PERCUTANEOUS ETHANOL INJECTION (PEI)

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percutaneous ethanol injection (PEI) is a non surgical procedure adopted by some medical centers as a therapeutic extension of US-FNA
Non surgical techniques for thyroid tissue ablation

- **irradiation**
  - $^{131I}$

- **chemical**
  - percutaneous injection:
    - sclerosing agents
    - ethanol

- **mini-invasive**
  - **physical ablation**
    - laser ablation (PLA)
    - radio frequency (RF)
    - micro-waves
    - cryoablation
    - HIFU
    - electroporation
Post-ablative histological changes

- coagulative necrosis
- endoarteritis and vascular thrombosis
- granulation tissue, scarring and shrinkage of the area.
Macroscopic appearance of an AFTN resected after (7 days) PEI
PEI treatment: immunohistochemical changes (SDH stain)
PEI Clinical Indications

- Hot & Cold benign solid thyroid nodules
- Parathyroid
- PTC Cervical lymph node metastases
- Cystic thyroid nodules
Hot & Cold benign solid thyroid nodules
Parathyroid
PTC Cervical lymph node metastases
Cystic thyroid nodules
Treatment of Large Cold Benign Thyroid Nodules Not Eligible for Surgery with Percutaneous Ethanol Injection

MATTEO ZINGRILLO, DANIELA COLLURA, MARIA ROSARIA GHIGGI, VINCENZO NIRCHIO, AND VINCENZO TRISCHITTA

* p < 0.01 vs. baseline nodule volume at the first PEI session
○ p < 0.01 vs. nodule volume at the last PEI session
PEI halves nodule volume in 50% of patients
Hot Thyroid Nodule treated by PEI
# Percutaneous Ethanol Injection of Hyperfunctioning Thyroid Nodules: Long-Term Follow-Up in 125 Patients

## Table 1: Results of Percutaneous Ethanol Injection (PEI) and Follow-Up

<table>
<thead>
<tr>
<th>Volume Range (mean) (mL)</th>
<th>Patients (Nodules)</th>
<th>Mean Injected Ethanol per Nodule (mL)</th>
<th>Mean No. Sessions per Patient</th>
<th>Complete Ablation (% Nodules)</th>
<th>Partial Cure (% Patients)</th>
<th>Major Complications (Time to Resolution)</th>
<th>Recurrences (Time at Follow-Up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 (2.5)</td>
<td>66 (67)</td>
<td>4.0</td>
<td>2.2</td>
<td>63/67 (94)</td>
<td>4/66 (6)</td>
<td>Two transient vocal chord paresis (24 h and 2 wk, respectively); one abscess (10 d)</td>
<td>Two (18 and 48 mo) with low to normal TSH and normal FT3 and FT4</td>
</tr>
<tr>
<td>&gt; 10 to ≤ 30 (13.8)</td>
<td>35 (35)</td>
<td>15.6</td>
<td>4.8</td>
<td>32/35 (91.4)</td>
<td>3/35 (8.6)</td>
<td>One transient vocal chord paresis (2 mo)</td>
<td>Two (12 and 18 mo) with low TSH and normal FT3 and FT4 in both</td>
</tr>
<tr>
<td>&gt; 30 to ≤ 60 (35.9)</td>
<td>18 (19)</td>
<td>36.0</td>
<td>7.6</td>
<td>17/19 (89.5)</td>
<td>2/18 (11)</td>
<td>One large hematoma (3 wk)</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 to maximum 90 (72.0)</td>
<td>3 (3)</td>
<td>81.0</td>
<td>10.3</td>
<td>3/3 (100)</td>
<td>0/3 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (12.5)</td>
<td>122 (124)</td>
<td>14.0</td>
<td>3.9</td>
<td>115/124 (92.7)</td>
<td>9/122 (7.4)</td>
<td>4/480 PEI sessions (0.8%)</td>
<td>4/122 patients (3.3%)</td>
</tr>
</tbody>
</table>

Note—Three (2.4%) of 125 patients refused treatment after the first PEI session and were considered treatment failures. This table includes only the 122 patients with 124 nodules who underwent at least one complete cycle of PEI sessions. TSH = thyroid-stimulating hormone, FT3 = free triiodothyronine, FT4 = free thyroxine.
Percutaneous Ethanol Injection Treatment in Benign Thyroid Lesions: Role and Efficacy

