

ORIGINAL ARTICLE

Long-term efficacy evaluation of a protocol for the management of symptomatic thyroid cysts with ultrasound-guided percutaneous ethanol injection



Jordi L. Reverter^{a,b,c,*}, Federico Vázquez^{a,b}, Carlos Puig-Jové^{a,b},
Alejandra Pérez-Montes de Oca^{a,b}, Manuel Puig-Domingo^{a,b,c}

^a Endocrinology and Nutrition Service, Germans Trias i Pujol Hospital and Research Institute, Badalona, Spain

^b Department of Medicine, Autonomous University of Barcelona, Spain

^c CIBERER, Instituto Carlos III, Madrid, Spain

Received 3 February 2020; accepted 10 July 2020

KEYWORDS

Thyroid cyst;
Percutaneous ethanol
injection;
Ultrasound

Abstract

Aim: To evaluate the long-term efficacy of percutaneous ethanol injection treatment (PEIT) as an alternative to thyroid surgery in symptomatic thyroid cysts.

Patients and methods: 100 subjects (48 ± 12 years; 58% women) with symptomatic thyroid cysts relapsing after drainage were prospectively included. PEIT was conducted using an established procedure, and the initial cyst volume, symptoms and pain perceived by the patient were assessed. The volume of instilled alcohol was ≤ 2 ml without re-extraction in all cases. Patients were followed-up for more than 3 years and final cyst volume and symptom improvement were assessed.

Results: Mean maximum cyst diameter before drainage was 3.1 ± 1.2 cm. In 71% of patients ≤ 2 PEIT sessions were required. Median maximum cyst volume was 12.7 (5.4–21.7) ml before the first drainage and median total volume extracted from the cysts was 13.0 (6.2–37.0) ml. After a mean follow-up period of 52 ± 10 months, 98% of patients reported a complete absence of symptoms. The final median volume for the whole group was 0.8 (0.1–2.0) ml with a median volume reduction of 94 (81–99)%. A final volume reduction greater than 65% was observed in 90% of cases. Reported pain during the procedure was absent or mild in 76.4% of cases.

Conclusions: PEIT is a safe and well-tolerated first-line treatment for symptomatic thyroid cysts with long-term effectiveness.

© 2020 SEEN y SED. Published by Elsevier España, S.L.U. All rights reserved.

* Corresponding author.

E-mail address: reverter.germanstrias@gencat.cat (J.L. Reverter).

PALABRAS CLAVE

Quistes tiroideos;
Inyección percutánea
de etanol;
Ecografía

Evaluación a largo plazo de la eficacia de un protocolo en el manejo de quistes tiroideos sintomáticos mediante inyección percutánea de etanol guiada por ecografía

Resumen

Objetivo: Evaluar la eficacia a largo plazo del tratamiento de inyección percutánea de etanol (IPE) como alternativa a la cirugía tiroidea en quistes tiroideos sintomáticos.

Pacientes y métodos: Se incluyeron 100 sujetos (48-12 años; 58% mujeres) con quistes tiroideos sintomáticos recidivados. Se realizó una IPE utilizando un procedimiento establecido, evaluando los síntomas, el volumen inicial del quiste y el dolor percibido por el paciente. El volumen de alcohol administrado fue ≤ 2 ml sin reextracción en todos los casos. Se realizó un seguimiento superior a los tres años y se evaluó el volumen final del quiste y la mejoría sintomática.

Resultados: El diámetro máximo medio de los quistes previo al drenaje fue de $3,1 \pm 1,2$ cm. En el 71% de los pacientes se requirieron ≤ 2 sesiones de IPE. La mediana del volumen máximo de los quistes previo al drenaje fue de 12,7 (5,4-21,7) ml y la del volumen total extraído de 13,0 (6,2-37,0) ml. Después de un período medio de seguimiento de 52 ± 10 meses en el 98% de los pacientes se consiguió la desaparición completa de los síntomas. El volumen final de todo el grupo fue de 0,8 (0,1-2,0) ml con una reducción del volumen del 94 (81-99)%. En el 90% de los casos se observó una reducción media del volumen final superior al 65%. El dolor notificado periprocedimiento fue nulo o leve en el 76,4% de los casos.

