



Roma, 8-11 novembre 2018



ITALIAN CHAPTER



PERCUTANEOUS ETHANOL INJECTION (PEI) TREATMENT OF CISTIC THYROID NODULES

Rinaldo Guglielmi

Endocrine and Metabolic Disease Unit

Ospedale Regina Apostolorum



Conflitti di interesse



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Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:



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PEI

- fine-needle aspiration biopsy (FNA) is a diagnostic complement of physical and ultrasound (US) examination of thyroid lesions
- percutaneous ethanol injection (PEI) is a non surgical procedure adopted by some medical centers as a **therapeutic extension of US-FNA**

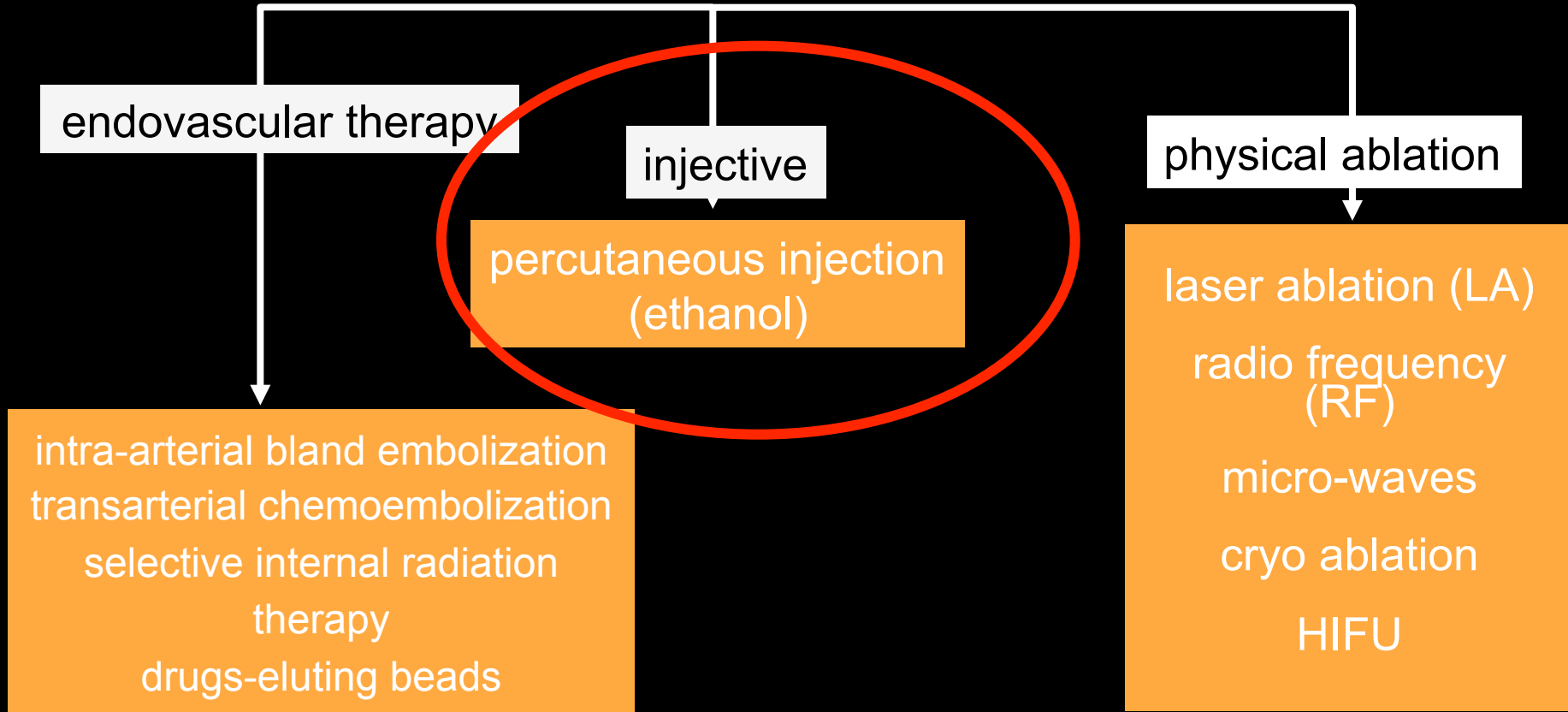


Minimally invasive techniques for tissue ablation



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Introduction 2



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- ethanol induces in thyroid tissue a complex damage including coagulative necrosis, vascular thrombosis and hemorrhagic infarction
- the treated areas are substituted by granulation tissue which causes scarring and progressive shrinkage of the nodules



