration of the follow up ranged from 10 to 23 months (mean 16.2).

RESULTS

A total of 11 sessions of PEIT were performed. PEIT was repeated 3 times in 3 patients and 2 times in one. The total dose of ethanol injected ranged from 5.9 to 38.5 ml (mean 19.7 ml), equivalent to 118.1–137.0% (mean 125.5) of V_b. The treatment outcome was successful in all subjects. Thyroid function became normal and hyperthyroidism was cured in the patients with the toxic nodule. The basal level of TSH and response in the TRH test was improved in those with the subclinically toxic nodule. Posttreatment Tg levels decreased by less than one-third of those at the baseline in all patients. The therapeutic effects became apparent until 4 months after the final session. There has been no recurrence or appearance of hypothyroidism during the follow up period. PTH-I values were normal at the baseline and remained within the normal range in posttreatment in all. Changes in laboratory studies at the baseline and after PEIT are listed in Table 2. On the posttreatment scintigram, the hot nodule had disappeared completely in 2 patients, and partially in the other 2. Although radioactivity in the extranodular tissue was completely suppressed on the pretreatment scan (Fig. 1, A and C), a posttreatment study showed complete recovery (Fig. 1, B and D) in all. One patient (case 1) underwent another needle biopsy 3 months after the final injection. A posttreatment specimen showed that the ethanol-perfused area had necrosed diffusely (Fig. 2).

The rate of regression (RR) in nodular volume was calculated with the formula: $RR = (V_b - V_a)/V_b \times 100(\%)$, where V_a is the nodular volume after PEIT. RR ranged from 81.2 to 93.0% (mean 86.6, Table 3). Although there were cystic changes within the nodule on pretreatment sonograms in 3 patients, follow up sonograms indicated that they had disappeared and the intranodular echo texture had changed to hypoechoic (Fig. 3).

The major side effect was pain and/or a burning sensa-

Table 2 Changes of thyroid and parathyroid function following PEIT

Case	At baseline					After PEIT*				
	FT ₃ (pg/ml)	FT ₄ (ng/dl)	TSH (μ U/ml)	Tg (ng/ml)	PTH-I (pg/ml)	FT ₃ (pg/ml)	FT ₄ (ng/dl)	TSH (μ U/ml)	Tg (ng/ml)	PTH-I (pg/ml)
1	8.1	4.00	UD**	650.2	28.0	2.9	1.31	0.95	18.0	37.0
2	3.2	1.29	UD	133.7	49.0	2.5	1.01	0.46	42.6	28.0
3	5.8	1.08	UD	187.6	18.0	3.1	1.39	0.41	41.0	22.0
4	3.8	1.61	UD	45.4	15.0	2.6	1.08	1.61	12.0	17.0

*: results at the latest examination, **: undetectable ($<0.02 \mu\text{U/ml}$)

