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ORIGINAL ARTICLE

Minimally invasive techniques for the management of benign thyroid nodules: Efficacy and impact on quality of life of percutaneous ethanol injection. Results from a high-resolution thyroid nodule unit

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KEYWORDS
Thyroid ultrasound;
Minimally invasive techniques;
Thyroid nodule

Abstract
Background and objective: The high incidence of thyroid nodular disease has raised concerns on the therapeutic management of benign thyroid nodules. The development of minimally invasive techniques is an alternative to surgery and has a low rate of complications. Our objective was to evaluate the safety and efficacy profile of percutaneous ethanol injections (PEI) with ethanol aspiration of symptomatic cystic and predominantly cystic thyroid nodules (cystic component > 50%) treated in the thyroid nodule high-resolution unit (TNHRU) of Hospital de Tortosa Verge de la Cinta Hospital, Tarragona, Spain.
Patients and methods: The present work is a prospective, observational and descriptive study of 32 patients (87.5% women, mean age of 43; SD, 12) evaluated at the TNHRU from August 2022 through December 2023. Demographic data such as age, sex, previous thyroid function, diagnostic method, initial nodular volume, nodular composition and nodular location were analyzed. Using ultrasounds, measurements of diameters and thyroid nodule volume were taken.

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We aspirated a total of 50% of the cystic content and injected between 2 mL and 5 mL of 99% ethanol (depending on cystic volume). After letting the ethanol act inside the nodule for 5 to 10 minutes, all the cystic content and the injected ethanol were aspirated. We performed an ultrasound follow-up at 1, 3 and 6 months, calculating the total volume and the volume reduction rate (VRR). The impact on health-related quality of life (HRQoL) was assessed using the ThyPRO-39es questionnaire, which was administered before and after the PEI treatment at the 6-month follow-up.

Results: The median volume reduction at the end of the 6-month follow-up was 0.23 mL (0.00–0.67), and the VRR, 98.57% (94.80–100.00). The difference between the initial volume and the mean volume at the 1-, 3-, and 6-month follow-ups was statistically significant, as was the VRR between the 1-month and the 3- and 6-month follow-ups. Six patients (18.80%) required 2 PEIs and only 2 patients (6.3%) required 3 PEIs. The overall quality of life, which was scored from 0 (good) to 4 (poor), significantly improved from 1.28; SD, 0.81 up to 0.19; SD, 0.40 ($p < 0.001$).

Conclusions: PEI is an effective alternative to treat cystic thyroid nodules resulting in an improved patients' HRQoL. It can be performed outpatiently with a low rate of complications, thus making it suitable for inclusion in the service portfolio of a HRTNU.

PALABRAS CLAVE
Ecografía tiroidea;
Técnicas mínimamente invasivas;
Nódulo tiroideo

Técnicas mínimamente invasivas para el manejo de los nódulos tiroideos benignos: eficacia e impacto sobre la calidad de vida de la inyección percutánea de etanol. Resultados en una unidad de alta resolución de nódulo tiroideo

Resumen

Antecedente y objetivo: La alta incidencia de la patología nodular tiroidea ha hecho que crezca la preocupación sobre el manejo terapéutico de los nódulos tiroideos benignos. El desarrollo de técnicas mínimamente invasivas (TMI) supone una alternativa a la cirugía con una baja tasa de complicaciones. Nuestro objetivo es evaluar la eficacia y el impacto sobre la calidad de vida relacionada con la salud (CVRS) del tratamiento mediante inyección percutánea de etanol (IPE) de los nódulos tiroideos sintomáticos, quísticos y mixtos de predominio quístico (componente quístico >50%) tratados en la unidad de alta resolución (UARNT) del Hospital Verge de la Cinta.