Conclusiones: La IPE es un tratamiento seguro y bien tolerado y por tanto de primera línea en el tratamiento de quistes tiroideos sintomáticos con eficacia demostrada a largo plazo.

© 2020 SEEN y SED. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Thyroid cysts are mostly benign lesions that can produce compressive or esthetic symptoms depending on size and location and are characterized by their liquid content. After percutaneous drainage, the majority refill and symptoms reappear.¹ In the last two decades, a new minimally invasive sonography-guided approach known as percutaneous ethanol injection treatment (PEIT) has been proposed as a safe and effective conservative alternative to open surgical excision²⁻⁵ with significant improvement of symptoms and health-related quality of life.^{8,9} Although PEIT is currently considered a first-line treatment for symptomatic thyroid cysts, this therapeutic is not always included in clinical guidelines^{10,12} and publications on its long-term results are scarce.^{13,14} Additionally, a standardized procedure has not been established and there are significant differences among authors regarding important issues such as optimal needle diameter, the volume of alcohol instilled, the re-aspiration or retention of alcohol, the number and interval of PEIT treatment sessions, and the length of follow-up.^{15,16} Here we report on the long-term effectiveness of our own PEIT protocol in a group of patients with symptomatic recurrent thyroid cysts.

Material and methods

A series of consecutive patients referred for evaluation of a cervical nodule or nodular goiter with cystic component and treated at the outpatient clinic of Endocrinology and Nutrition Department of Germans Trias i Pujol University Hospital in Badalona, Spain, were prospectively included in the study.

A case was considered for PEIT if it met all the following criteria: (1) age >18 years; (2) normal thyroid function tests; (3) no major comorbidities; (4) no history of neck irradiation; (5) cystic or predominantly cystic (>80% cystic component) thyroid nodule relapsed after the first simple drainage; (6) a benign cytopathological study and (7) compressive symptoms or esthetic complaints. All patients were followed-up for more than 3 years. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Human Research Ethics Committee of the Hospital Germans Trias i Pujol. All participants gave their written informed consent.

In all cases, the patient's medical history was reviewed, a physical examination was performed and blood samples were obtained for hormone measurement (serum-free thyroxine, fT4 and TSH), and thyroid anti-peroxidase and anti-thyroglobulin antibodies.

Ultrasound examination

An echographic examination was performed on each patient by an experienced operator (JLR) using a 12–15 MHz linear transducer device (General Electric Logiq E9®). Morphological evaluation included description of the thyroid echostucture and measurement of the diameters and ultrasound characteristics of each detected nodule. Volumetric assessment of the nodules was based on the use of an ellipsoid model.¹⁷ With this rotating ellipsoid model, the height, width and depth of each nodule were measured and used to calculate the nodule's volume, with the obtained result then multiplied by the mathematical correction factor 0.524.¹⁰ Fine-needle aspiration (FNA) was performed in all cases to obtain cytologic samples and rule out

malignancy in the capsule or solid portion of the cyst¹⁰ and also to drain the liquid content, and cytological analysis was performed. Patients were offered PEIT if (1) the cyst presented significant regrowth as indicated by the reappearance of compressive symptoms or esthetic complaints after the first drainage, (2) the cytological analysis of the first aspiration had been benign and (3) the patient preferred not to undergo thyroid surgery after extensive explanation of the procedure.

Percutaneous ethanol injection treatment procedure

All PEIT procedures were performed by the same operator (JLR) with 10 years of experience in ultrasound-guided techniques. The positions of patient and operator were similar to those adopted during the FNA procedure, with the patient lying supine with their neck in hyperextension. After skin sterilization, and under ultrasound guidance, a 0.5–0.8 mm needle mounted on a connector with a line extension and a 20 ml syringe were used to empty the contents of the cyst. Subsequently, 99% ethanol was injected in successive 0.2 ml amounts, with a slow movement of the needle to reach the major part of the inner face of the cyst capsule. The patient was instructed to signal any feeling of pain. The amount of ethanol injected was approximately 30% of the volume of liquid extracted, with a maximum of 2 ml. The needle tip was constantly monitored during the procedure in order to ensure that it remained within the cyst. In no case were more than 2 ml injected. The ethanol was not re-extracted and patients were discharged after a 20–30-min observation period.