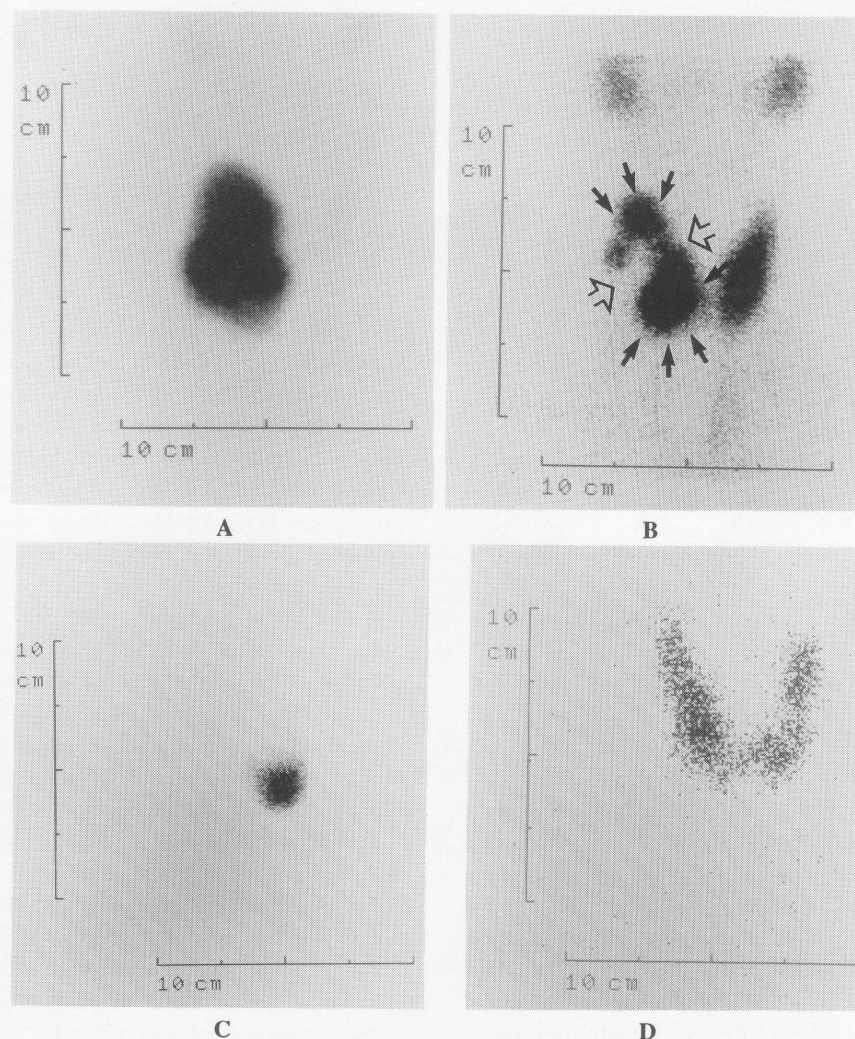


Fig. 1 Thyroid scintigrams at baseline and at posttreatment. A, B—case 1. A) Baseline $^{99\text{m}}\text{Tc}$ scan shows that large hot nodule occupies the right lobe. Radioactivity in the extranodular tissue and the left lobe is completely suppressed. B) Posttreatment scan shows remarkable decrease in the nodular size and change of the radioactivity to be partially cold (open arrow). The extranodular tissue (closed arrow) and the left lobe are reactivated. C, D—case 3. C) Baseline ^{123}I scan shows a hot nodule in middle part of the left lobe with complete suppression of the normal tissue. Radioiodine uptake rate at 24 hours (24 h RIU) is 21.0(%). D) Hot nodule is no longer visible and the normal tissue is completely recovered on posttreatment scan. 24 h RIU is 10.0(%).

tion at injection, observed in 7 out of 11 sessions (63.6%). It was mild and transient, fading away on stopping the injection for a minute. Intravenous administration of midazolam (10–15 mg/body) was effective for a nervous

patient. A feeling of drunkenness, low grade fever (less than 38.0°C), and mild subcutaneous hemorrhage was observed in 1 session (9.1%). No other complications were observed.