Pacientes y métodos: El presente trabajo es un estudio prospectivo, observacional y descriptivo en 32 pacientes (87.5% mujeres, una edad media de 43 de = 12) evaluados en la UARNT durante el periodo de Agosto 2022-Diciembre 2023. Se analizaron datos demográficos (edad y sexo), función tiroidea previa, forma de diagnóstico, volumen nodular inicial, composición y localización nodular. Mediante ecografía se realizaron mediciones de diámetros y volumen, aspiramos el 50% del contenido quístico e inyectamos entre 2-5 ml de etanol al 99% (según volumen quístico). Tras dejar actuar el etanol durante 5-10 minutos se procede a aspirar todo el contenido quístico y el etanol inyectado. Realizamos un seguimiento ecográfico al mes, 3 y 6 meses, calculando el volumen total y la tasa de reducción de volumen (TRV). Se valoró el impacto sobre la CVRS mediante el cuestionario ThyPRO-39es que se administró antes de la IPE y posterior al control de 6 meses.

Resultados: La mediana de reducción de volumen al final del periodo de seguimiento de 6 meses fue de 0,23 (0,00-0,67) ml y la TRV del 98,57% (94,80-100,00), siendo estadísticamente significativa la diferencia tanto entre el volumen inicial y el volumen medio en los controles al mes, 3 meses y 6 meses como la TRV entre el control al primer mes y los controles a los 3 y 6 meses. 6 pacientes precisaron (18,80%) precisaron dos sesiones de IPE y solo 2 pacientes (6,3%) precisaron 3 sesiones de IPE. La calidad de vida general, que se puntuó de 0 (buena) a 4 (mala), mejoró de 1,28 de = 0,81 a 0,19 de = 0,40 de forma significativa ($p < 0,001$).

Conclusiones: La IPE es una alternativa eficaz para el tratamiento de los nódulos tiroideos quísticos asociando una mejoría de la CVRS de los pacientes. Puede realizarse de forma ambulatoria asociando una baja tasa de complicaciones, por lo que puede incluirse en la cartera de servicios de una UARNT.

Introduction

Thyroid nodular disease has a prevalence of nearly 60%, depending on how it is detected (through physical examination or via imaging modalities). Most lesions are benign, do not require treatment, and can be monitored via ultrasound.[1,2]

Cystic or mixed nodules with a predominant cystic component (> 50% cystic component) account for 20% of thyroid nodular disease.[3] Although thyroid cysts are generally benign they can be symptomatic in some cases. Symptom relief can be achieved by simply aspirating the cystic material. However, this technique is associated with a high recurrence rate, close to 80% of cases.[4,5]

Surgery has traditionally been the first-line therapy for benign thyroid nodules. However, since the emergence of minimally invasive techniques (MIT), current clinical practice guidelines position percutaneous ethanol injection (PEI) as the first-line therapy for cystic thyroid nodules.[6,7] The efficacy and safety of PEI have been demonstrated in several studies, including clinical trials conducted on large cohorts and meta-analyses.[8] However, despite the widespread use of PEI, its impact on health-related quality of life (HRQoL) has not been fully studied.[9–11] Additionally, there are still aspects related to the PEI technique—required ethanol volume, whether to aspirate the injected ethanol—that are not fully defined in clinical practice guidelines.[12]

The objective of our study is to analyze the efficacy and effects on the quality of life of patients undergoing PEI in the High-Resolution Thyroid Nodule Unit (UARNT) of Hospital de Tortosa Verge de la Cinta, Tarragona, Spain (the referral center for the Terres de l'Ebre Health Management).

Patients and methods

We conducted a prospective, observational, and descriptive study to analyze the efficacy of PEI performed at Hospital de Tortosa Verge de la Cinta UARNT. For this purpose, we studied a total of 32 patients with cystic thyroid nodules who underwent PEI from August 2022 through December 2023 (Fig. 1). This study was approved by L'institut d'Investigació Sanitària Pere Virgili Ethical Committee for Drug Research.

All patients had cystic nodules with a volume > 5 mL and reported discomfort related to thyroid nodular disease (sensation of a cervical foreign body, cosmetic discomfort, and/or compressive symptoms). Patients included in the study had to be older than 18 years and without any major comorbidities. All patients received detailed information about the procedure and signed an informed consent form.

Procedure description

Thyroid ultrasound and PEI were performed by 2 operators trained in thyroid ultrasound and MIT applied to thyroid nodules: PEI and radiofrequency ablation (RFA). The Phillips Affiniti 50 G ultrasound machine with a 9–14 MHz linear probe was used for the ultrasound evaluation.