Follow-up

Patients were followed up biweekly for one month, monthly for three months and every three months thereafter. Ultrasound examination was performed at each appointment to evaluate the characteristics and volume of the residual lesion. TSH and thyroid auto-antibodies were performed annually.

In cases of symptomatic cyst regrowth confirmed by echography, a new PEIT was performed with the same protocol followed by weekly appointments. This procedure was repeated until a permanent and significant reduction of the cyst was achieved, defined as a complete resorption or a reduction of at least 50% compared to the initial value with a significant reduction in symptoms. No pre-established limits were set on the number of PEIT procedures.

Response parameters

In each patient, the percentage of volume reduction was calculated by the formula $[(V1 - V2)/V1] \times 100$ in which V1 is the initial cyst volume and V2 the final cyst volume.

Patients were asked to rate the degree of pain they had felt during with the alcohol injection immediately after the procedure, using a 10-cm visual analog scale (VAS) with one end indicating 'no pain' (0) and the other 'excruciating pain'

(10) and each third of the scale corresponding, from lowest to highest, to mild pain, moderate pain and severe pain.

In order to assess the specific symptoms of neck cysts, patients were administered a 10-item questionnaire related to the symptoms of goiter most frequently described in the literature, namely visible enlargement of the neck (cosmetic complaint), a feeling of pressure in the neck, throat pressure, sore throat, pain in the throat radiating to the ears, difficulty in swallowing, throat clearing often, shortness of breath and hoarseness. Patients had to rate each item for frequency ('1 none of the time, 2 very occasionally, 3 some of the time, 4 most of the time and 5 all of the time'), and the final score was the sum of the ten items. These scores were then classified as 'absence of symptoms' (<10), 'mild symptoms' (11–20), 'moderate symptoms' (21–30), 'intense symptoms' (31–40) and 'worst possible symptoms' (40–50). Compressive symptoms involving the trachea, if present, were evaluated by chest X-ray.

Statistical analysis

All continuous normally distributed values were given as mean \pm SD and all other values were given as median (interquartile range) and categorical variables as percentages. Student's *t*-test was used for comparisons between continuous variables. For comparison of categorical variables, the chi-square test or Fisher's exact test was used where appropriate. For the correlation studies it was required that Pearson's coefficient be greater than $r \geq .25$. A *p* value <.05 was considered statistically significant. Data analyses were carried out using the Statistical Package for Social Sciences, Version 15.0 (SPSS®, Chicago, IL, USA).

Results

Of the initial cohort of 102 patients, two cases (1.9%) presented no recurrence of thyroid cyst after the first FNA drainage and sample collection for cytological evaluation. Therefore, a total of 100 subjects with symptomatic thyroid cysts (48 ± 12 years; 58% women) were included in the protocol. Mean duration of symptoms was 8 (1–12) months and in all cases. Mean TSH was within the normal range (2.0 ± 1.4 mU/L) and positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies were detected in 4.5% of patients. The most frequent symptoms reported by patients were compressive (91%) and esthetic (10%) symptoms, and throat pain (8%). The reported intensity of symptoms was 'mild' in 7% of patients, 'moderate' in 40% and 'intense' in 53%. With respect to type of cyst, 58% were pure liquid lesions with a capsule, 16% were septate cysts and 26% were mixed but predominantly cystic nodules. The cytological studies of samples obtained by FNA from the cystic nodules were benign (hemorrhagic-cystic lesion, colloid cyst or non-malignant lesion) in all cases. One case required liquefaction of the thick colloid that could be subsequently drained without difficulty with the 21G needle.