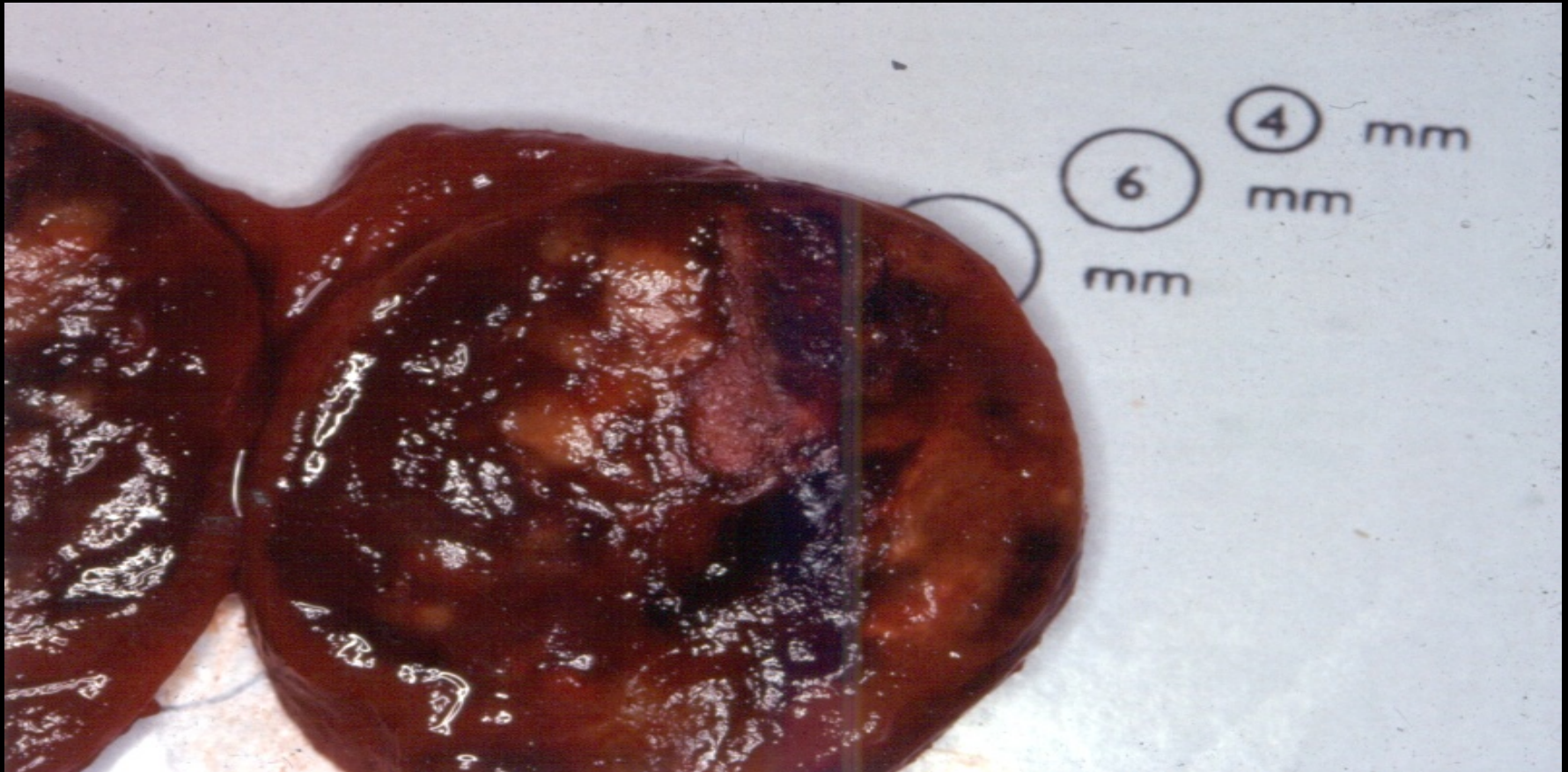
Macroscopic appearance of an AFTN

resected after (7 days) PEI



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PEI

Limits in Solid Nodules



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- 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 sessions, the cost, the discomfort and the risk of the procedure increase while the probability of persistent therapeutic efficacy decreases



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1. Which lesion should be treated?



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- Hot & Cold benign solid thyroid nodules
- Parathyroid
- PTC Cervical lymph node metastases
- **Cystic thyroid nodules**



2. How frequent are Cystic Nodules?



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Thyroid nodules are cystic in about 20% of cases

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

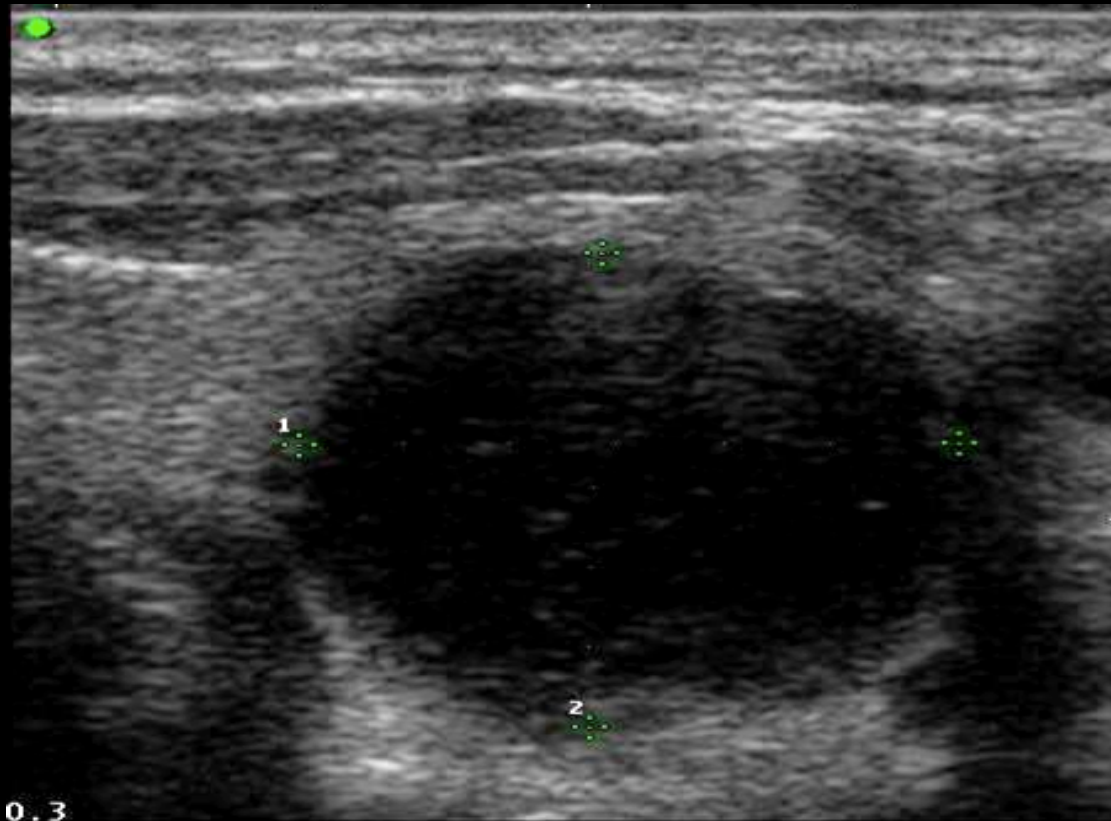


Pure Cystic Nodule



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0.3



Mostly Cystic Nodule



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19 Feb 99

2:46:02 am

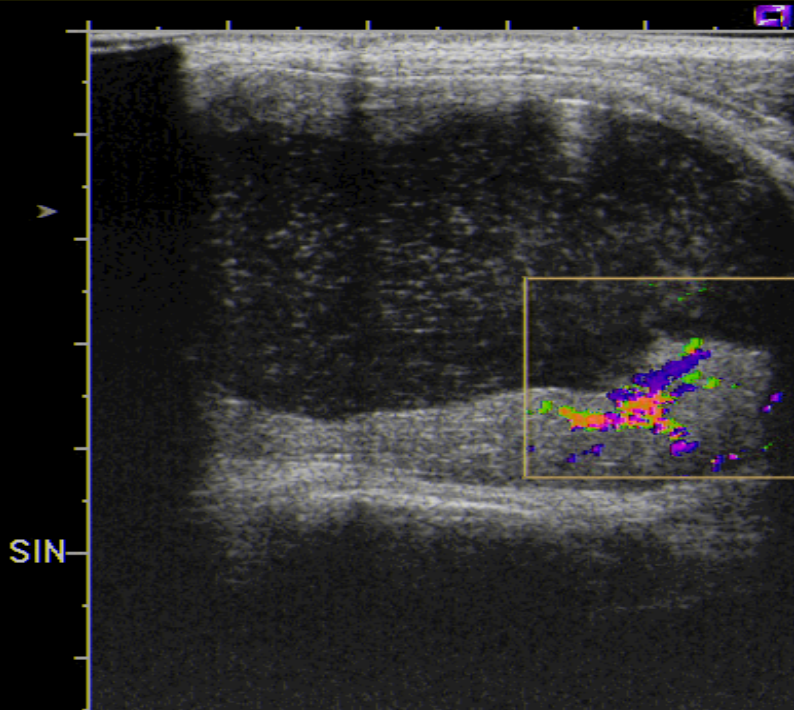
15L8w 9Hz
13.0MHz 65mm
Small Parts

S1/-1/ 2/V:2
2/1 **CD: 10.0MHz**
Guad CD= 58

Memo in corso

.040

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CDE/CDV

CD Pan.