First, an ultrasound assessment of the lesion was performed following this scheme:

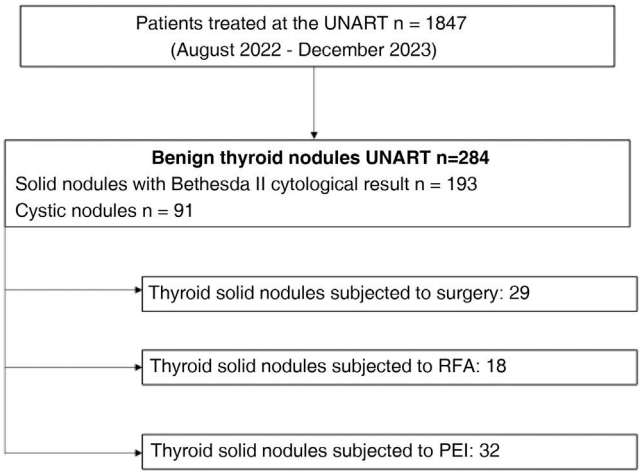

Figure 1 Flowchart: total number of patients seen at the high-resolution thyroid nodule unit (UARNT). Total benign nodules (solid with Bethesda II cytological results and cystic). Total benign thyroid nodules undergoing surgery vs minimally invasive techniques.

1 Evaluation of the cystic or predominantly cystic component, following the ACR-TIRADS 2017 criteria.[13]
2 Measurement of the anteroposterior, transverse, and longitudinal diameters.
3 Calculation of thyroid volume following the formula proposed by the American Thyroid Association (ATA)[1]: AP diameter × T diameter × L diameter × $\pi/6$.

After explaining the procedure in detail and the possible associated complications, the patients signed the informed consent form and were scheduled at the UARNT to undergo outpatient PEI.

Prior to the intervention, antiseptic measures were taken on the neck with povidone-iodine. Patients lay on a stretcher in a supine position with the neck hyperextended. Afterwards, local pericapsular anesthesia was administered with 5% lidocaine under ultrasound guidance using a 25 G subcutaneous needle to avoid local procedure-related local discomfort.

Next, a 21 G needle was inserted under ultrasound guidance using a transisthmic approach connected to a 2-way extension tube. The needle was guided into the central cystic component of the lesion. Subsequently, the cystic content was aspirated with gentle negative pressure (to avoid abrupt emptying and bleeding of the nodular wall) until approximately 50% of the volume was evacuated. Immediately afterward, 2–4 mL of 99% ethanol was introduced.

The volume of ethanol introduced was maintained for 5–10 minutes inside the cyst to allow thrombosis of the pericapsular blood vessels and coagulative necrosis of the cyst wall. Finally, the remaining cystic content and the injected ethanol volume were aspirated to avoid ethanol leakage into adjacent tissues.

After the procedure, the patient was monitored by the day hospital endocrinology nursing staff for 45 minutes. Oxygen saturation and possible immediate complications (pain and/or local hematoma) were monitored. If clinically sta-