Mean maximum cyst diameter before drainage was 3.1 ± 1.2 cm with a calculated median initial volume of 12.7 (5.4–21.7) ml. Median total volume extracted from the cysts in all procedures performed in one patient was 13.0 (6.2–37.0) ml. Panels A and B in Fig. 1 show respectively the

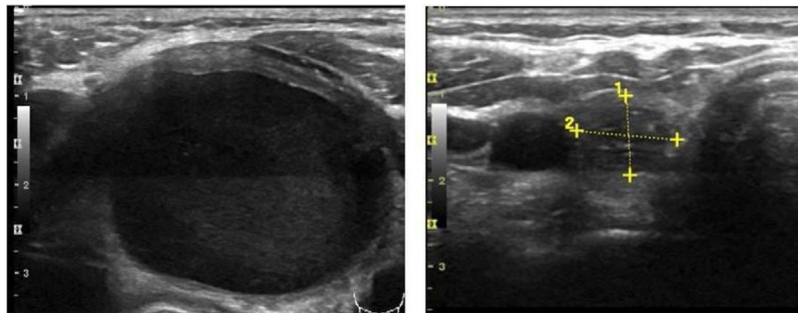


Figure 1 Initial and final ultrasound appearance of a treated thyroid cysts. Transverse ultrasound scans of one cyst before (panel A) and after (panel B) percutaneous ethanol injection treatment (PEIT), showing a marked decrease in size.

Table 1 Results obtained in patients treated with percutaneous ethanol injection treatment (PEIT) according to the initial cyst volume. Values are presented as median (interquartile range).

| | Volume (ml) | | |
|-------------------------------|---------------|-------------------------------|---------------------------------|
| | ≤10 (n=40) | 10–20 (n=29) | ≥20 (n=31) |
| Baseline volume (ml) | 5.1 (2.8–8.5) | 14.4 (13.6–18) ^{a,c} | 34.9 (23.5–42.6) ^{a,b} |
| Number of PEIT (n) | 1.9 (1–4) | 1.8 (1–5) ^c | 3.2 (1–5) ^{a,b} |
| Total fluid drained (ml) | 7.0 (4–12) | 16 (10–31) ^{a,c} | 61 (16–117) ^{a,b} |
| Alcohol injected/session (ml) | 0.9 (0.3–2) | 1.5 (0.5–2) | 1.6 (0.5–2) |
| Total alcohol injected (ml) | 1.5 (0.8–2.3) | 2.0 (1.5–4) ^c | 3.5 (2.7–9) ^{a,b} |
| Final volume (ml) | 0.4 (0–1.4) | 1.3 (0.1–2) | 1.1 (0.3–4.8) |
| Volume reduction (%) | 91 (72–98) | 92 (85–99) | 97 (87–100) ^a |

^a $p < .05$ with respect to ≤10 ml group.

^b $p < .05$ with respect to 10–20 ml group.

^c $p < .05$ with respect to ≥20 ml group.

initial and final ultrasound appearance of a treated thyroid cyst.

After a follow-up period of 52 ± 10 months, all patients reported significant symptom improvement. After treatment, 98% of patients reported a score corresponding to 'absence of symptoms', the remaining 2% perceiving 'mild symptoms'. No cases of hypo or hyperthyroidism or *de novo* appearance of anti-thyroid autoantibodies were observed.

The number of PEITs required for a permanently symptom-free situation was one in 38% of cases, two in 33%, three in 15%, and more than three in 14%. Patients requiring more than one PEIT presented significant greater initial cyst volume compared to those who required only one procedure [14.0 (8.5–33.9) ml vs. 7.6 (2.6–18.0) ml, respectively; $p < .01$]. The mean final volume for the whole group was 0.8 (0.1–2.0) ml with a mean volume percentage reduction of 94 (81–99)%. A final volume reduction greater than 65% was observed in 90% of the patients and a reduction greater than 85% in 70% of all cases. In 4 patients, follow-up ultrasound examination showed total disappearance of the lesion.

With regard to nodule characteristics, cystic nodules were significantly greater than mixed nodules in baseline volume [14.2 (8.1–24.7) vs. 8.5 (3.9–14.7) ml, respectively; $p = .01$]. The number of PEIT sessions required were similar [2.4 vs. 2.1, $p = .5$; respectively]. At the end of the follow-up, the final volume were similar [0.8 (0.1–1.5) vs. 1.1 (0.1–2.1) ml, respectively; $p = .02$] but pure cysts showed greater volume reduction with respect to mixed nodules [96 (86–99) vs. 87.6 (68–97)%, respectively; $p = .007$].