CD Pos./Mis

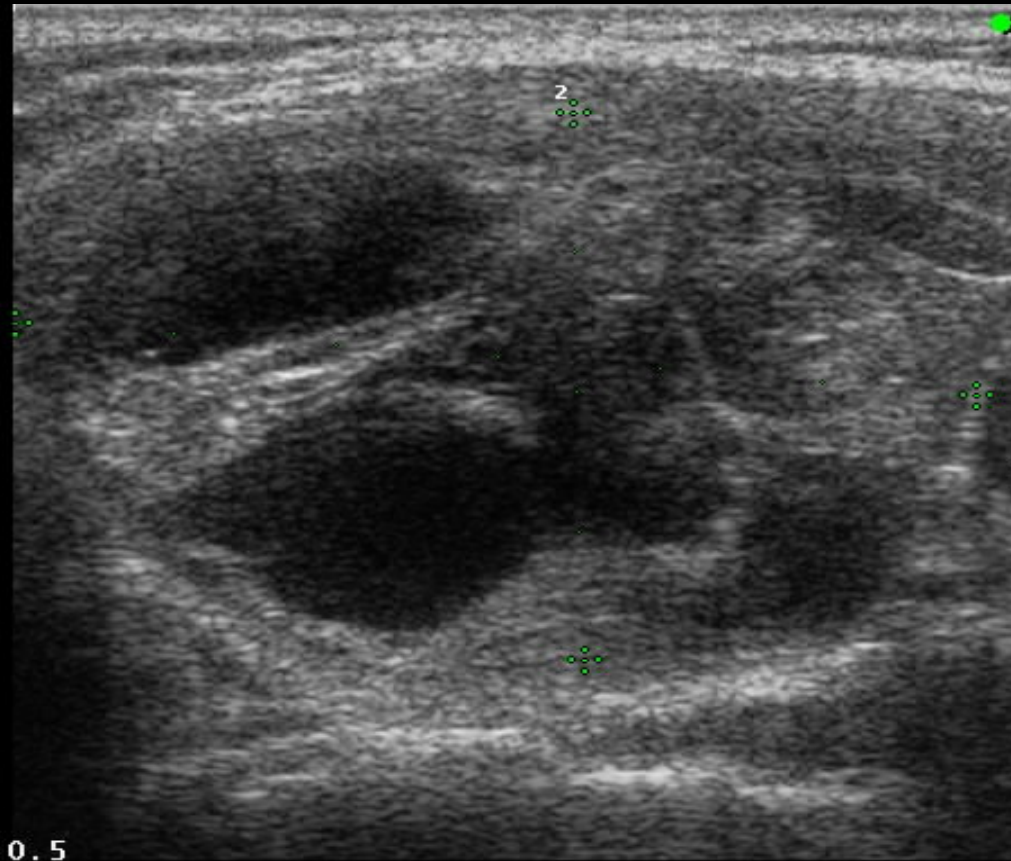


Mixed Nodule



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THYROID
Volume 26, Number 1, 2016
© American Thyroid Association
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DOI: 10.1089/thy.2015.0020

SPECIAL ARTICLE



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2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer

Bryan R. Haugen,^{1,*} Erik K. Alexander,² Keith C. Bible,³ Gerard M. Doherty,⁴ Susan J. Mandel,⁵ Yuri E. Nikiforov,⁶ Furio Pacini,⁷ Gregory W. Randolph,⁸ Anna M. Sawka,⁹ Martin Schlumberger,¹⁰ Kathryn G. Schuff,¹¹ Steven I. Sherman,¹² Julie Ann Sosa,¹³ David L. Steward,¹⁴ R. Michael Tuttle,¹⁵ and Leonard Wartofsky¹⁶

■ **RECOMMENDATION 28**

Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection (PEI) based on compressive symptoms and cosmetic concerns. Asymptomatic cystic nodules may be followed conservatively.

(Weak recommendation, Low-quality evidence)



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AACE/ACE/AME Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ASSOCIAZIONE MEDICI ENDOCRINOLOGI MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES – 2016 UPDATE

APPENDIX

*Hossein Gharib, MD, MACP, MACE¹, Co-Chair; Enrico Papini, MD, FACE², Co-Chair;
Jeffrey R. Garber, MD, FACP, FACE³; Daniel S. Duick, MD, FACP, FACE⁴;
R. Mack Harrell, MD, FACP, FACE, ECNU⁵; Laszlo Hegedüs, MD⁶; Ralf Paschke, MD⁷;
Roberto Valcavi, MD, FACE⁸; Paolo Vitti, MD⁹;
on behalf of the AACE/ACE/AME Task Force on Thyroid Nodules**

7.2.4. Percutaneous ethanol injection for benign nodules

- PEI is a safe and effective outpatient therapy for benign thyroid cysts or complex nodules with a large fluid component [BEL 1, GRADE A].



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3. Are Cystic Nodules always benign?



AMERICAN THYROID ASSOCIATION

DEDICATED TO SCIENTIFIC INQUIRY, CLINICAL EXCELLENCE, PUBLIC SERVICE, EDUCATION, AND COLLABORATION.



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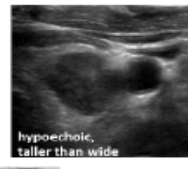
High Suspicion
70-90%



microcalcifications, hypoechoic nodule, irregular margin



hypoechoic, irregular margins



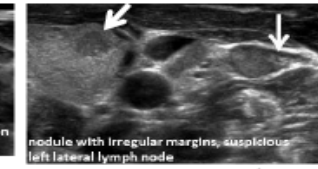
hypoechoic, taller than wide



hypoechoic, irregular margins, extrathyroidal extension



hypoechoic, interrupted rim calcification with soft tissue extrusion



nodule with irregular margins, suspicious left lateral lymph node

Intermediate Suspicion
10-20%



hypoechoic solid regular margin



hypoechoic solid regular margin

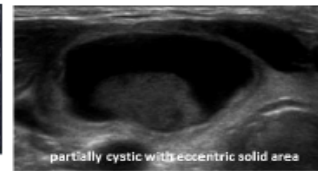
Low Suspicion
5-10%



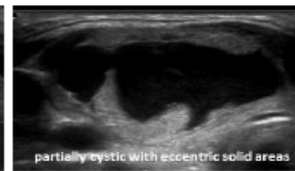
hyperechoic solid regular margin



isoechoic solid regular margin



partially cystic with eccentric solid area



partially cystic with eccentric solid areas

Very low Suspicion
<3%



spongiform

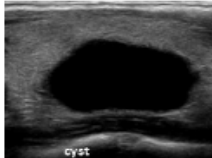


partially cystic no suspicious features

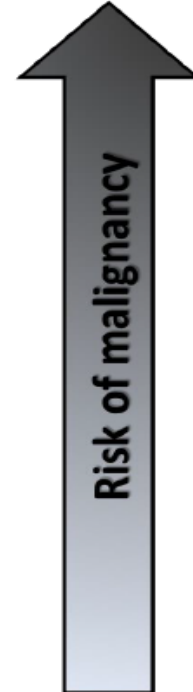


partially cystic no suspicious features

Benign
<1%



cyst



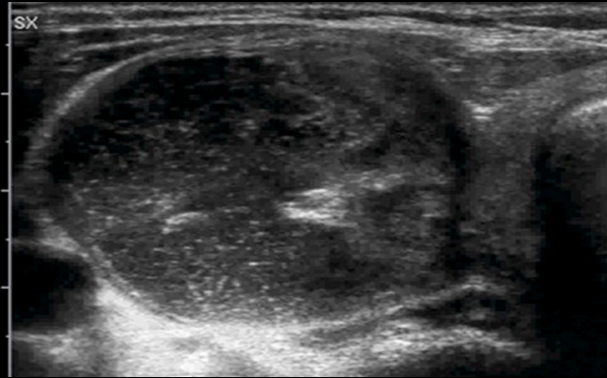
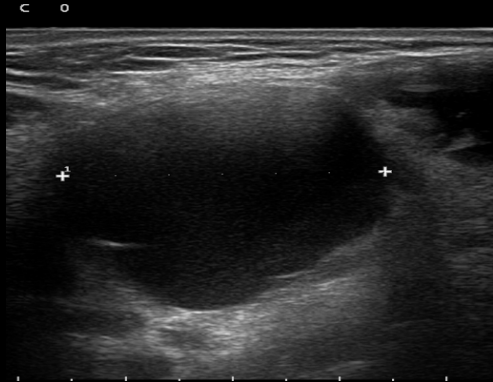


Class 1. Ultrasound Low-Risk Thyroid Nodules



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A. Thyroid cyst

B. Mostly cystic nodule with reverberating artifacts, not associated with suspicious signs

C. Spongiform nodule

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The incidence of carcinoma in cytologically benign thyroid cysts

Ghulam Abbas, MD, Keith S. Heller, MD, Ali Khoynzhad, MD, Sanford Dubner, MD, and Laura A. Szynter, MD, *New Hyde Park, NY*



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MEDIAN OF MALIGNANCY: 15%

Presented at the 22nd Annual Meeting of the American Association of Endocrine Surgeons, Atlanta, Ga, April 28-May 1, 2001.