Rinaldo Guglielmi,1 Claudio Maurizio Pacella,2 Antonio Bianchini,2 Giancarlo Bizzarri,2 Roberta Rinaldi,1 Filomena Maria Graziano,3 Lucilla Petrucci,1 Vincenzo Toscano,3 Enzo Palma,1 Maurizio Poggi3 and Enrico Papini1

- AFTN > 5 ml: 60% effective, 40% ineffective
- AFTN < 5 ml: 20% ineffective
Percutaneous Ethanol Injection plus Radioiodine Versus Radioiodine Alone in the Treatment of Large Toxic Thyroid Nodules

Matteo Zingrillo, MD; Sergio Modoni, MD; Matteo Conte, MD; Vincenzo Frusciante, MD; and Vincenzo Trischitta, MD

1Unità di Endocrinologia, Scientific Institute “Casa Sollievo della Sofferenza,” San Giovanni Rotondo, Italy; 2Centro di Ripertorio Oncologico Regionale della Basilicata, Rionero in Vulture, Italy; 3Servizio di Medicina Nucleare, Scientific Institute “Casa Sollievo della Sofferenza,” San Giovanni Rotondo, Italy; 4Istituto di Clinica Medica Università di Foggia, Foggia, Italy; and 5Dipartimento di Scienze Cliniche, Università di Roma “La Sapienza,” Rome, Italy

Therapeutic options for toxic thyroid nodules (TTNs) are surgery, radioiodine (RAI), and percutaneous ethanol injection (PEI). Surgery is generally considered for TTNs larger than 4 cm.

**Key Words:** toxic thyroid nodules; radioiodine treatment; alcohol ablation; interventional procedures

*J Nucl Med 2003; 44:207–210

### TABLE 2

**NV and Thyroid Function in the 2 Subgroups at the 12th Month**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subgroup A: 11 subjects (RAI)</th>
<th>Subgroup B: 11 subjects (PEI + RAI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule volume (mL)</td>
<td>21.9 ± 12.3 (5.1–41.5)</td>
<td>13.2 ± 10.0 (1.2–40.3)</td>
</tr>
<tr>
<td>Percentage of NV reduction</td>
<td>57.2 ± 16.3 (30.0–82.9)</td>
<td>79.3 ± 14.7* (56.0–96.5)</td>
</tr>
<tr>
<td>SYS</td>
<td>2.3 ± 0.6 (1–4)</td>
<td>1.4 ± 0.3 (0–4)</td>
</tr>
<tr>
<td>FT₄ (pmol/L)</td>
<td>12.7 ± 2.7 (8.6–18.3)</td>
<td>14.5 ± 1.9 (12.4–19.2)</td>
</tr>
<tr>
<td>FT₃ (pmol/L)</td>
<td>4.4 ± 0.9 (3.0–5.9)</td>
<td>4.2 ± 0.7 (3.1–5.7)</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>3.64 ± 5.52 (0.01–18.4)</td>
<td>1.9 ± 1.2 (0.2–4.2)</td>
</tr>
</tbody>
</table>

*P < 0.01 vs. group A
Modified percutaneous ethanol injection of parathyroid adenoma in primary hyperparathyroidism


### Table 1 Laboratory findings before each injection and during follow-up (case 1)

<table>
<thead>
<tr>
<th></th>
<th>I Step</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>II Step</th>
<th></th>
<th>Follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1°</td>
<td>2°</td>
<td>3°</td>
<td>4°</td>
<td>5°</td>
<td></td>
<td>1st month</td>
<td>45th month</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>10.4</td>
<td>9.9</td>
<td>10.3</td>
<td>10.1</td>
<td>10.4</td>
<td>10.3</td>
<td>8.0</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>Ionized calcium (mg/dl)</td>
<td>6.2</td>
<td>5.9</td>
<td>6.1</td>
<td>6.1</td>
<td>6.3</td>
<td>6.2</td>
<td>1.0</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>186</td>
<td>145</td>
<td>157</td>
<td>163</td>
<td>177</td>
<td>162</td>
<td>35</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Laboratory findings before each injection and during follow-up (case 2)