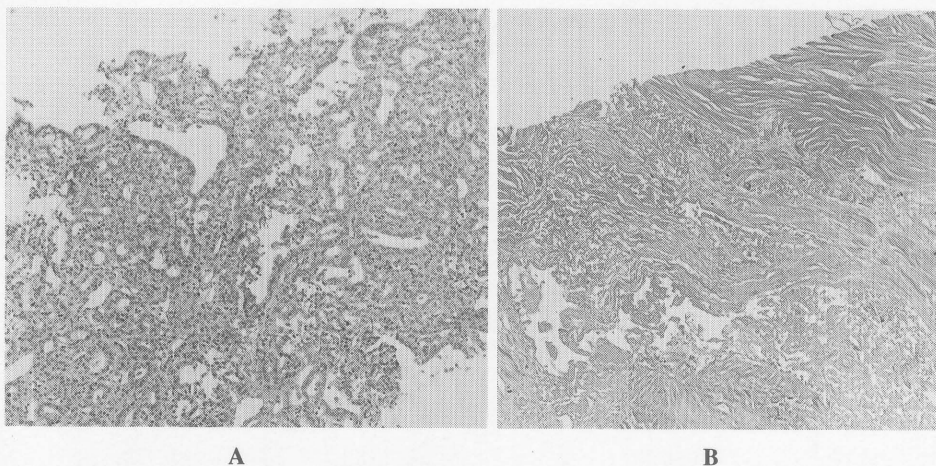


Fig. 2 Histological changes following PEIT in case 1. A) Pretreatment histological findings of the nodule ($\times 20$) is compatible with adenomatous nodule. B) Posttreatment specimen ($\times 20$) shows diffuse necrosis of the lesion. The sample is obtained from the cold area on the post treatment scan.

Table 3 Nodular volume at baseline and after PEIT

Case	Total dose of ethanol (ml)	Nodular volume (ml)		RR*** (%)
		V _b *	V _a **	
1	38.5	32.6	4.4	86.5
2	24.0	19.7	3.7	81.2
3	10.5	8.4	1.2	85.7
4	5.9	4.3	0.3	93.0

*: volume at baseline, **: volume after PEIT, ***: rate of volume regression

DISCUSSION

Treatment of AFTN has been either ablation by ^{131}I or excision by surgery. Generally ^{131}I has been the treatment of choice for elderly and/or surgically high risk patients, and the surgical approach that seeks the removal of the nodules has been preferred for younger patients and bigger nodules, or as a prophylactic treatment for non-toxic nodules. Both methods have some drawbacks or side effects. ^{131}I does not work as fast as surgery and is not universally curative.^{1,2,5,8} The dose of ^{131}I administered is sometimes more than that required for Graves' disease and it subjects the extranodular normal tissue to significant radiation, apart from the risks of whole body irradiation. Although some authors⁸ included non-toxic AFTN where extranodular tissue was not suppressed, the incidence of permanent hypothyroidism following ^{131}I therapy was relatively higher than that following surgery.^{5,7,8,10,11} Huysmans et al.¹¹ insisted that ^{131}I therapy had to be postponed when pretreatment scintigraphy revealed radioiodine uptake in extranodular parenchyma.

Enucleation or lobectomy is a standard surgical procedure for AFTN. The risks of hypothyroidism is generally lower than with radioiodine, and surgery can exclude any

doubt concerning malignant nodule. But there are risks of cosmetic injury, hypoparathyroidism and recurrent nerve paralysis,⁴⁻⁶ and those complications are usually permanent.

Recent studies have demonstrated that PEIT was effective in treating AFTN.¹²⁻¹⁷ Although there were some differences in the treatment protocol and the assessment of therapeutic effects among the authors, their procedure for performing PEIT was very simple. The treatment was performed on the outpatient basis and most of the authors did not use any pretreatment medication for PEIT. Ethanol was injected without local anesthesia and was given as a single bolus. Moreover, although the criteria for 'cure of the nodule' were more strictly defined than in past reports on conventional therapy,⁴⁻¹¹ the initial results of PEIT seem to be excellent, both in curability and patient safety.

Parrachi et al. treated 28 patients with AFTNs (22 toxic and 6 nontoxic).¹⁵ Complete cure (a condition of normal serum free thyroid hormones, normal TSH in the basal condition and after TRH injection, and reactivation of extranodular tissue on scintigram with nodule no longer visible) was obtained in 17 patients and partial cure (a condition of normal serum free hormone levels, detectable TSH levels with normal or blunted response to TRH, and partial reactivation of extranodular tissue on scintigram with nodule or parts still visible) was obtained in 10. Fifteen of their patients experienced mild and rapidly transient pain, 2 experienced transient dysphonia, and 1 hyperpyrexia. None encountered any serious side effects. Martino et al. treated 37 patients (18 pretoxic and 19 toxic).¹⁶ Twenty-nine out of 37 glands (78.3%) achieved total recovery of the extranodular tissue with normalization of serum TSH, and all nodules strikingly decreased in size. They performed a total of 305 injections. Side effects were observed in only 30 (9%) of the injections and 24 among the 30 was pain at injection. Two cases (0.6%)