SURGERY 1035



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4. Is a benign FNAB of cysts as reliable as in solid nodule?



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- 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



Efficacy of Ultrasound-Guided Fine-Needle Aspiration Biopsy in the Diagnosis of Complex Thyroid Nodules

MILENA BRAGA, TERESA CRISTINA CAVALCANTI, LUIZ MARTINS COLLAÇO, AND HANS GRAF

Serviço de Endocrinologia e Metabologia do Paraná do Hospital de Clínicas (M.B., H.G.) and Serviço de Anatomia Patológica do Hospital de Clínicas (T.C.C., L.M.C.), Universidade Federal do Paraná, Curitiba 80.060-240, Brazil

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%



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5. Could Cystic Nodules be cured with simple fluid aspiration?



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Cyst resolution occurs in about 10% patients after FNA

Recommendations for management of cystic thyroid disease.
McHenry et al, Surgery. 1999 Dec;126(6):1167-71

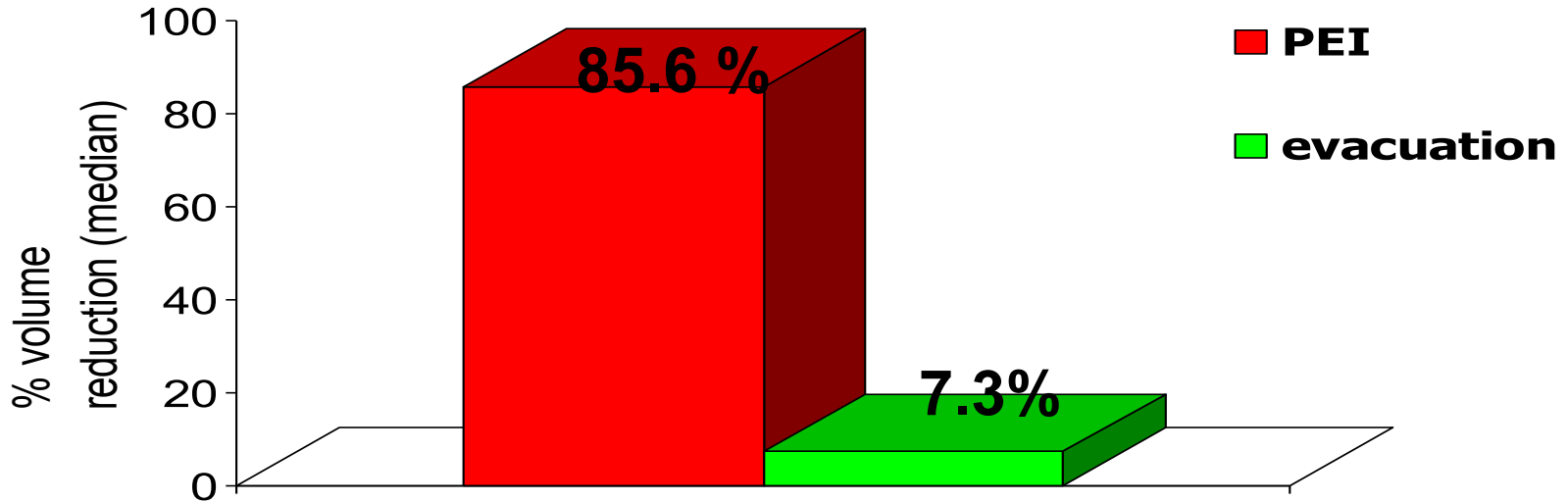


PEI of Cystic Thyroid Nodules % volume reduction after 1 yr



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Valcavi R & Frasoldati A., Endocrine Practice, 2004



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6. Why not L-T4 therapy in Thyroid Cystic Nodules?



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.**



Otolaryngology–Head and Neck Surgery (2005) 133, 391-396

Efficacy of Thyroid Hormone Suppression for Benign Thyroid Nodules: Meta-analysis of Randomized Trials

Matthew T. Sdano, MD, Mercedes Falciglia, MD, Jeffrey A. Welge, PhD, and David L. Steward, MD, Cincinnati, Ohio

Table 1
Studies included in meta-analysis

Study	Length	Patients	Nodule type	TSH (mU/mL)	T4 dose (mcg/kg/d)
Wemeau	18 m	123	Nodules had <20% cystic component	TSH<0.3	T4 ave: 2.24
Larijani	12 m	62	<u>Cystic nodules included</u>	TSH ave: 0.18	T4: 1.5-2
Zelmanovitz	12 m	45	Nodules had <20% cystic component	TSH<0.3	T4: 2.5-3
LaRosa	12 m	45	Cystic nodules excluded	TSH<0.3	T4 ave: 1.8
Papini	12 m	101	Nodules excluded if >1 mL fluid	n/a	T4 ave: 2
Reverter	12 m	40	<u>Solid-cvstic nodules included</u>	TSH<0.1	T4 ave: 2.82
Gharib	6 m	53	<u>Cystic nodules included</u>	n/a	T4 ave: 3
Koc	12 m	40	Nodules had <20% cystic component	n/a	T4 ave: 3.2 ^a T4 ave: 1.4 ^b
Uzunkoy	12 m	100	Cystic nodules excluded	TSH ave: 0.1	T4: 1.5-3

n/a, not available; m, months.

