REVIEW

Percutaneous ethanol injection therapy in the treatment of thyroid and parathyroid diseases

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Abstract

Relevant English language articles published from 1966 to 1995 regarding ethanol therapy in the treatment of thyroid and parathyroid diseases were identified through a MEDLINE search and manual searches of identified articles.

The sclerosing properties of ethanol have been recognized for many years and have offered interventional possibilities in the management of various benign as well as malignant lesions. The mechanism of action of ethanol appears to be related to a direct coagulative necrosis and local partial or complete small vessel thrombosis. Ultrasound-guided percutaneous ethanol injection therapy (PEIT) is rapid and performed on an out-patient basis and has now gained wide acceptance due to the accumulating evidence of the efficacy and safety of this therapeutic tool. Yet, there is a lack of prospective, randomized clinical trials comparing PEIT with 131I therapy or surgery with regard to its effects, especially long-term ones and it should therefore still be considered an experimental procedure.

In benign endocrine diseases, PEIT has shown promising results in the treatment of autonomous thyroid nodules, benign solitary cold solid as well as cystic thyroid nodules and parathyroid tumours. Its use in pretoxic and toxic thyroid nodules has been evaluated in several uncontrolled studies, all demonstrating a high success rate in spite of the large number of treatments needed. So far efficacy and cost-effectiveness seem inferior to 131I and surgery. Short-term results of PEIT in benign cystic thyroid nodules are convincing with a high cure rate, but no controlled studies with long-term results are available. Preliminary results suggest that PEIT could become an alternative to surgical excision or levothyroxine therapy in the symptomatic solid cold benign thyroid nodule.

Ultrasound-guided PEIT of parathyroid tumours has proven to be a useful method in highly selected patients in whom surgery has been found non-attractive and medical treatment ineffective. However, no prospective randomized trials have been published comparing the results of PEIT in parathyroid tumours with conventional surgical and medical treatments.

PEIT has never been tested against standard therapy, but seems inferior to 131I and surgery. Side-effects caused by ethanol injection are generally few and transient and are related to the injection into solid nodules rather than cysts. Ethanol injection into solid profound nodules may seriously jeopardize subsequent surgery because of perinodular fibrosis. As an experimental procedure, not yet evaluated sufficiently, it should be reserved for patients who cannot or will not undergo standard therapy. Caution in routine use is advisable.

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Introduction

Ultrasound (US)-guided percutaneous ethanol injection therapy (PEIT) has been used for more than 15 years in selected cases to achieve therapeutic control in both malignant and non-malignant lesions (1, 2). There have been numerous applications, and beneficial effects have been demonstrated in both cystic as well as solid lesions in endocrine glands as well as various other organs, soft tissues and bone.

Autonomously functioning thyroid nodules (AFTN) often prompt surgical excision as it is effective in providing immediate relief and safe with a low morbidity (3). But surgery is not devoid of side-effects and as radioiodine (131I) is a low-cost and atraumatic alternative, it is often preferred in the treatment of AFTN (4). Based on the concern of late hypothyroidism and reluctance to use 131I, PEIT as an alternative treatment has received much attention (5–8).
Table 1 PEIT in autonomous thyroid nodules. Listing of published studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Patients treated* (n/PTA/TA)</th>
<th>Follow-up (months)</th>
<th>No. of treatments</th>
<th>Success rate (%)</th>
</tr>
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<tbody>
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<td>PT A</td>
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<tr>
<td></td>
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<td></td>
<td></td>
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</tr>
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<td>60</td>
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<td>4–8</td>
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<td>40/0/40</td>
<td>12</td>
<td>4–10</td>
<td>100</td>
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</table>

* n = total number, PTA = pretoxic thyroid adenomas, TA = toxic thyroid adenomas.
† CC = complete cure (normalization of total thyroid (TT₄) and total tri-iodothyronine (TT₃) and TSH and scintigraphic reactivation of extranodular tissue), PC = partial cure (normalization of TT₄ and TT₃, detectable TSH and partial reactivation of extranodular tissue), NC = no cure.