<table>
<thead>
<tr>
<th></th>
<th>I Step</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>II Step</th>
<th></th>
<th>Follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1°</td>
<td>3°</td>
<td>4°</td>
<td>5°</td>
<td>6°</td>
<td>7°</td>
<td>(17th month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>12.6</td>
<td>10.3</td>
<td>12.2</td>
<td>12.2</td>
<td>11.7</td>
<td>12.0</td>
<td>11.6</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Ionized calcium (mg/dl)</td>
<td>7.2</td>
<td>6.2</td>
<td>7.0</td>
<td>7.0</td>
<td>6.9</td>
<td>7.0</td>
<td>6.0</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>401</td>
<td>162</td>
<td>393</td>
<td>363</td>
<td>405</td>
<td>374</td>
<td>362</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>
The Coming of Age of Ultrasound-Guided Percutaneous Ethanol Ablation of Selected Neck Nodal Metastases in Well-Differentiated Thyroid Carcinoma

Ian D. Hay and J. William Charboneau
Efficacy of Ultrasound-Guided Percutaneous Ethanol Injection Treatment in Patients with a Limited Number of Metastatic Cervical Lymph Nodes from Papillary Thyroid Carcinoma

Arne Helio, Eva Sigstad, Kristin Holgersen Fagerlid, Olav Inge Håskjold, Krystyna Kotanska Grøholt, Aasmund Berner, Trine Bjørø, and Lars H. Jørgensen

J Clin Endocrinol Metab, September 2011, 96(9):2750–2755

- Recurrent (n=2)
- Unchanged (n=2)
- Complete response-regression (n=9)
- Incomplete response-regression (n=9)
- Complete response-other criteria (n=20)
- In progress (n=4)
- Complete response-disappeared (n=72)
Nonsurgical, Image-Guided, Minimally Invasive Therapy for Thyroid Nodules

Hossein Gharib, MD, Laszlo Hegedus, MD, Claudio Maurizio Pacella, MD, Jung Hwan Baek, MD, and Enrico Papini, MD

PEI was the first mini-invasive procedure proposed for nonsurgical control of thyroid cancer metastases.

Possible limitations of PEI are the difficulty of inducing a predictable area of necrosis, the risk of ethanol leakage, and the need of repeated injections for a complete ablation (2,13).
Limits of PEI. Solid Nodules

• The volume of thyroid tissue ablated by each injection is small and the injection of a large amount of ethanol in solid lesions increases the risk of extracapsular diffusion

• the number of ethanol injections, cost, discomfort and risk of the procedure increase while the probability of persistent therapeutic efficacy decreases
RESULTS. The mean volume reduction rate for cysts (65%) was greater than that for solid nodules (38.3%) \((p < 0.01, \text{Student’s } t \text{ test})\). The volume of the instilled ethanol correlated significantly with the volume reduction rate of cysts but not with that of solid nodules \((p < 0.01, \text{Student’s } t \text{ test})\).

CONCLUSION. Sonographically guided percutaneous ethanol injection is more effective for thyroid cysts than for solid thyroid nodules.
PEI
Indications Proposed

• Hot & Cold benign solid thyroid nodules
• Parathyroid
• PTC Cervical lymph node metastases
• Cystic thyroid nodules
How frequent are Cystic Nodules?

Thyroid nodules are cystic in about 20% of cases.

Percentage of fluid is variable (at least 20% of whole nodule volume)

Are Cystic Nodules always benign?
The incidence of carcinoma in cytologically benign thyroid cysts

Ghulam Abbas, MD, Keith S. Heller, MD, Ali Khoynazhad, MD, Sanford Dubner, MD, and Laura A. Sznyter, MD, New Hyde Park, NY

**Table I. Final pathologic findings (number of patients)**

<table>
<thead>
<tr>
<th>Pathologic finding</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary cancer</td>
<td>4</td>
</tr>
<tr>
<td>Adenomas</td>
<td>13</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>8</td>
</tr>
<tr>
<td>Colloid cyst</td>
<td>4</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>3</td>
</tr>
<tr>
<td>Hashimoto’s disease</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

>10%
The incidence of carcinoma in cytologically benign thyroid cysts

Ghulam Abbas, MD, Keith S. Heller, MD, Ali Khoynezhad, MD, Sanford Dubner, MD, and Laura A. Sznyter, MD, New Hyde Park, NY

Presented at the 22nd Annual Meeting of the American Association of Endocrine Surgeons, Atlanta, Ga, April 28-May 1, 2001.
The incidence of carcinoma in cytologically benign thyroid cysts

Ghulam Abbas, MD, Keith S. Heller, MD, Ali Khoynezhad, MD, Sanford Dubner, MD, and Laura A. Sznyter, MD, New Hyde Park, NY

Dr Robert Udelsman (Baltimore, Md). I want to challenge you a little bit. You conclude that there was a 12% incidence of malignancy in the cystic lesions. But we have to remember this is a surgically based retrospective series. I suggest to you that the vast majority of patients with thyroid cysts are not coming to your practice and do not have recurring illnesses but are being aspirated by the endocrinologists.