^ahigh dose suppression group

^blow dose suppression group



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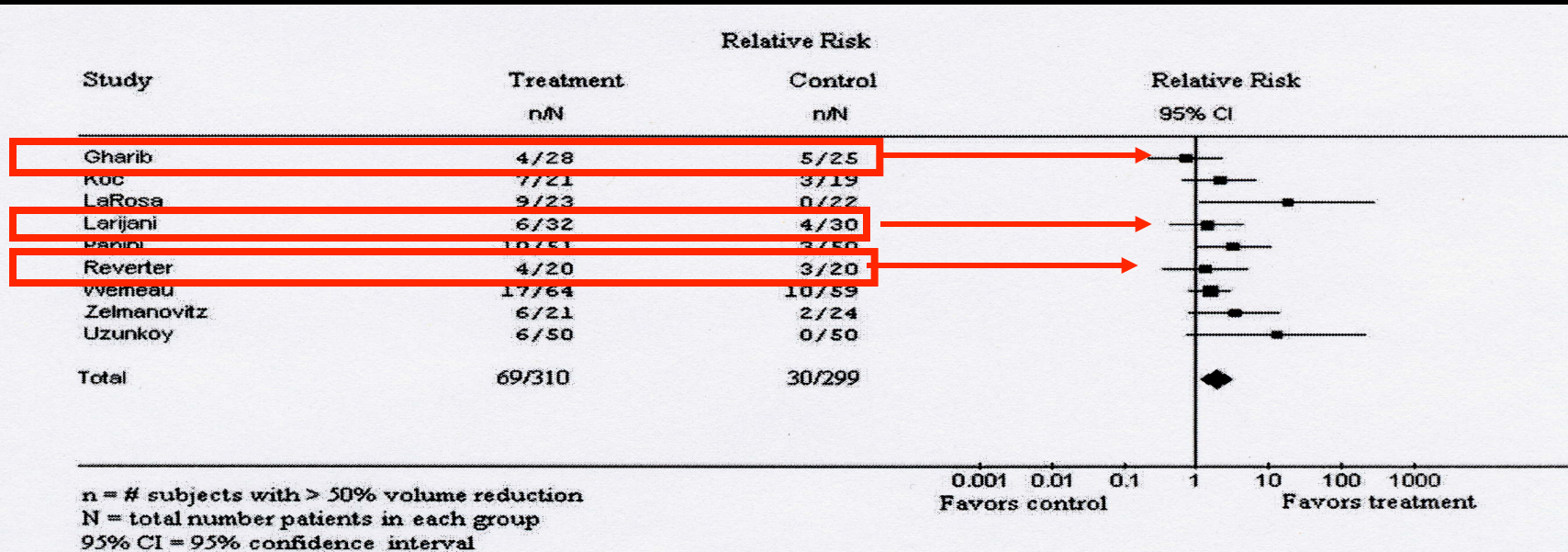


Figure 1 Individual and total relative risk (with 95% confidence intervals) for number of patients having >50% reduction in thyroid nodule volume (using random effects analysis).



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7. Which are the results in Cystic thyroid nodules?



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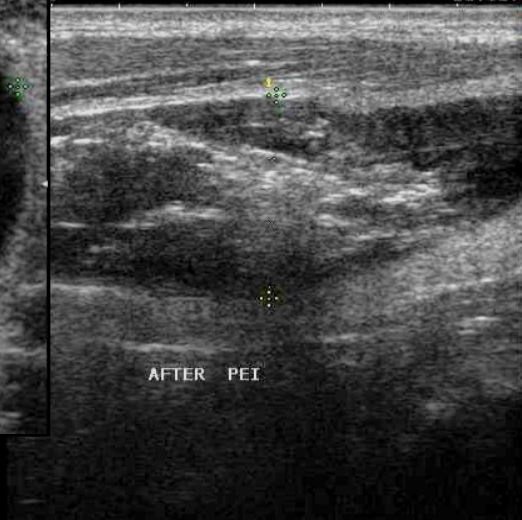
Case 1



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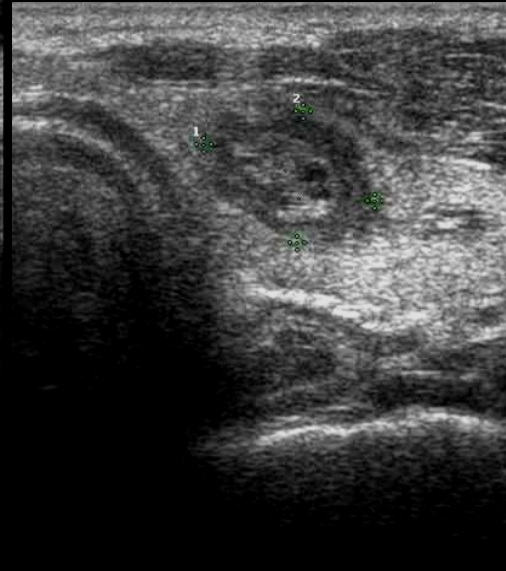


Pre-treatment:
Vol 17.6 ml

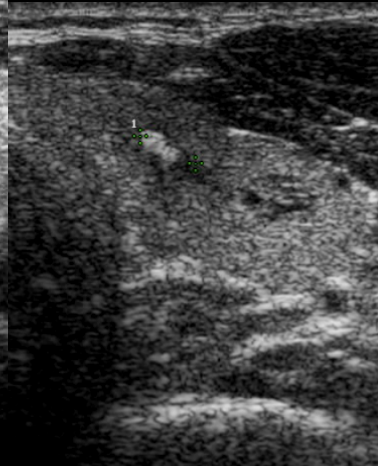


Ethanol infusion:
Vol 10 ml

1 month:
Vol 3.6 ml



12 months:
Vol 0.04 ml



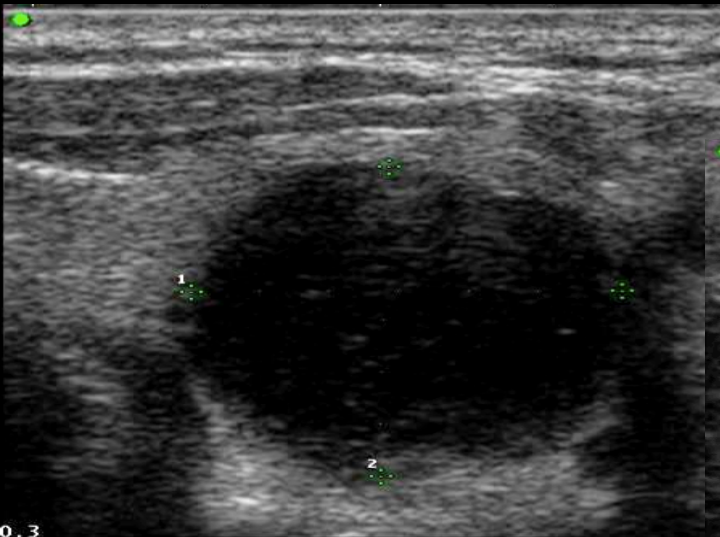


Case 2

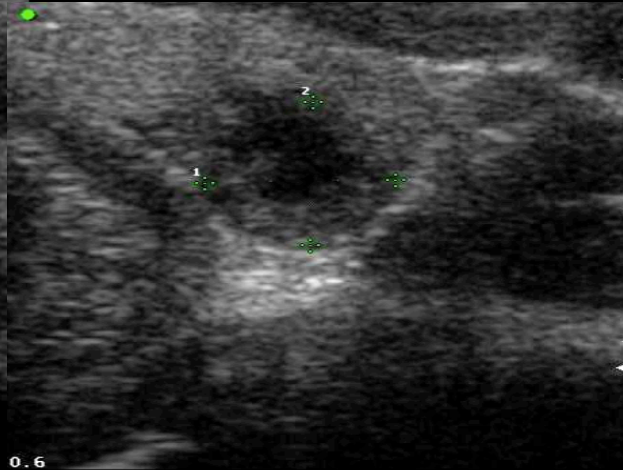


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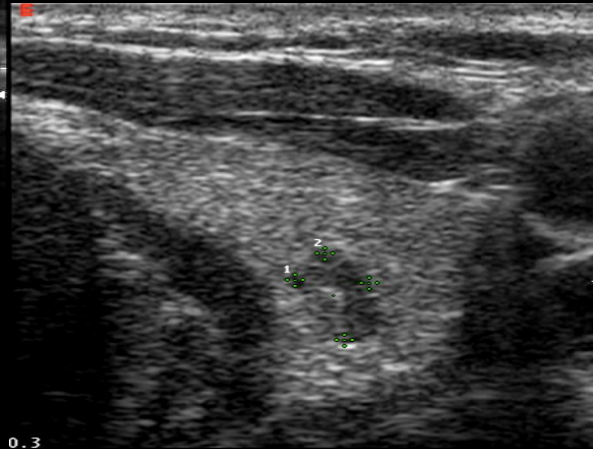