In Denmark approximately 50% of thyroid surgery is performed on the solitary cold thyroid nodule (9). Regardless of the US-guided fine-needle aspiration biopsy (FNAB) results less than 5% of these patients operated on have thyroid cancer (L Hegedüs, unpublished data). The key to a selective non-surgical approach to cold thyroid nodules is thorough clinical and biochemical evaluation in addition to cytologic evaluation by means of FNAB of the lesion. Based on this strategy, selecting only colloid nodules, the risk of overlooking thyroid cancer is reduced to less than 1% (10.11). Many centres, including ours, have abandoned routine operation for the solitary cold thyroid nodule resulting in a 50% reduction in the number of operations. Since levothyroxine treatment for shrinkage of these nodules has little or no effect (12) a selective non-surgical strategy often implies observation, but many patients require treatment because of local discomfort or for cosmetic reasons. PEIT has recently been suggested as a proper alternative in selected cases (13,14).

Benign cystic thyroid lesions often recur after aspiration. Based on the experience of PEIT in various parenchymatous cysts, the technique has been applied in thyroid cysts since 1989 (15). Ethanol injections have been used for treatment of parathyroid tumours since 1985 and the effect is amply documented (16). The principle treatment is surgery, but the fact that many patients either refuse surgery or are poor surgical risks has made PEIT an alternative in some centres.

The aim of the present review is to offer a critical summary of the present knowledge on PEIT in disorders of the thyroid and the parathyroid. Possible applications, clinical indications, effects and side-effects, as well as unsolved questions and areas of future research will be dealt with.

Thyroid gland

Autonomous thyroid nodules

PEIT was first proposed by Livraghi et al. (5) in 1990 as a novel therapeutic tool in the treatment of AFTN and with the advantage of being performed on an outpatient basis. The promising preliminary results have encouraged further evaluation of PEIT in several Italian centres during the last 5 years. Three hundred and ninety-four patients with a solitary pretoxic or toxic thyroid nodule have been treated with PEIT (Table 1) (5–8,17–23). Evaluation of treatment results differed in the 11 studies but comprises thyroid scintigraphy, thyroid US including changes in nodular volume and thyroid function. Success rate differed in pretoxic thyroid adenomas compared with toxic thyroid adenomas in those trials where results were evaluated separately (6,8,17,19,21,22). Complete cure, defined as normalization of serum-free thyroid hormones and serum thyrotrophin (TSH) and scintigraphic reactivation of extranodular tissue was achieved in 68% to 100% of the pretoxic nodules and in 50% to 89% of the toxic nodules (Table 1). In three studies only toxic nodules were included (5,7,23) and in two studies pretoxic and toxic nodules were not evaluated separately (18,20). Results in these five trials are comparable to the results in the former six and show success rates between 60% and 88% (5,7,18,20,23). Partial cure, defined as normalization of serum-free thyroid hormones, detectable serum TSH and partial reactivation of extranodular tissue, varied considerably from 0 to 39% in both pretoxic and toxic patients (5–8,17–23). In three studies the distinction between partial and no cure in the toxic nodomas was unclear and the...
additive frequency of partial and no cure varied from 15% to 38% (6, 7, 22). In the largest series comprising 101 patients followed for 6 to 48 months, complete cure was achieved in 50% of the toxic nodules and in 68% of the pretoxic nodules (8). The success rates were lower than in the other ten studies but the reduction in nodule volume as estimated by means of US was strikingly high at 73–83% (Table 1). The change in nodule volume is no reliable indicator of success as seen in two other studies demonstrating high cure rates (85–88%) and a concomitant smaller reduction in nodule volume (33–47%) (Table 1) (5, 23). Generally, scintigraphy demonstrated recovery of extranodular thyroid uptake of radionuclide in more than 50% of hyperthyroid patients and symptoms resolved in more than 75% of hyperthyroid subjects. Follow-up was 2–10 months in four studies (5, 6, 17, 19) and a year or more in five studies (7, 18, 21–23). It seems that the success of PEIT depends in part on the volume of the nodule and on whether the subject is hyperthyroid prior to treatment. The best result was obtained in the euthyroid patient with a thyroid nodule volume less than 10–13 ml (20, 22).

Several aspects of this novel treatment have not been assessed sufficiently and all the published studies have been open. The amount of ethanol to be injected depends on intranodular dissemination assessed by US, rather than predetermined based on nodule volume. The amount of ethanol that has a necrotizing effect does not necessarily relate to the diffusion of ethanol visually controlled during the procedure, as this differs considerably in different nodules. Success has not been adequately defined but has generally been related to normalization of serum thyroid hormone and TSH levels regardless of the number of treatments. The most important factors in predicting a clinically relevant response to PEIT are thyroid nodule volume before treatment, thyroid hormone and TSH levels and the experience of the operator. PEIT seems less effective in achieving complete cure in toxic nodules with a nodule volume larger than 10–13 ml (20, 22). Therefore, the best-suited patient with AFTN is probably euthyroid with a small non-toxic nodule.