Table 1 summarizes the final volume observed and reduction relative to the initial volume of the cysts. No significant differences were observed between cysts of ≤10 ml, 10–20 ml and ≥20 ml regarding the final volume achieved. As expected, volume reduction and the number of PEITs required was significantly greater in nodules ≥20 ml with respect to those ≤10 ($p < .01$), but similar compared to cysts with initial volume ranging from 10 to 20 ml ($p = .2$). Larger nodules required a significantly greater number of PEITs with respect to smaller ones ($p < .01$) but not with respect to intermediate nodules ($p = .6$).

In correlation studies, final volume was significantly related to initial volume ($r = .3$), volume reduction ($r = -0.5$), and instilled ethanol ($r = .5$) ($p < .05$ in all the cases).

The two cases in which the cyst did not recur after the first simple evacuation remained asymptomatic and ultrasound examinations showed the resolution of the liquid part with a follow-up similar to that of the treated patients.

With regard to complications, reported pain during the procedure was mild in 55.2% and moderate in 23.6% of cases. Of note, virtually absent pain perception was observed in 21.2%. In all cases, this pain sensation was transient with relief within minutes. Two patients presented intranodular bleeding in one PEIT, which was self-limited with external compression and local cold application with spontaneous partial reabsorption and totally with a subsequent PEI performed two weeks after (Fig. 2). Cyst recurrence in cases

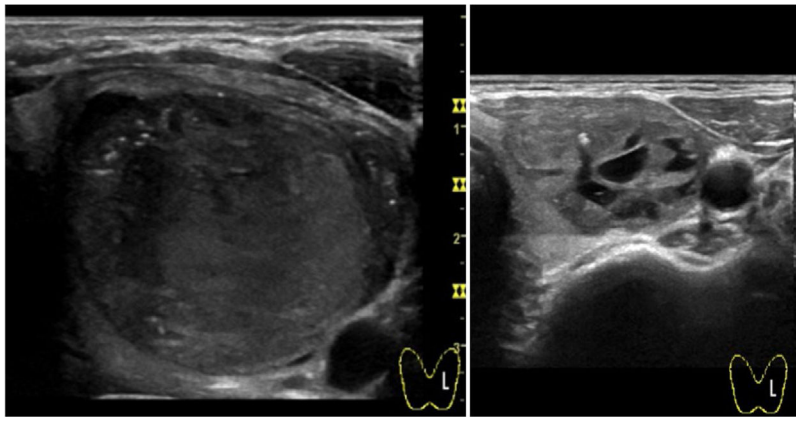


Figure 2 Intracystic hemorrhage during percutaneous ethanol injection procedure. Self-limited intracystic hemorrhage that occurred after the first drainage showing partial spontaneous absorption over time and which was totally extracted with the following PEI procedure.

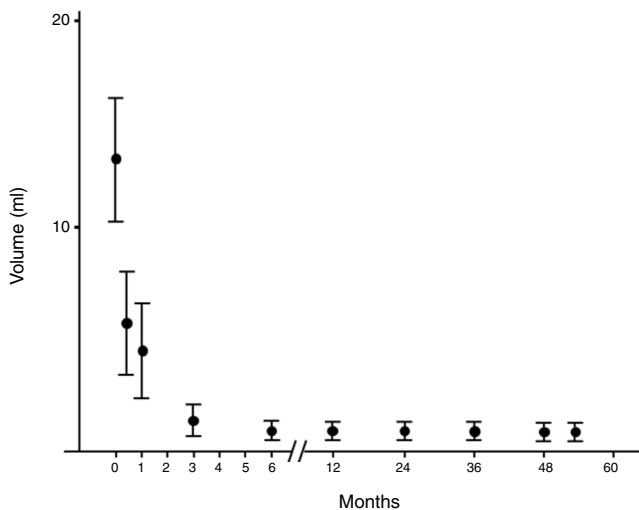


Figure 3 Evolution of the volume of cysts treated by percutaneous percutaneous ethanol injection. Evolution of the volume expressed as median (interquartile range) of the cysts treated by percutaneous alcoholization during the follow-up period. It is observed that once a significant reduction has been obtained, it persists over time.

treated more than once occurred from hours to a few days after each PEIT procedure (Fig. 3).