Pre-treatment:
Vol 2.2 ml



1 month:
Vol 0.6 ml

6 months:
Vol 0.086 ml
Reduction 96.9%





PEI in cystic thyroid nodules



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

* $P < 0.001$ vs. baseline



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Reverter *et al. BMC Endocrine Disorders* (2015) 15:73
DOI 10.1186/s12902-015-0069-3

BMC Endocrine Disorders

RESEARCH ARTICLE

Open Access



Evaluation of efficacy, safety, pain perception and health-related quality of life of percutaneous ethanol injection as first-line treatment in symptomatic thyroid cysts

Jordi L. Reverter^{1*}, Núria Alonso¹, Marta Avila², Anna Lucas¹, Dídac Mauricio¹ and Manel Puig-Domingo¹

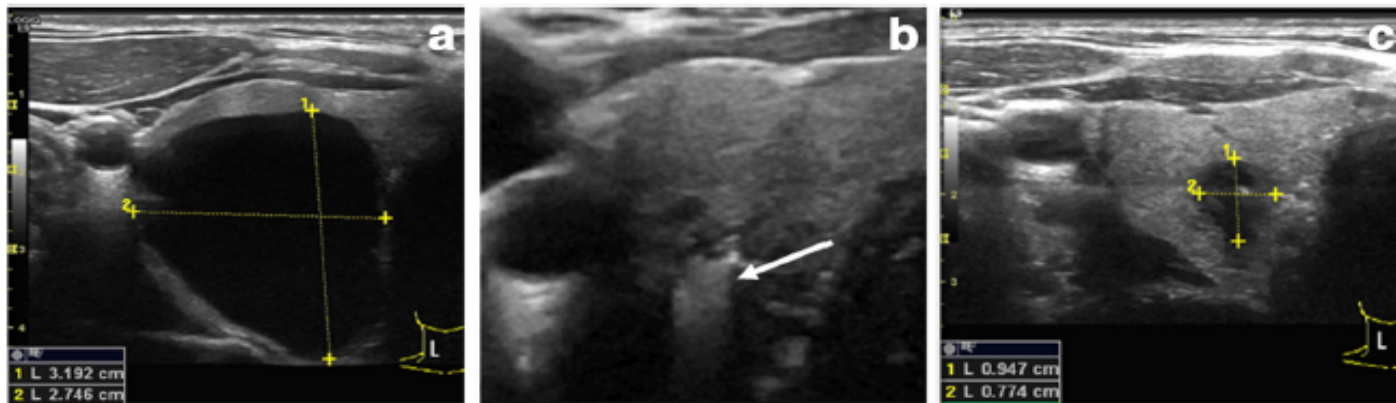


Fig. 1 Transverse ultrasound scans of one cyst before (panel a), during (panel b) and after (panel c) percutaneous ethanol injection treatment (PEIT). During PEIT, cystic lumen was filled with instilled ethanol (arrow). Panel c shows marked decrease in size



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8. How long the effectiveness of the therapy lasts?



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THYROID
Volume 14, Number 2, 2004
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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

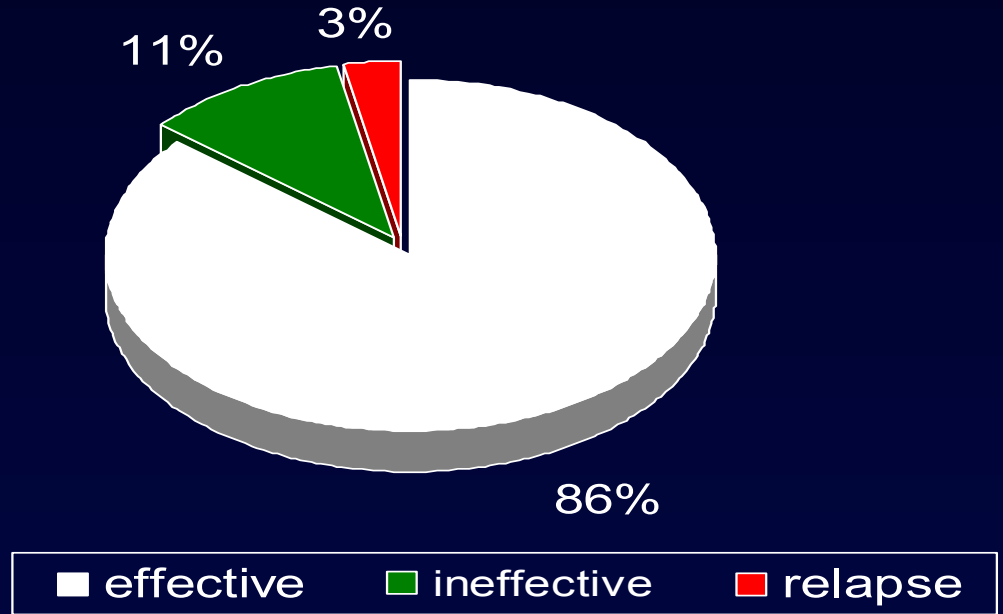
TABLE 1. MAIN OUTCOMES OF PEI IN CYSTIC THYROID NODULES AND TOTAL AFTN FIVE YEARS AFTER TREATMENT

	Cases	Baseline volume (mL)	Ethanol injected (mL)	Volume after 5 yrs (mL)	Volume reduction (%)	Normal serum TSH after 5 yrs (%)
Cysts	58	13.7 ± 14.0	7.3 ± 5.5	2.3 ± 3.5	86.6 ± 34.3	—
Total AFTN	112	8.5 ± 10.9	10.4 ± 7.4	2.97 ± 7.05	64.2 ± 27.1	56.2 (63/112)

PEI, percutaneous ethanol injection; AFTN, autonomously functioning nodules; TSH, thyrotropin.

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





9. How safe is PEI?



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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

Bennedbaek et al. Eur J Endocrinol., 1997.

Although most complications have been transient in nature we observed ethyl toxic necrosis of the larynx: the patient was admitted to hospital, treated conservatively and ten month later microsurgically...

The patient must be informed about possible severe complications. The examiner should have substantial experience in these methods.

Mauz et al., Acta Otolaryngol. 2004



Side effects



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Volume 14, Number 2, 2004
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Percutaneous Ethanol Injection Treatment in Benign Thyroid Lesions: Role and Efficacy

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Maurizio Poggi³ and Enrico Papini¹

- **no side effects were registered during the treatment of cystic nodules**
- in two cases (1.8%) of AFTN was observed a transient dysphonia
- The paresis of the homolateral cord appeared immediately after PEI and the recovery (confirmed by laryngoscopy) was obtained within one and seven weeks, respectively



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10. Which is the Tolerability? Experience of the procedure



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- ***thyroid cysts***

no patient defined the treatment as very painful and a new session would be accepted without any problem, if needed

- ***AFTN***

30% of patients defined PEI as very painful procedure and a different treatment would be considered if needed

THYROID
Volume 14, Number 2, 2004
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Percutaneous Ethanol Injection Treatment in Benign Thyroid Lesions: Role and Efficacy

Rinaldo Guglielmi,¹ Claudio Maurizio Pacella,² Antonio Bianchini,² Giancarlo Bizzari,² Roberta Rinaldi,¹ Filomena Maria Graziano,³ Lucilla Petrucci,¹ Vincenzo Toscano,³ Enzo Palma,¹ Maurizio Poggi¹ and Enrico Papini¹



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Some further Clinical Problem



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11. Which result with Mixed Thyroid Nodules?