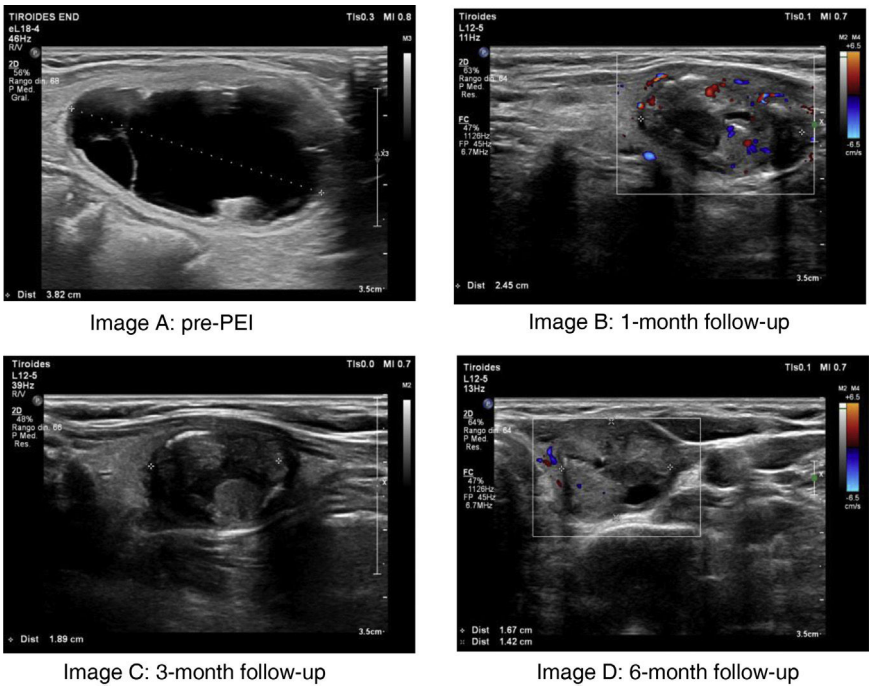

Figure 2 Initial and final ultrasound images of a thyroid nodule treated with percutaneous ethanol injection and ethanol aspiration. A) Pre-PEI cystic thyroid nodule with a maximum diameter of 3.8 cm (nodule volume, 17.10 mL). B) Color Doppler mode ultrasound image at the 1-month follow-up showing minimal peripheral Doppler uptake and a reduction in nodule size with a maximum diameter of 2.4 cm (nodule volume, 2.69 mL, VRR, 84.28%). C) Ultrasound image at the 3-month follow-up showing a reduction in nodule size with a maximum diameter of 1.89 cm (nodule volume, 1.72 mL, VRR, 89.94%). D) Color Doppler mode ultrasound image at the 6-month follolw-up showing persistent minimal peripheral Doppler uptake and almost complete disappearance of the cystic component (final nodule volume, 1.64 mL, VRR, 90.42%).

ble, the patient was discharged with clinical and ultrasound follow-up scheduled at 1, 3, and 6 months. Fig. 2 shows the evolution of a cystic thyroid nodule subjected to PEI.

Variables under study

Demographic data (age and sex), clinical data related to thyroid nodular disease (physical examination: non-palpable nodules, palpable nodules, visible on swallowing, or visible to the naked eye; symptoms: compressive dysphagia and/or dyspnea, foreign body sensation, or cosmetic discomfort; and method of diagnosis: physical examination, cervical ultrasound, CT, MRI, PET, or referral by self-perception of a cervical nodule by the patient, analytical changes, or associated compressive symptoms), biochemical data (thyrotropin [TSH] and free thyroxine [fT4]), and ultrasound data (nodule location, nodule composition, measurements of volume and anteroposterior, transverse, and longitudinal diameters) were analyzed. Nodules were classified based on whether they had an initial volume $\geq$ 15 mL or < 15 mL and whether they were purely cystic or mixed with a predominant cystic component (> 50% cystic volume).

Analysis of treatment efficacy

Follow-up visits were conducted at 1, 3, and 6 months. During these visits, the volume of the treated nodule was calculated following the formula proposed by the American Thyroid Association (ATA)[1]: AP diameter $\times$ T diameter $\times$ L diameter $\times \pi/6$, and the volume reduction rate (VRR) was defined as VRR (%) = (initial volume - post-treatment volume)/initial volume $\times$ 100. If there was a lack of response, defined as a VRR < 50%, an additional PEI session was performed. The number of treatments administered and ethanol volume used in each PEI session were recorded.

Impact on health-related quality of life

The patients' HRQoL of was evaluated using a specific questionnaire for patients with benign thyroid nodular disease that has been validated and translated into Spanish (ThyPRO-39es).[10] The ThyPRO-39 survey is a shortened version of the ThyPRO questionnaire developed by Watt et al.,[11] and consists of 4 scales that assess thyroid disease symptoms, 7 scales that evaluate physical, psychological, and social aspects, as well as the overall impact on quality of life. Each item is rated on a scale from 0 (no impact on HRQoL) to 4 (great impact on HRQoL). The questionnaire is provided to all patients with thyroid nodular disease undergoing MIT before and at the 6-month follow-up visit as a measure of Patient-Related Outcome Measures (PROMS) at the UARNT. Appendix A provides the questionnaire Supplemented in Annex 1.