One of the limitations is clearly the need of repeat ethanol injections to achieve complete cure. Success rate must be seen in relation to the number of treatment sessions and this has clearly not been done in any of the reported studies (5–8, 17–23). The mean number of treatments needed varied from 4·2 in pretoxic thyroid adenomas to 9·0 in toxic thyroid adenomas (range 2–23) in six studies where these figures were sufficiently elucidated (5, 6, 17, 19, 20, 22). From the available data PEIT seems most effective in small nodules that are not causing thyrotoxicosis – that is in patients where therapy is least necessary – and still requires multiple injections. Larger nodules causing thyrotoxicosis require an even larger number of injections and the success rate is lower.

In very selected cases there is a need for an alternative to $^{131}$I and surgery. Hyperthyroidism due to toxic nodular goitre revealed during pregnancy represents a difficult dilemma. Radioiodine is absolutely contraindicated, while surgical treatment (because of the low but definite anaesthetic risk) may be contemplated in the case of drug intolerance or extremely poor compliance. For these reasons, early treatment with antithyroid drugs is to be preferred for maternal hyperthyroidism during pregnancy (24). Though rare, medical treatment may cause fetal complications. Based on these facts there could be a need for an alternative treatment in pregnant women and so far there has been one report on the successful resolution of overt hyperthyroidism by PEIT in a pregnant woman with a toxic thyroid nodule (25).

Ethanol injection of autonomously hyperfunctioning thyroid nodules is inferior to $^{131}$I and surgery, and should be reserved for patients who cannot or will not be so treated. So far PEIT must be considered an experimental procedure that has never been tested against standard therapy.

### Table 2 PEIT in cystic thyroid nodules. Listing of published studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Patients treated ($n$)</th>
<th>Follow-up (months)</th>
<th>Study design</th>
<th>No. of treatments</th>
<th>Success rate §</th>
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<td>Open</td>
<td>1–2</td>
<td>95</td>
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<td>10</td>
<td>1</td>
<td>Randomized</td>
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<td>Antonelli</td>
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<td>10 (1)</td>
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<td>1</td>
<td>30</td>
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<tr>
<td></td>
<td></td>
<td>44†</td>
<td>12</td>
<td>Open</td>
<td>1</td>
<td>36</td>
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* Treated with simple aspiration. † Control group treated with saline. ‡ Mean number of ethanol instillations: 1–3. § Near disappearance or marked (>50%) size reduction of cystic lesion.
cystic or predominantly cystic (11). Thyroid cysts are often regarded to be benign, but partially or purely cystic thyroid lesions comprise both simple cysts (a cuboidal lined structure), degenerating benign adenomas or colloid nodules, thyroiditis and malignant lesions (26). While it is rare for a simple cyst to be malignant, it is in fact common for cystic thyroid lesions to be malignant (26). Fine-needle aspiration is diagnostic and requires enough cellular material but additional cytological evaluation of a possible solid component of the cystic lesion is mandatory (27). Based on cytology, surgery is not routinely performed. Suspicious or malignant cystic lesions require surgical treatment. Simple aspiration in the benign lesion is the treatment of choice but the recurrence rate is 10–80% depending on the number of aspirations and the cyst volume – the greater the volume the greater the risk of recurrence (28–31). In most centres the first step in handling the symptomatic cystic nodule is aspiration but repeated aspirations are often needed due to recurrence. Surgery is performed when the aspiration is unsuccessful, the threshold for this being very variable. Levothyroxine suppressive therapy has no effect on the cystic thyroid nodule (32).

In 1981, Bean suggested that renal cysts can be treated effectively by PEIT (33). This success was the basis for introducing the new technique in the treatment of cystic lesions in other parenchymatous organs or soft tissues such as thyroid cysts (15, 34–37). Various sclerosing agents – such as tetracycline – for the treatment of thyroid cysts have been suggested but results have been conflicting (38–40). In a randomized study, Hegedüs et al. (41) were not able to demonstrate a significant reduction in recurrence rate with this procedure. It should be emphasized that changes over a prolonged period (years) in untreated benign thyroid nodules, including cystic lesions, have been reported and in fact some cystic lesions resolve spontaneously (42).