Discussion

The results presented in this report clearly demonstrate that percutaneous ethanol treatment is a safe procedure with long-term effectiveness in cases of symptomatic benign thyroid cysts which achieves significant volume reduction of cysts and a total disappearance of symptoms in practically all patients without significant complications. With respect to patient comfort, with our protocol pain was reported to be virtually absent or only mild in most patients and in no case was reported to be greater than moderate. This well-tolerated discomfort is similar to what we⁸ and other groups have previously reported^{16,2} and confirm that PEIT is safe

and comfortable and no local anesthesia is necessary. The following characteristics of our protocol deserve to be highlighted and in our experience they have proven to be safe and effective

Needle diameter

We used a needle diameter not greater than 0.8 mm, which was good enough to remove the cyst contents even when it was dense colloid. Liquefaction through the introduction of alcohol allowed in one of our cases the extraction of the content, and it was not necessary to consider thicker needles. The pain caused by such a needle gauge tends to be limited. Furthermore, in cases in which the first drainage extracted a clear liquid, a fine 0.5 mm needle diameter was used with efficacy. This technique is similar to that described in some published protocols¹⁸ while others report using larger diameter needles, with greater risk of pain and complications.^{16,19} In light of our results, we do not advise the use of needles over 0.8 mm in diameter.

Needle connector

In our protocol, the needle was connected to a line extension. The flexibility of this set-up allows the needle to be mobilized without difficulty and without causing injuries while also allowing it to be collapsed to change extraction syringes and for the instillation of alcohol. To the best of our knowledge, there is no description of this technique elsewhere in the literature.

Alcohol retention

In our experience, retention (as opposed to re-aspiration) of the ethanol inside the cyst cavity is safe and effective and reduces PEIT time. Some authors have reported similar results comparing ethanol retention and aspiration but have found less reported pain with the aspiration technique.¹⁶ The 2–5 min with the needle inserted in place, increases the duration of the procedure and probably produces discomfort in the patient. The retention technique reduces the

number of injections and minimizes the risk of needle protrusion from the cyst cavity due to longer procedure. The consistent results obtained here in volume reduction and the considerable number of patients who expressed having suffered no pain at all or only mild pain are clear arguments in favor of using alcohol retention as a technique.

Initial simple aspiration and cytology

We offered PEIT after confirming the benignity of the lesion by fluid aspiration and cytological examination of the solid parts of the cyst, and the refilling of cysts that occurred in all cases except two. Previous studies have not described this aspect clearly.^{4,6,7,9,13} Although we confirm a high recurrence rate (98%), it is reasonable to perform a first simple drainage and wait for cytological results and eventual refill, which tends to be the case, or stable cyst collapse.

Number of PEIT

In our protocol, though the number of PEIT sessions required ranged from one to eight, it should be noted that 71% of patients showed disappearance of symptoms and significant cyst reduction after just one or two procedures. This result is similar to previous reports^{20,21} and, depending on the initial cyst volume, patients can be advised in advance about the number of procedures that may prove necessary.

Volume of ethanol injected

There is a great diversity of opinion in the literature regarding the volume of ethanol instilled in each PEIT.^{18,22,23} The most frequent approach is to introduce 50% of the liquid volume extracted with a maximum limit that ranges from 2 ml^{8,24} to 10 ml.^{11,15} However, greater amounts have been described in the literature.²⁵ We use a maximum ethanol volume of less than 2 ml in all cases to minimize pain and decrease the risk of ethanol leakage. In addition, the shrinkage of the cyst walls after liquid extraction allows a broad exposure to ethanol.

The main strengths of our study are its prospective nature, with a systematic and homogeneous procedure in all cases performed by the same experienced thyroid and ultrasound expert, and the overall 4-year follow-up, in which no cyst refilling was observed one month after the last treatment performed.