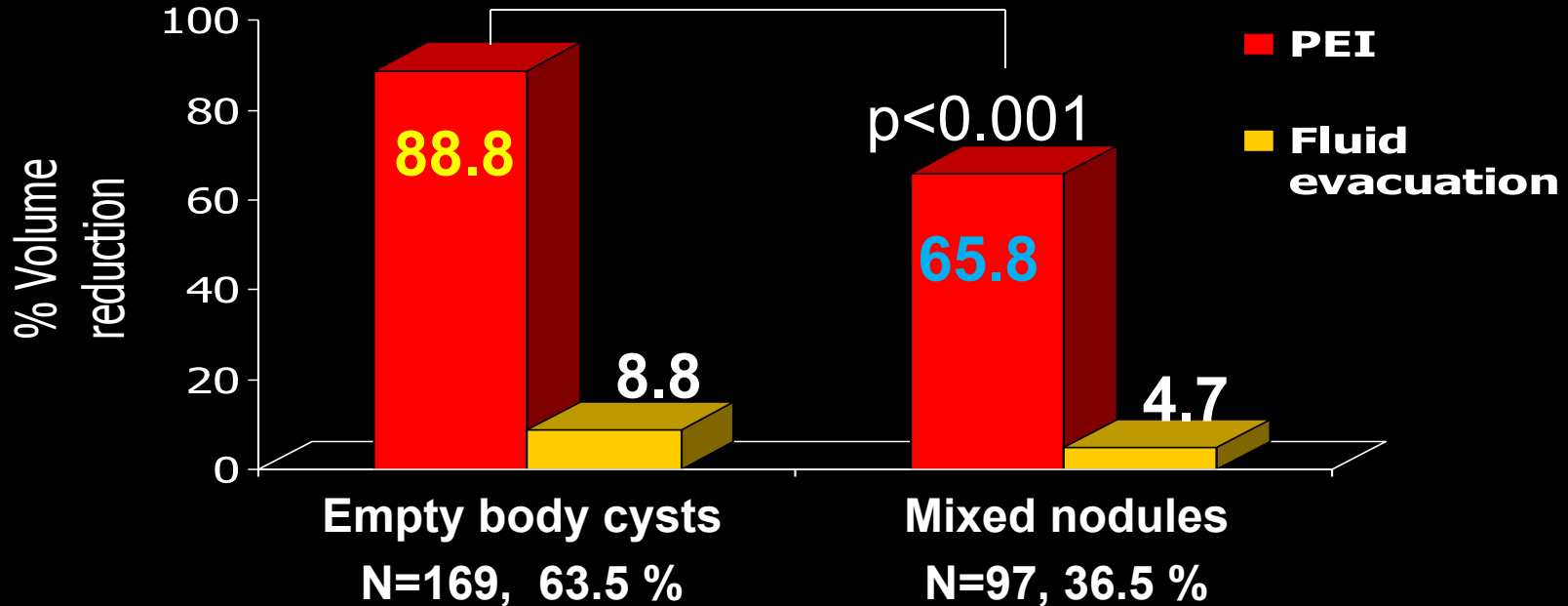
Results of PEI

empty body vs mixed cysts



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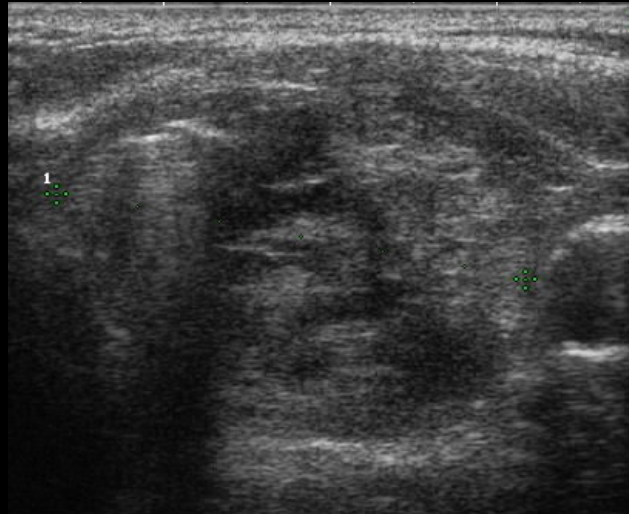
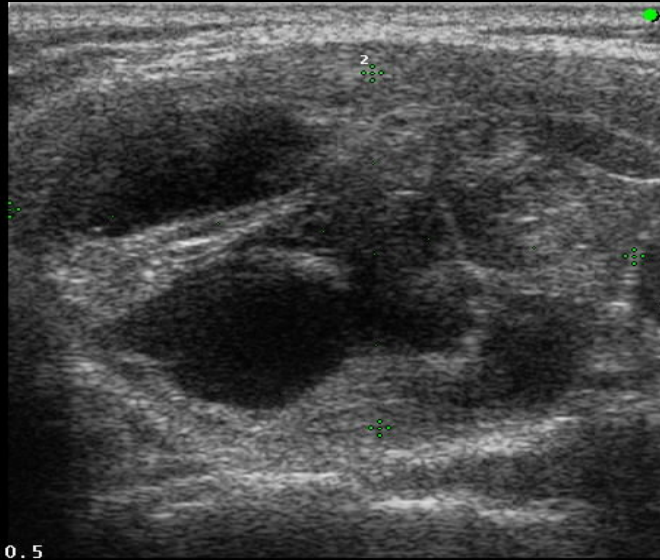


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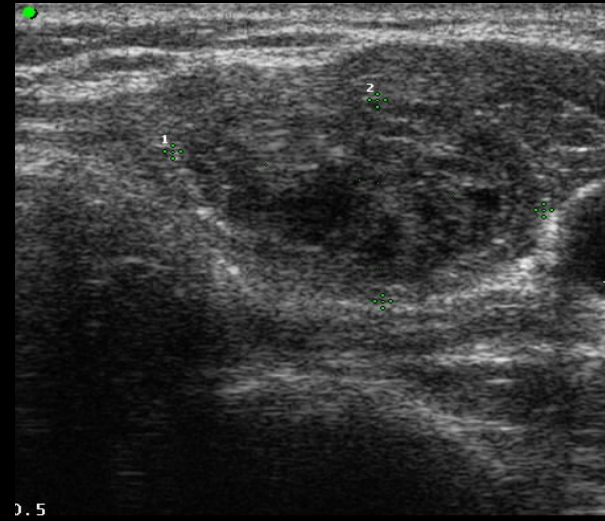
Case 3



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12 months:
Vol 3.3 ml
Reduction 76%





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12. What to do with Cystic Nodules with Viscous Colloid?



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- 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 all, Thyroid , 2005
Vol 15, n° 7, pp 683



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13. Is there a nodule volume not suitable for PEI treatment?