Absolute alcohol (90–99.9%) has been evaluated in the treatment of recurrent thyroid cysts since 1989 (15, 34–37). One hundred and sixty-two patients with a cystic thyroid nodule have been treated with PEIT (Table 2). The success rate, defined as near disappearance or marked (>50%) size reduction varies from 72 to 95%. In the only placebo-controlled study with one treatment only, the short-term (1 month) success rate was 80% in the group treated with ethanol and 30% in the group treated with simple aspiration (36). Long-term follow-up (12 months) in 32 consecutive patients treated once with ethanol confirms the preliminary results obtained in the smaller randomized study (36) (Table 2). Other studies lack an evaluation of success rate based on number of ethanol instillations and an adequate control group (15, 34, 35, 37). In an open study with a control group (37) 26 patients treated with one to five ethanol instillations had a 77% success rate but the control group treated with saline underwent only one treatment, hampering the evaluation because repeated treatments with saline will also increase the cure rate (41).

The technique used by us is flushing with absolute alcohol in an amount of 25–50% of the cyst volume (maximum 10 ml) preceded by a submaximal aspiration (approximately 90%) of the cyst fluid under US guidance. Alcohol is left in place for 2 min and subsequently a complete aspiration is performed. There is no need for local anaesthesia. The ethanol dose depends on the cyst volume and intracystic dissemination of ethanol. The exact amount of ethanol and whether a subsequent complete aspiration is recommended has yet to be clarified. However, avoidance of serious side-effects has first priority and further evaluation and refining of the technique must take this into account. The fact that a number of benign cystic nodules resolve spontaneously, given sufficient time (42), makes therapy superfluous in some. Indications for therapy are recurrence after repeat(ed) aspiration(s) and compression or cosmetic complaints. Smaller cysts (<2–3 ml) are generally best left untreated.

**Solitary solid benign cold thyroid nodules**

In Denmark approximately 1500 thyroidectomies are performed every year (43). The indication is mainly non-toxic nodular goitre and half of the operations are performed due to a solitary solid or predominantly solid scintigraphically cold nodule. Less than 5% of these patients operated for solitary solid thyroid nodules have thyroid cancer (L Hegedüs, unpublished data). Based on these facts many clinicians have been eager not to expose their patients to the risks and inconveniences of superfluous thyroid surgery. This can be achieved by thorough clinical and biochemical evaluation and by US-guided FNAB, reducing the risk of overlooking thyroid cancer to less than 1% (10, 11). By performing the FNAB under US guidance and selection of the cold nodules – approximately 60–70% of the nodules – one can minimize sampling errors and misclassification as causes of false-negative diagnoses (11, 44). Inadequate biopsies must be considered as non-diagnostic and imply rebiopsy. The high accuracy of the fine-needle biopsy strongly depends on the technique of FNAB, the experience of the physician performing it and on the cytopathologist examining the sample (44).

There is no consensus on therapy and the question as to whether or not to perform thyroid surgery has been given enormous attention in the past and has often been answered evasively in literature reviews. The possibilities are simple observation, thyroxine-suppressive therapy or surgery. After careful selection according to the above-mentioned criteria it is considered safe to observe a euthyroid patient with a nonsymptomatic solitary solid colloid cold nodule. Follow-up and rebiopsy in the case of sudden growth of the nodule or clinical suspicion of malignancy is mandatory. Several authors have addressed the conflicting
issue of thyroxine-suppressive therapy either as a short-term trial as evidence of benignity or to achieve shrinkage of a symptomatic nodule. Generally, the results have been disappointing in the placebo-controlled studies. Most studies are hampered by unclear inclusion criteria - cystic as well as solid, mixed nodules or even multinodular goitres have been included - lack of documentation of TSH suppression, imprecise measurement of thyroid nodule volume and too short a follow-up (12). Furthermore, the life-long medication which is required poses a risk to the postmenopausal patient for the development of osteoporosis. The life-long control is an additional argument for an effective alternative.

Three years ago we changed our treatment strategy for patients with a solitary cold nodule. Based on a thorough clinical evaluation combined with US-guided biopsy and abandoning routine operation of patients with a colloid nodule, we have reduced the surgical rate by approximately 50% (L Hegedüs, unpublished data). The next question is what to do with the patient with a symptomatic nodule such as local discomfort due to slight pressure symptoms or cosmetic complaints, when surgery is refused or when the patient is a poor surgical risk.