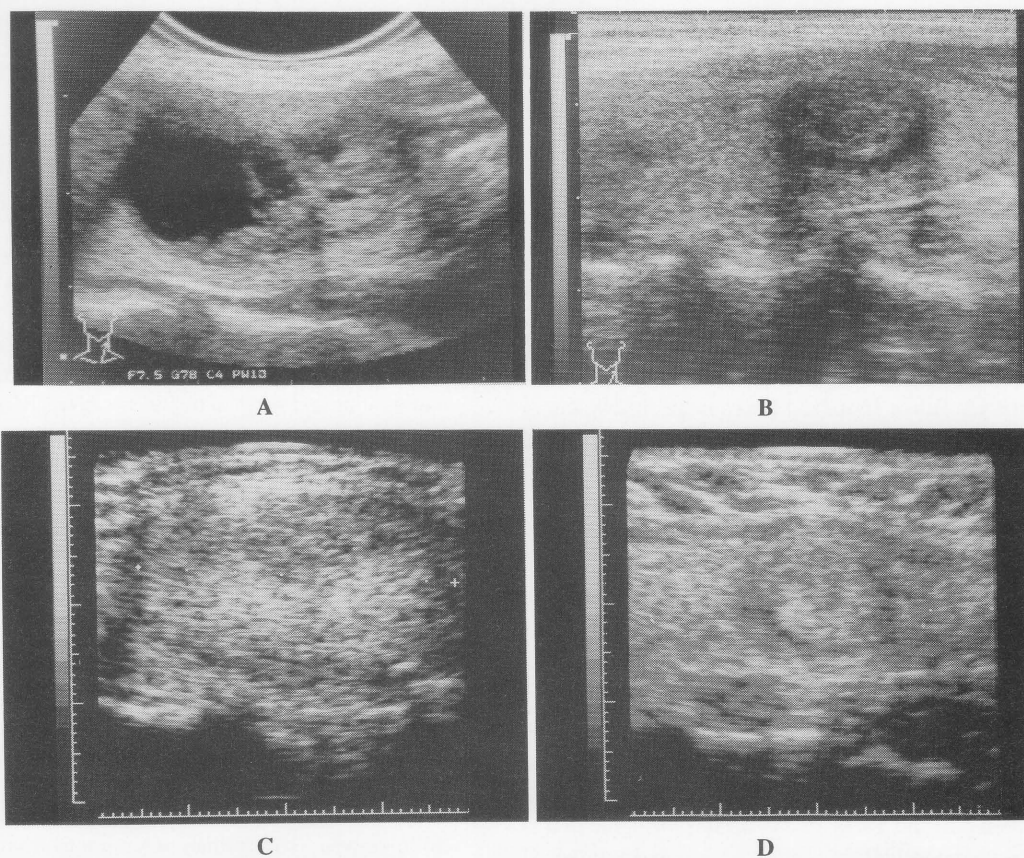


Fig. 3 Longitudinal ultrasonograms at baseline and at posttreatment. A, B—case 3. A) Baseline sonogram shows a solid and cystic nodule in the left lobe. Echo texture in the solid parts is isoechoic. B) Posttreatment sonogram shows significant decrease in the nodular size and disappearance of the cystic parts. The intranodular echo texture has become inhomogeneously low. C, D—case 4. C) Baseline sonogram shows a solid isoechoic nodule in the right lobe. The nodule has smooth contour with halo sign. D) Posttreatment sonogram shows remarkable shrinkage of the nodule.