The official recommendations for the treatment of symptomatic thyroid cysts in the published guidelines^{10,11} propose that recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection based on compressive symptoms and cosmetic concerns (weak recommendation, low-quality evidence). In addition, some authors note as a drawback of PEIT that the procedure may require several injections of large or multilocular thyroid cysts.¹¹ Based on the results described in this and a previous study with more than a hundred patients treated, and with the evidence reported by others in the literature,^{13,14} we recommend that PEIT should be included as the treatment of choice after a failed drainage and confirmation of benignity. The repeated

number of procedures, which in any case did not exceed three in 86% of the cases reported here, would not seem to be an impediment considering the tolerability, safety and efficacy of the technique.

In conclusion, the introduction of ultrasound-guided percutaneous techniques such as radiofrequency, microwaves, lasers and ablation with ethanol, among others, are changing the paradigm in the management of benign thyroid nodules by reducing the number of cases referred to surgery and thus decreasing the risk of major and invalidating complications. We have demonstrated that PEIT for the treatment of thyroid cysts is an effective and safe method for improving and eliminating symptoms over the long term that causes little pain and has minimal complications. We support the inclusion of PEIT as a first-line treatment for thyroid cysts prior to surgical removal in future guidelines. Finally, we suggest that the specific protocol we have described here could be used to create a consensual procedural model.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no conflict of interest associated regarding the publication of this article.

References

- Burman KD, Wartofsky L. Thyroid nodules. *N Eng J Med*. 2015;373:2347–56, <http://dx.doi.org/10.1056/NEJMc1415786>.
- Bennedbaek FN, Hegedüs L. Treatment of recurrent thyroid cysts with ethanol: a randomized double-blind controlled trial. *J Clin Endocrinol Metab*. 2003;88:5773–7, <http://dx.doi.org/10.1210/jc.2003-031000>.
- Monzani F, Lippi F, Goletti O, Del Guerra P, Caraccio N, Lippolis PV, et al. Percutaneous aspiration and ethanol sclerotherapy for thyroid cysts. *J Clin Endocrinol Metab*. 1994;78:800–2, <http://dx.doi.org/10.1210/jcem.78.3.8126160>.
- Cho YS, Lee HK, Ahn IM, Lim SM, Kim DH, Choi CG, et al. Sonographically guided ethanol sclerotherapy for benign thyroid cysts: results in 22 patients. *AJR Am J Roentgenol*. 2000;174:213–6, <http://dx.doi.org/10.2214/ajr.174.1.1740213>.
- Guglielmi R, Pacella CM, Bianchini, Bizzarri G, Rinaldi R, Graziano FMA, et al. Percutaneous ethanol injection treatment in benign thyroid lesions: role and efficacy. *Thyroid*. 2004;14:125–31, <http://dx.doi.org/10.1089/105072504322880364>.
- Valcavi R, Frasoldati A. Ultrasound-guided percutaneous ethanol injection therapy in thyroid cystic nodules. *Endocr Pract*. 2004;10:269–75, <http://dx.doi.org/10.4158/EP.10.3.269>.
- Gharib H, Hegedüs L, Pacella CM, Baek JH, Papini E. Nonsurgical, image-guided, minimally invasive therapy for thyroid nodules. *J Clin Endocrinol Metab*. 2013;98:3949–57, <http://dx.doi.org/10.1210/jc.2013-1806> [clinical review].
- Reverter JL, Alonso N, Avila M, Lucas A, Mauricio D, Puig-Domingo M. Evaluation of efficacy, safety, pain perception and health-related quality of life of percuta-