In 1994 Goletti et al. (13) reported the preliminary results of PEIT in 20 patients. Sixteen patients refused surgical treatment and nine of the 20 patients had unchanged or enlarged nodules after 1 year of thyroxine-suppressive therapy. The goal of the treatment was to cause shrinkage of the nodules to small fibrous, calcified masses. A mean nodule volume reduction of 84% (range 73–98%) was obtained after three to ten treatments. Success rate was not evaluated according to the number of ethanol instillations.

We have treated 13 patients with 96% ethanol under US guidance (14). All had a solitary solid benign cold thyroid nodule evaluated clinically, biochemically and by FNAB and all had either pressure symptoms or cosmetic complaints. A maximum dose of a third of the nodule volume was injected into the nodule in one session. The median dose was 1·3 ml (range 0·5–2·5 ml). Initial mean nodule volume measured by US was 9·0 ml (range 2·7–14·0 ml) and decreased within 1 month to 5·6 ml (range 0·8–11·4 ml) (Fig. 1). After this, no significant reduction in nodule size was seen during another 5 months. Overall nodule volume reduction was 43%.

Why treat patients with a benign solitary solid cold nodule? When the diagnosis 'benign colloid nodule' has been established, many patients do not want treatment. Thus, indications for non-surgical treatment are local discomfort due to pressure symptoms or cosmetic complaints when surgery is refused or the patient is a poor surgical risk. The end-point of therapy is relief of symptoms rather than a definite reduction in nodule volume, though a correlation seems logical. Smaller nodules, nodule volume <1–2 ml, are best left untreated. Whether larger nodules, nodule volume >10–15 ml, respond sufficiently has yet to be clarified.

**Side-effects**

Side-effects of ethanol instillation into thyroid nodular structures seem to be few and are generally described as mild and transient. When performing a huge number of treatments in each patient, e.g. 2–23 sessions, the 9% prevalence of reported side-effects – mild and transient – is still low (19). Local or radiating pain representing 8% and transient dysphonia, fever and lipothymia representing 1% in this report. One could argue that lipothymia and dysphonia, though transient, are not mild.

The incidence of side-effects increases with the number of treatment sessions and the severity of side-effects seems to increase when the goal is ablation of profound thyroid nodules (19, 22). Several authors note that ethanol during injection was distributed entirely within the nodule and did not seep into the surrounding parenchyma (21). However, seepage into the extra-nodular parenchyma cannot always be hindered, especially in the case of repeat treatments when the gland has undergone fibrotic changes (45). When chemical ablation is unsuccessful, fibrosis of the para-nodular tissue can have serious implications by rendering subsequent surgery extremely difficult, thus increasing the risk of complications. Others deny any major hazard due to PEIT and a limitation in the feasibility of subsequent surgical treatment (7), but long-term results are as yet not available.

In PEIT of AFTN, multiple treatments are needed to achieve partial or complete cure. In one report, a moderate worsening in hyperthyroid symptoms was noticed in 38% of toxic patients at the beginning of treatment which partially remitted with the last
sessions (6). In fact, serum thyroid hormone levels increased after each injection in most patients (6). Thyrotoxicosis has been described in a case report (46). It seems advisable to pretreat severely thyrotoxic patients with antithyroid medication or β-blockers to prevent an exacerbation of thyrotoxic symptoms (7). In spite of release of thyroid antigen, formation of autoantibodies is rarely seen and has been estimated to be only 0–1% after 1–3 years of follow-up (7, 22). This suggests a low probability of immunological activation and subsequent late hypothyroidism. Transient hypothyroidism is rarely encountered and so far reported in 0–3% of the cases (5–8, 17–23).

The sudden increase in intranodular pressure due to rapid ethanol injection can cause temporary recurrent nerve damage, and ethanol seeping into the extranodular parenchyma can cause irreversible damage to the recurrent nerve. Transient dysphonia has been described in two of 37 patients treated for pretoxic and toxic adenomas (19) but no permanent vocal cord paralysis has been encountered in PEIT of thyroid cysts (15, 34–37), solitary solid cold benign nodules (13, 14) or autonomous thyroid nodules (5–8, 17–23).

Local haematomas are insignificant and rarely extend into the adjacent neck structures. PEIT demands an aseptic technique and so far infections have not been described. During the injection of ethanol, numerous transient echoes can be observed in the ipsilateral jugular vein, indicating rapid drainage of ethanol through the thyroid veins. This finding may explain the report of jugular vein thrombosis in an Italian study (47), hitherto not reported by others.