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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 al
Indian J Radiol Imaging
August 2009



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ITALIAN CHAPTER

Reverter *et al.* *BMC Endocrine Disorders* (2015) 15:73
DOI 10.1186/s12902-015-0069-3

BMC Endocrine Disorders

RESEARCH ARTICLE

Open Access

Evaluation of efficacy, safety, pain perception and health-related quality of life of percutaneous ethanol injection as first-line treatment in symptomatic thyroid cysts



Jordi L. Reverter^{1*}, Núria Alonso¹, Marta Avila², Anna Lucas¹, Dídac Mauricio¹ and Manel Puig-Domingo¹

Table 1 Cyst volume results

	<15 ml (<i>n</i> = 15)	>15 ml (<i>n</i> = 15)	<i>P</i> value
Baseline volume (ml)	8.4 ± 4.1	28.8 ± 13.1	0.001
Final volume (ml)	1.6 ± 1.5	1.9 ± 2.9	0.7
Volume reduction (%)	78.1 ± 15.8	93.7 ± 7.5	0.002

Results on calculated cyst volume and percentage of volume reduction in patients treated with percutaneous ethanol injection treatment (PEIT) according to their initial volume



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Hindawi
Journal of Thyroid Research
Volume 2017, Article ID 9536479, 4 pages
<https://doi.org/10.1155/2017/9536479>



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Research Article

Outcome, Pain Perception, and Health-Related Quality of Life in Patients Submitted to Percutaneous Ethanol Injection for Simple Thyroid Cysts

Roberto Negro,¹ Ermenegildo Colosimo,² and Gabriele Greco¹

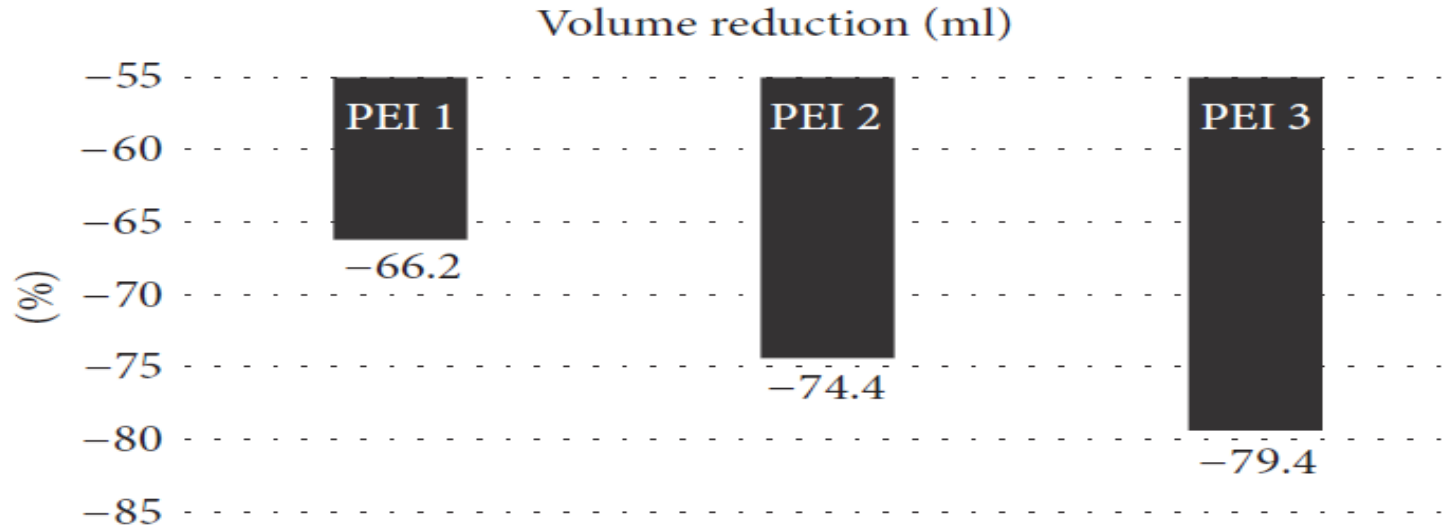


FIGURE 1: Volume reduction of thyroid cyst.



Research Article

Outcome, Pain Perception, and Health-Related Quality of Life in Patients Submitted to Percutaneous Ethanol Injection for Simple Thyroid Cysts

Roberto Negro,¹ Ermenegildo Colosimo,² and Gabriele Greco¹

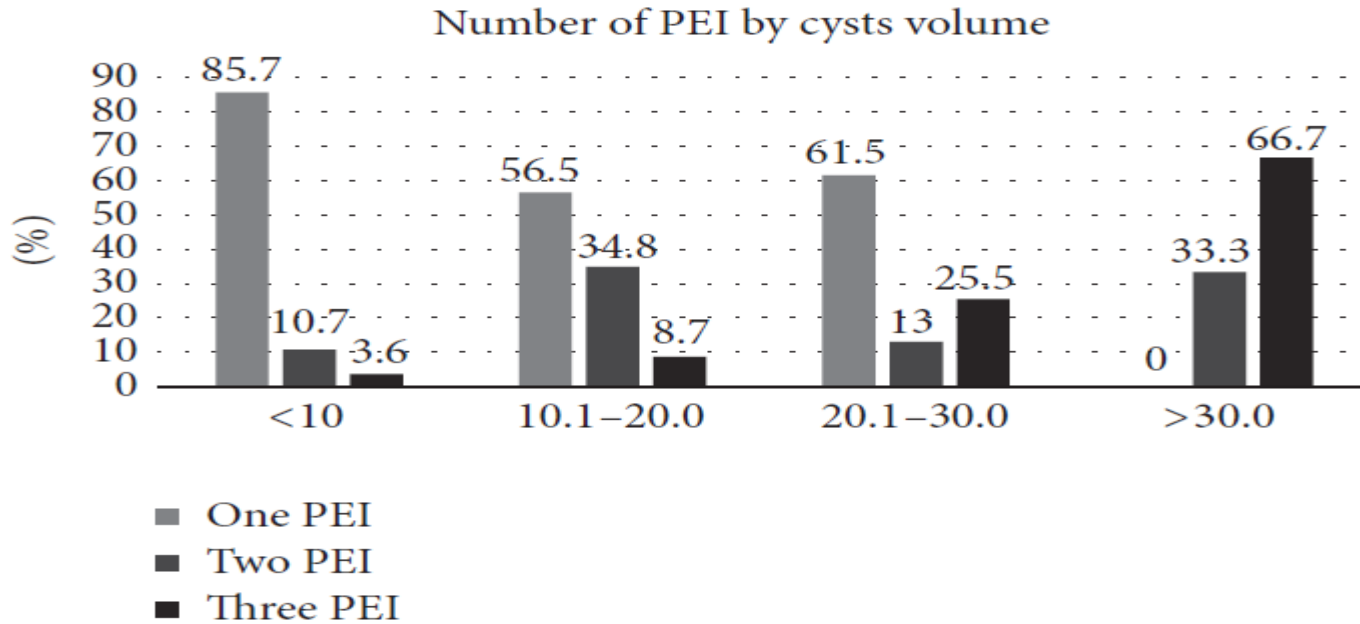


FIGURE 2: Number of percutaneous ethanol injections (PEI) practiced for thyroid cysts divided by baseline volume.



14. Which is the Cost of PEI ?



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Thyroid Cysts

- PEI (9929) two session (DH) = 476 €
- Surgery (conventional) = 3450 €

No Hypothyroidism after PEI

Italian National Institute of Health Refunds



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ITALIAN CHAPTER

15. Which Conclusion?



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Indications and limitations of PEI

Conclusion 1



ITALIAN CHAPTER



- aspiration by itself may cure a few thyroid cysts but relapse is common and surgery is often the final treatment of large recurring lesions
- PEI is highly effective in the treatment of thyroid cysts and of complex thyroid nodules
- the cost of PEI is quite low as the procedure is rapid and needs to be performed an average of 2 times to be effective



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Indications and limitations of PEI

Conclusion 2



ITALIAN CHAPTER



- PEI treatment of cystic lesions is well tolerated and the procedure is completed in about 15'
- surgery is more expensive, time-consuming with risk to produce transient or permanent complications



Thank you for attention



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Alberto Sughi: Viaggio di notte (1955)