- neous ethanol injection as first-line treatment in symptomatic thyroid cysts. *BMC Endocr Disord.* 2015;15:73, <http://dx.doi.org/10.1186/s12902-015-0069-3>.
9. Negro R, Colosimo E, Greco G. Outcome pain perception, and health-related quality of life in patients submitted to percutaneous ethanol injection for simple thyroid cysts. *J Thyroid Res.* 2017;9536479, <http://dx.doi.org/10.1155/2017/9536479>.
 10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2015;26:1–13, <http://dx.doi.org/10.1089/thy.2015.0020>.
 11. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, et al. AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract.* 2010;16:1–43, <http://dx.doi.org/10.4158/EP.16.3.468>.
 12. Martin-Hernandez T, Diez-Gomez JJ, Diaz-Soto G, Torres A, Navarro E, Oleaga A, et al. Consensus statement for use and technical requirements of thyroid ultrasound in endocrinology units. *Endocrinol Diabetes Nutr.* 2017;64:23–30, <http://dx.doi.org/10.1016/j.endinu.2016.10.007>.
 13. Zingrillo M, Tortolano M, Chiarella R, Ghiggi MR, Nirchio V, Bisceglia M, et al. Percutaneous ethanol injection may be a definitive treatment for symptomatic thyroid cystic nodules not treatable by surgery: five-year follow-up study. *Thyroid.* 1999;9:763–7, <http://dx.doi.org/10.1089/thy.1999.9.763>.
 14. Del Prete S, Caraglia M, Russo D, Vitale G, Giuberti G, Marra M, et al. Percutaneous ethanol injection efficacy in the treatment of large symptomatic thyroid cystic nodules: ten-year follow-up of a large series. *Thyroid.* 2002;12:815–21, <http://dx.doi.org/10.1089/105072502760339398>.
 15. Barile A, Quarchioni S, Bruno F, Ierardi AM, Arrigoni F, Giordano AV, et al. Interventional radiology of the thyroid gland: critical review and state of the art. *Gland Surg.* 2018;7:132–46, <http://dx.doi.org/10.21037/gs.2017.11.17>.
 16. Park HS, Yim Y, Baek JH, Choi YJ, Shong YK, Lee JH. Ethanol ablation as a treatment strategy for benign cystic thyroid nodules: a comparison of the ethanol retention and aspiration techniques. *Ultrasonography.* 2019;38:166–71, <http://dx.doi.org/10.14366/usg.18033>.
 17. Shabana W, Peeters E, De Maeseneer M. Measuring thyroid gland volume: should we change the correction factor? *AJR Am J Roentgenol.* 2006;186:234–6, <http://dx.doi.org/10.2214/AJR.04.0816>.
 18. Felicio JS, Conceição AM, Santos FM, Sato MM, Bastos Fde A, Braga de Souza AC, et al. Ultrasound-guided percutaneous ethanol injection protocol to treat solid and mixed thyroid nodules. *Front Endocrinol (Lausanne).* 2016;7:52, <http://dx.doi.org/10.3389/fendo.2016.00052>.
 19. Gong X, Wang F, Du H, Chen X, Shi B. Comparison of ultrasound-guided percutaneous polidocanol injection versus percutaneous ethanol injection for treatment of benign cystic thyroid nodules. *J Ultrasound Med.* 2018;47:1423–9, <http://dx.doi.org/10.1002/jum.14482>.
 20. Popoveniuc G, Jonklaas J. Thyroid nodules. *Med Clin North Am.* 2012;96:329–49, <http://dx.doi.org/10.1016/j.mcna.2012.02.002>.
 21. Papini E, Pacella CM, Hegedus L. Diagnosis of endocrine disease: thyroid ultrasound (US) and US-assisted procedures: from the shadows into an array of applications. *Eur J Endocrinol.* 2014;170:133–46, <http://dx.doi.org/10.1530/EJE-13-0917>.
 22. Perez CL, Figuera TM, Miasaki F, Mesa Junior CO, Paz Filho GJ, Graf H, et al. Evaluation of percutaneous ethanol injections in benign thyroid nodules. *Arq Bras Endocrinol Metabol.* 2014;58:912–7, <http://dx.doi.org/10.1590/0004-2730000003444>.
 23. Lee SJ, Ahn IM. Effectiveness of percutaneous ethanol injection therapy in benign nodular and cystic thyroid diseases: long-term follow-up experience. *Endocr J.* 2005;52:455–62, <http://dx.doi.org/10.1507/endocrj.52.455>.
 24. Halenka M, Karasek D, Frysak Z. Ultrasound-guided percutaneous ethanol injection of small and medium-sized thyroid cysts with relatively small amounts of ethanol. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2015;159:417–21, <http://dx.doi.org/10.5507/bp.2014.009>.
 25. Kim DW, Rho MH, Kim HJ, Kwon JS, Sung YS, Lee SW. Percutaneous ethanol injection for benign cystic thyroid nodules: is aspiration of ethanol-mixed fluid advantageous? *Am J Neuroradiol.* 2005;26:2111–27.