Ethanol injection into thyroid cysts is well tolerated, causing little or no pain and no serious side-effects have been reported (15, 34–37). In our experience local anaesthesia is not needed when thyroid cysts are treated by simple aspiration or subsequent ethanol flushing. Thus, side-effects seem to be related to the injection into solid nodules rather than cysts.

In 13 patients with a solitary solid cold benign thyroid nodule treated with a small amount of ethanol (1/5–1/3 of the estimated nodule volume), slight to moderate pain was present in all patients lasting from 5 min to 7 days (in one case) (14). The instant pain and concomitant tenderness can be alleviated but not hindered by the preceding local anaesthesia and administration of mild oral analgesics.

Conclusions
In benign thyroid nodular disease PEIT has been introduced as an alternative to surgery or 131I therapy; however, it has never been tested against standard therapy and long-term results have been evaluated in uncontrolled studies only. Generally, PEIT seems less effective than surgery or 131I therapy.

The best-suited patient with AFTN is probably euthyroid with a small nodule – patients where therapy is least necessary. The need for several ethanol injections to achieve a complete cure makes PEIT less obvious as a first choice compared with radioiodine in the treatment of AFTN. Complications related to PEIT are in no way negligible and the greater efficacy of 131I and surgery should be measured against those of ethanol in light of the complications listed above. PEIT should be reserved for patients who cannot or will not undergo standard therapy.

In cystic thyroid disease, the feasibility, safety and effectiveness of PEIT make it attractive as the next step when recurrence occurs after simple cyst aspiration and as an alternative to surgery. So far efficacy seems less than that for surgery and the implementation should await randomized studies to ascertain the efficacy, safety and long-term effects. The end-point of therapy is cure, that is a reduction in recurrence rate in order to avoid surgery.

As a rule, the solitary solid cold thyroid nodule prompts surgical intervention, but based on clinical and biochemical evaluation in addition to FNAB, it is considered safe to observe smaller colloid nodules. Symptomatic nodules may be treated with PEIT, as suggested recently (13, 14), but efficacy is inferior to surgery. Further studies will have to address long-term effects, side-effects and optimum management strategy including proper ethanol dose and treatment intervals. So far PEIT is considered an experimental treatment, and should be reserved for patients who cannot or will not undergo surgery.

Parathyroid glands
Ultrasoundography is widely applied in the localization of abnormal parathyroid glands. The ability to visualize parathyroid tumours and to obtain a reliable tissue diagnosis by US-guided FNAB has formed the basis for US-guided PEIT (US-guided chemical parathyroidectomy) (16). US-guided PEIT (Fig. 2) may be performed on an out-patient basis using local anaesthesia and has been used in patients with primary hyperparathyroidism (P-HPT) as well as in patients with hyperparathyroidism – secondary or tertiary – due to renal disease.

Primary hyperparathyroidism
The conventional treatment of patients with P-HPT is neck surgery. In experienced hands a high cure rate (>95%) and a low complication rate can be expected (48). However, the diagnosis of P-HPT and the decision to operate is often made by non-surgical specialists and thus the published surgical series clearly comprise selected materials probably influencing the excellent surgical results reported. Several patients, particularly the elderly in whom the symptoms of hypercalcaemia...
may be severe, are reluctant to have an operation. Also patients with coexisting cardiopulmonary diseases or other severe chronic or malignant diseases may be ineligible for surgical intervention. Finally, some patients refuse surgery (16, 49). In these patients US-guided PEIT may be an alternative (16).

In 1987 and 1988 a few successful and selected case histories of US-guided PEIT were reported (50–53). In 1989 Karstrup et al. (54) reported the first results of a prospective study including a series of patients with P-HPT offered ethanol injections instead of surgery. Eight of 18 patients (44%) completing the treatment protocol became normocalcaemic within 6 months. A subsequent follow-up study (55) comprising 12 of the 18 patients treated initially demonstrated that four patients were normocalcaemic 33 to 58 months following treatment (last serum value) and four patients were mildly hypercalcaemic after 30 to 55 months. In all, eight of the 18 patients (44%) underwent neck surgery, two of whom presented with parathyroid hyperplasia. The authors’ main conclusion from this study was only to offer ethanol injections to patients not fit for surgery because of the high number of inadequate responders and that the intervals between treatments should be shortened to avoid puncturing fibrotic tumours during subsequent treatments (54, 55).