I suggest that the incidence of malignancy in a simple thyroid cyst is more in the range of 0.1%. You are reporting a highly selective series by definition since the patients were referred to a surgeon and underwent resection. You might be over-interpreting the data based on the retrospective nature of the study.

Presented at the 22nd Annual Meeting of the American Association of Endocrine Surgeons, Atlanta, Ga, April 28-May 1, 2001.
Is a benign FNAB as reliable as in solid nodule?

- The answer is **Yes**

- FNABs is generally performed in two stages:
  - a. the cyst is relieved of the fluid and subsequently
  - b. material is aspirated under US control from the remaining tissue complex
proceed directly to biopsy the solid part of the nodule to avoid a non negligible rate of hemorrhage within the cavity of the nodule after partial aspiration:

**Diagnostic cytology: >90%**
Could Cystic Nodules be cured with simple fluid aspiration?

Cyst resolution occurs in about 10% patients after FNA

PEI of Cystic Thyroid Nodules

% volume reduction after 1 yr

Valcavi R & Frasoldati A., Endocrine Practice, 2004
The role of thyroid therapy in patients with thyroid cysts. McCowen KD, Reed JW, Fariss BL.

Twenty patients with benign thyroid cysts were studied in a prospective double-blind fashion to determine the effect of thyroid therapy on the recurrence of these cysts after aspiration. When the 10 patients receiving placebo medication were compared with the 10 patients ingesting thyroid hormone, no significant difference was found in the time either group was free of cyst recurrence. We conclude that thyroid therapy is not effective in preventing the recurrence of benign thyroid cysts after initial aspiration.
Resolution of Recurrent Thyroid Cysts With Tetracycline Instillation
LTC Gary L. et al

Nine patients with recurrent purely cystic thyroid nodules after one or two previous cyst aspirations were treated with repeat cyst aspiration and instillation of intracystic tetracycline hydrochloride. All but two of the patients' cysts resolved completely and have not recurred after a follow-up period of 12 to 50 months (mean=40). The remaining patients had a partial response that left them with clinically insignificant lesions. The procedure was well tolerated and obviated the need for further therapy in all patients. **Cyst aspiration and tetracycline instillation is a safe and effective treatment of recurrent purely cystic thyroid nodules that eliminates the need for surgical excision.**

*Arch Intern Med.* 1983;143(12):2285-2287
Sclerotherapy with OK-432 for Recurrent Cystic Thyroid Nodule

Hang-Seok Chang, Jong Ho Yoon, Woung Youn Chung, and Cheong Soo Park

We have adopted OK-432 as a sclerosing agent in the treatment of cystic predominant thyroid nodules and have analyzed our findings to assess the efficacy of intralesional instillation of OK-432. From 1992 through 1993, 48 patients with recurrent or progressive cystic thyroid nodules after 2 or 3 aspirations alone, and whom were cytologically negative for malignancy, were used for this study. The OK-432 solution was prepared by dissolving 0.1 mg of OK-432 in 2 ml of physiologic saline and it was instilled in the amount of 1/10-to-1/5 of the aspirated cystic fluid. A repeated course of therapy was given up to 3 times when sufficient resolution was not obtained 4-to-6 weeks after treatment. The mean number of treatment sessions per patient was 1.5. Throughout the follow-up period from 30-to-45 months (mean, 38 months), 32 (66.7%)
PEIT: materials
PEI Procedure

• a disposable 22-G needle is inserted (without anesthesia) into the lesion.

• fluid is nearly completely removed.

• aspirating syringe is substituted with a syringe containing ethanol.
Procedure (2)

• 95% sterile ethanol (volume: 35 - 50% of the aspirated fluid) is slowly injected.

• needle is withdrawn during the injection of 0.5 ml of xylocaine.