had transitory dysphonia which completely recovered. Monzani et al. treated 56 patients (30 pretoxic, 26 toxic).¹³ A biochemical and clinical remission of hyperthyroidism was observed in 18 out of 22 (81.8%) toxic patients and a significant increase in TSH levels was seen in all patients. US studies showed 85–90% reduction in nodular volume in all patients. Functional activity of extranodular tissue was found in 40 out of 56 (71.4%) patients at post-treatment scintiscan. A transient burning sensation was experienced in 9% of the sessions but no relevant complications took place. They reported that symptoms of hyperthyroidism became worse in 10 out of 26 toxic patients at the beginning of their treatment but at least remitted with the last sessions. But other authors did not encounter thyroid storm after PEIT.^{12,14–17} No permanent complication or development of hypothyroidism has ever been reported by Italian authors.^{12–17}

Though the incidence of AFTN, especially that of toxic nodule, is lower in Japan than in Western countries¹⁹ and the number of the subjects is small, our preliminary results are favorable. Clinical or subclinical hyperthyroidism is

cured without developing hypothyroidism in all patients. There have been no recurrences during follow up. The volume reduction rate was more than 80% in all. Symptoms such as pain, fever or subcutaneous hemorrhage, that spontaneously recovered, were not significant. No severe complication such as cosmetic injury, or damage to the trachea, esophagus or recurrent nerve were observed. There was no worsening of cardiac symptoms during treatment in our patient (case 4) with ischemic heart disease. These facts are in accordance with previous reports. Though only 2 of our patients had toxic nodule, there was no worsening of hyperthyroidism under pre-treatment by β blocker and inorganic iodine.

As we confirmed, direct necrosis in the ethanol-permeated area was the histological change following PEIT. Therefore, so far as the injected ethanol is homogeneously localized within the nodule, the risks of injuries to extranodular tissue or organs adjacent to the thyroid can be ignored. This may be a benefit of PEIT in treating AFTN. Although the capsule or pseudocapsule around the nodule and/or the extranodular tissue may act as a

barrier, it is important to minimize unnecessary leakage of the ethanol from the nodule for successful treatment. The ethanol should be injected with the utmost care and as slowly as possible under US guidance. The intranodular diffusion of the ethanol is easily recognizable. Instead of injecting the ethanol as a single bolus, we allowed multiple and at least 5 minute injections at each session even for smaller nodules. Local anesthesia is meaningful not only to relieve the injection pain, but also to facilitate make injection from a different angle in order to distribute the ethanol more homogeneously and stereotactically. Although our experience is limited, the BIOSUC C-7 needle seems useful in reducing leakage probably because the existence of a side-hole decreases the pressure resistance at injection.

There have been no studies on the action of PEIT on parathyroid function. Although our series was small, it suggests that PEIT is not harmful to parathyroid function and this may be another benefit of PEIT.

There is no consensus as to what amount of ethanol could sufficiently damage AFTN. Our experience in recurrent thyroid cancer¹⁸ suggests that tissue necrosis following PEIT is induced in proportion to the amount of ethanol injected. We tentatively repeated the injection until the total ethanol dose exceeded V_b . The actual dose ranged between 120 and 140% of the V_b . It is probable that some parts within the nodule remain viable and recover during the treatment, for PEIT is administered in fractionated sessions. This may account for the fact that the required ethanol volume for sufficient ablation comes to a little more than the V_b . Therefore, in case of a giant nodule, complete ablation by PEIT may be difficult.

Although we took more time to finish the injection than the Italian researchers, it took no more than 15 minutes in all sessions. The treatment time is short and elderly patients or those who have radical complications can be candidates for PEIT. Furthermore, no exposure to radiation is preferable for younger patients. The long term results of PEIT still remain uncertain, but it will be safe and easy to perform additional injections when there is recurrence.

Although there are arguments for prophylactic treatment of non toxic AFTN, Hamberger found²⁰ that nodules 3 cm in diameter or larger had the risk of developing hyperthyroidism in a follow up of 1 to 6 years. Our sub-clinical toxic patients, whose nodular diameter was more than 3 cm, were successfully treated by PEIT. Technical simplicity and cost performance support the usefulness of PEIT as a prophylactic treatment.

In agreement with the other authors, our results suggest that PEIT is an attractive program in treating AFTN.

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