A second study by Karstrup et al. (55) included treatment and follow-up of 14 highly selected patients with a prohibitive surgical risk. Long-term follow-up disclosed that eight patients (57%) were normocalcaemic 18 to 50 months following treatment and three (21%) patients were mildly hypercalcaemic after 6 to 25 months. In three patients – of whom two underwent neck surgery – no permanent biochemical improvement could be seen. In a study by Vergés et al. (56) comprising 13 patients with P-HPT and a follow-up of 1 to 49 months (median 20 months) as many as 11 patients (85%) became normocalcaemic following treatment.

The time-course of alterations in serum ionized calcium and parathyroid hormone (PTH) levels after two or three ethanol injections with 24-h intervals were investigated in seven highly selected patients not fit for surgery (57). In six of seven patients normocalcaemia was achieved within 36 to 120 h and normalization of serum intact PTH within 6 to 78 h. Thus the speed of normalization of ionized calcium levels may be of help in the acute treatment of a hypercalcaemic crisis (16, 53).

A major restriction for PEIT is the possible difficulty in accurately localizing the parathyroid tumour using US. Thus, in a study by Karstrup et al. (54) six out of 31 (19%) patients with P-HPT initially offered treatment had to be excluded due to non-visualization of a parathyroid tumour. Also, the identification of a solitary parathyroid tumour does not exclude the presence of diffuse parathyroid hyperplasia or a double adenoma. US performs very poorly in identification of multiglandular disease. Information obtained by US-guided biopsies cannot differentiate between parathyroid adenoma, hyperplasia or carcinoma (16). The possibility of parathyroid hyperplasia or double adenoma should therefore always be considered when no obvious biochemical improvement is seen following treatment by PEIT (54, 57). Additionally, should the need arise, PEIT could pose a problem in the interpretation of a subsequent biopsy.
Secondary and tertiary hyperparathyroidism

Secondary hyperparathyroidism (S-HPT) is a state of compensatory hypersecretion of PTH and is typically found in patients with chronic renal diseases. The condition leads to hyperplasia of the parathyroid glands. As a result of long-term consequences of S-HPT, hypercalcemia and 'autonomous-like' parathyroid gland function may develop. This condition is termed tertiary hyperparathyroidism (T-HPT). In both S-HPT and T-HPT the aim of the ethanol treatment has been to reduce the total amount of parathyroid mass in uraemic patients and thus to decrease serum levels of PTH.

In 1985 an Italian group (58) first reported on US-guided PEIT as a new promising treatment in 12 selected patients with S-HPT. Since then there have been several case reports with successful ethanol injections in uraemic patients (50, 59, 60). In 1992 the same Italian group presented their experience with the first 50 patients treated over a period of 8 years (61). Forty-eight of the patients could be followed biochemically 6 months after the last treatment. They demonstrated a decrease of 30% or more in serum C-terminal PTH in 25 (52%) patients ('responders') and a decrease of 50% or more in 13 patients (27%) ('high responders'). Only 25 patients completed a 12-month follow-up. Fifteen patients (60%) had a reduction of 30% or more in serum C-terminal PTH and nine patients (36%) had a reduction of 50% or more. Although the study does not indicate the number of glands visualized and treated per patient, a conclusion was made to treat every possible parathyroid tumour detected. Non-responders were found to be patients in whom only one parathyroid gland was treated or patients in whom additional parathyroid tumours were detected during follow-up. All the patients were given medical therapy during the follow-up period and no patient underwent neck surgery.

Kitaoka et al. (62) reported their experience with PEIT in nine chronic dialysis patients with severe S-HPT who were resistant to calcitriol therapy. Multiple parathyroid tumours (two or three) were detected in seven of the nine patients. Initially, PEIT was performed in the largest parathyroid tumour visualized. In cases of an inadequate decrease in serum PTH levels ethanol was additionally injected in the second largest tumour (six patients). Within 1 week a significant decrease in serum PTH to less than 200 pg/ml was observed in seven of nine patients. In the two remaining patients serum PTH became controllable with calcitriol therapy. Long-term follow-up (6–36 months) disclosed recurrence of increased serum PTH in one patient. In a study by the previously mentioned Italian group (63), 15 consecutive patients with recurrent symptomatic S-HPT occurring 7 to 127 months after subtotal parathyroidectomy were treated with two to six ethanol injections into US-detected parathyroid tumours. At 12 months following treatment serum C-terminal PTH was decreased by 30% or more in 11 of 15 (73%) patients. At 24 months this was the case in nine of eleven patients.