• a neck dressing is applied without pressure on the lesion.
Thyroid cysts: volume changes after PEIT

Pre-treatment: 17.6 ml

After ethanol: 10 ml

1 month after PEIT: 3.6 ml

12 months: 0.4 ml
PEI in cystic thyroid nodules volume before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>N pts</th>
<th>Pre-PEI Volume (ml) base-line</th>
<th>Post-PEI Volume (ml) 12 months</th>
<th>Post-PEI Volume (ml) 60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zingrillo 1999</td>
<td>40</td>
<td>33.7±25.3</td>
<td>3.0±2.4*</td>
<td>0.6±0.6*</td>
</tr>
<tr>
<td>Verde 1994</td>
<td>32</td>
<td>14.5</td>
<td>2.5*</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 1.5-65.8</td>
<td>Range 0.4-34.5</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 vs. baseline
Efficacy of PEI treatment
Thyroid Cysts

- cases treated by PEI: 58 (at least 5-years follow-up)
- median number of treatments: 2
- **effective**: volume decrease > 75% and improvement of local symptoms
- **ineffective**: volume decrease < 75% and/or persistence of local symptoms

![Pie chart showing distribution of effective, ineffective, and relapse cases]

86% effective
11% ineffective
3% relapse
Some Clinical Problems

Which result with Mixed Thyroid Nodules?
Complex nodules: volume changes after PEIT

Pre-treatment:
13.7 ml

After ethanol infusion:
9.1 ml

12 months:
3.3 ml
Decrease: 76%
Results of Percutaneous Ethanol Injection (PEI) in cystic thyroid nodules

% vol.reduction: empty body vs mixed cysts

**Empty body cysts**
- N=169, 63.5%
- % Volume reduction: 88.8%
- Fluid evacuation: 8.8%
- p<0.001

**Mixed nodules**
- N=97, 36.5%
- % Volume reduction: 65.8%
- Fluid evacuation: 4.7%

Valcavi R & Frasoldati A., Endocrine Practice, 2004
What to do with Cystic Nodules with Viscous Colloid?

- **Stage 1**: in case of ineffective aspiration, inject 1 ml di ethanol for each 10 ml of nodule volume.

- **Stage 2**: 2 weeks later, repeat procedure as in stage 1, then use a 20-gauge needle for aspiration. When the cyst is empty do the usual procedure of PEI.

- Nodule volume shrinkage reported after 1 yr: **91%**

Zieleznik W et al., Thyroid, 2005
Vol 15, n° 7, pp 683
Is there a maximum nodule volume for PEI treatment

Thyroid cystic nodules relapse more frequently after PEI if baseline volume is greater than 20 ml and need more number of ethanol injection and longer follow up

Jayesh SR et all
Indian J Radiol Imaging
August 2009
While many do not report side-effects at all, there is agreement on most patients having mild to severe transient pain, lasting for minutes, and many have low grade fever. Serious side-effects are rare, but recurrent nerve palsy with transient dysphonia, Graves’ disease, Graves’ orbitopathy, Horner’s syndrome, facial dysesthesia with increased tear flow, necrosis of the larynx and skin, as well as impairment of post-PEIT surgery, due to local fibrosis, have been reported (5). These, and other side-effects, are most likely linked to seepage of alcohol along the needle tract, and not only due to insufficient training.
Tolerability
Experience of the procedure

• **thyroid cysts**
  no patient defined the treatment as very painful and a new session would be accepted without any problem

• **AFTN**
  30% of patients defined PEI as very painful procedure and a different treatment would be considered if needed
Risk- and cost-benefit ratio of PEIT

**Advantages:**
- Effective volume reduction
- No cosmetic damage
- Mild or absent pain
- No hypothyroidism
- Negligible cost
- No heavy technology
- No general anesthesia
- Outpatient clinics (15 minutes).

**Disadvantages:**
- Nodule persistence
- Operator with experience in US-guided FNA
- Complications: rare and transitory (learning period)
- Repeated treatments in large or multilocular cysts.
7.6.2.4. US-Guided PEI

- PEI is effective in the treatment of benign thyroid cysts and complex nodules with a large fluid component (Grade B; BEL 1)
- PEI should not be performed in solitary solid nodules, whether hyperfunctioning or not, or in MNGs (Grade C; BEL 3)
RECOMMENDATION 15

Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or PEI based on compressive symptoms and cosmetic concerns. Recommendation rating: B
Thank you for your attention