In a study by Cintin et al. (64) nine hypercalcaemic uraemic patients with T-HPT were treated. In five patients US detected one parathyroid tumour. In three patients two parathyroid tumours were detected and one patient had four parathyroid tumours visualized. In general, the treatment included a maximum of three ethanol injections in every parathyroid tumour detected. Follow-up at 18 months revealed that three patients did not respond to the treatment. In the remaining six patients serum ionized calcium values were normalized and serum PTH was reduced by 30% or more.

Side-effects

As with US-guided PEIT in thyroid diseases our experience is that most patients complain of moderate to severe pain extending unilaterally to the jaw and teeth, disappearing when injections are stopped. A major complication of PEIT is damage to the recurrent laryngeal nerves (Table 3); a complication also reported

### Table 3 Complications after US-guided PEIT in patients with hyperparathyroidism.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Patients treated (n)</th>
<th>Dysphonia (transient/permanent)</th>
<th>Extraglandular fibrosis*</th>
<th>Haematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karstrup54</td>
<td>1989</td>
<td>20 (P-HPT)</td>
<td>3/1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Karstrup55</td>
<td>1993</td>
<td>15 (P-HPT)</td>
<td>0/1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Verges66</td>
<td>1993</td>
<td>13 (P-HPT)</td>
<td>4/0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Karstrup57</td>
<td>1993</td>
<td>7 (P-HPT)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Solbiati58</td>
<td>1985</td>
<td>12 (S-HPT)</td>
<td>1/0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Giangrande61</td>
<td>1992</td>
<td>50 (S-HPT)</td>
<td>10/0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kitaoka62</td>
<td>1994</td>
<td>9 (S-HPT)</td>
<td>2/0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Giangrande63</td>
<td>1994</td>
<td>15 (S-HPT)</td>
<td>2/0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cintin64</td>
<td>1994</td>
<td>9 (T-HPT)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>n = 150</td>
<td></td>
<td></td>
<td>24</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*Extraglandular fibrosis = only patients operated on.
in about 0.5 to 2.0% of patients undergoing neck surgery by an experienced surgeon (65). Another serious side-effect – also related to the ethanol escaping outside the tumour capsule – is development of extraglandular fibrosis. This condition may impede subsequent surgery and should therefore be considered in every patient in whom subsequent surgery may be indicated (16, 54, 55).

Conclusions

At present no prospective randomized study has been published comparing the results of PEIT in parathyroid tumours with the conventional surgical and medical treatments. However, based on the results of the existing studies, US-guided chemical parathyroidectomy has proven to be a useful method in highly selected patients in whom surgery has been found non-attractive and medical treatment ineffective (16).

It is important to recognize that each ethanol injection carries a risk of ethanol escaping outside the tumour capsule. Thus we find that both the volume of ethanol and the number of treatments should be limited. There seems to be consensus regarding the use of small doses of ethanol – about half the volume of the parathyroid tumour – and as few alcohol injections as necessary, separated by short (days) intervals (16, 54–58, 61–63, 66). Nevertheless, in patients with S-HPT and T-HPT it seems irrational to treat solitary detected parathyroid tumours as these patients most likely present with parathyroid hyperplasia (61). One should also keep in mind the possibility of subsequent surgery. Several studies have shown a long-term (12 months) biochemical improvement in these patients; however, randomized studies are surely needed, i.e. which patients to treat, which and how many glands to treat and how many treatments should be given. In view of the lack of alternative treatment possibilities in most of these selected patients the side-effects are acceptable and generally transient. PEIT should be reserved for patients with P-HPT who cannot or will not undergo surgery and for patients with S-HPT or T-HPT only when medical treatment has failed and surgery cannot be performed.

Future aspects

Today interventional US emerges as a most powerful diagnostic as well as therapeutic tool with an increasing number of applications (67). In the near future tumours of several different organs – the thyroid and parathyroid glands included – may be treated percutaneously using hyperthermia. Thermal tumour ablation may be achieved by heating using laser (68), radiofrequency electrocautery (69), high intensity focused US (70), or by freezing using cryosurgery (71). The immediate advantage of thermal destruction is that the spread of energy – and thus the extent of tissue destruction – can be controlled. This in opposition to chemical destruction by injection of a fluid. Alcohol spreads along the cleavages and interstices in the tissue during injections and thus the dissemination may be difficult to control. We believe there is a need for supplemental techniques including PEIT but only when standard therapy has failed or when patients cannot or will not undergo standard therapy.

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References


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