Statistical analysis

Cysts were classified by volume (<15 and $\geq$15 mL) and as pure or mixed with a predominant cystic component (> 50%

cystic volume). Descriptive analysis was conducted using the median and 1st and 3rd quartile for continuous variables and frequency and percentage for categorical variables.

The Wilcoxon non-parametric test was used to detect statistically significant differences between variables at 1, 3, and 6 months vs baseline values. The Mann-Whitney U non-parametric test and the test for differences in proportions were used to detect inter-group statistically significant differences for continuous variables.

Quality of life was described using the mean, standard deviation, and mode (most repeated value) of the questionnaire item values. To detect statistically significant differences across questionnaire values prior to the intervention and 6 months after the intervention, the Wilcoxon non-parametric test was also used.

The statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS®) version 20.0 for Windows, assuming a statistical significance of $p < 0.05$.

Results

During the first year of operation of the UARNT, 32 PEIs were performed. A total of 50% of the patients who underwent PEI reported cosmetic discomfort prior to treatment. Eighteen patients (56.25%) exhibited nodules with an initial volume < 15 mL, and 15 (43.75%) had nodules with an initial volume ≥15 mL. The demographic characteristics of the patients are summarized in Table 1.

Table 1 Demographic characteristics of patients undergoing PEI at Hospital Verge de la Cinta UARNT.

	n	%
Total patients undergoing PEI	32	
Sex		
Female	28	87.50
Male	4	12.50
Age (mean, SD)	43	12.00
Method of diagnosis		
Physical examination (palpable nodule)	9	28.13
CT scan	1	3.13
Self-perception of thyroid nodule	21	65.63
Analytical changes	1	3.13
Physical examination		
Palpable nodule	7	21.88
Visible with swallowing	4	12.50
Visible to the naked eye	21	65.63
Thyroid function		
Normofunction	29	90.63
Hypofunction	2	6.25
Hyperfunction	1	3.13
TSH (mean, SD)	1.96	1.24
fT4 (mean, SD)	1.36	0.38
Clinical symptoms		
Cosmetic discomfort	16	50.00
Foreign body sensation	9	28.13
Compressing symptoms	7	21.88
Initial volume		
Cysts < 15 mL	18	56.25
Cysts ≥ 15 mL	14	43.75
Composition		
Pure cyst	25	78.13
Mixed nodules predominantly cystic	7	21.88
Location		
Right thyroid lobe	15	46.88
Left thyroid lobe	16	50.00
Isthmus	1	3.13

SD: standard deviation; fT4: free thyroxine; PEI: ultrasound-guided percutaneous ethanol injection with ethanol aspiration; CT: computed tomography; TSH: thyroid-stimulating hormone; UARNT: high-resolution unit.

Treatment efficacy

Table 2 presents the results of the efficacy of PEI in the total group of treated patients (n = 32). The volume at the 6-month follow-up was 0.23 (0.00–0.67) mL and the VRR, 98.57% (94.80–100.00), with a statistically significant difference between the initial volume and the volume at the 1-, 3-, and 6-month follow-ups, as well as the VRR among the 1-, 3- and 6-month follow-ups. A clinically significant response (volume reduction > 50%) was achieved in 96.875% of the cases undergoing PEI at the 1-, 3-, and 6-month follow-ups but not at the 5-month follow-up.

We evaluated possible differences between nodules with an initial volume < 15 mL and ≥ 15 mL and based on nodule composition (pure cysts vs cyst-dominant mixed nodules) (Table 2). The volume reduction was greater in the < 15 mL cyst group at 1-, 3-, and 6 months ($p < 0.001$).

The VRR was statistically higher at 6 months in the < 15 mL cyst group (100 [99.09–100] vs 96.78 [92.21–98.28]; $p = 0.001$). The volume reduction at 6 months was greater in the pure cyst group vs the mixed nodules (0.03 [0.00–0.51] vs 1.50 [0.54–1.79]; $p < 0.001$). The VRR was also significantly higher in the pure cyst group vs the mixed nodules at both 3- (99.09 [95.98–100] vs. 90.10 [76.81–90.68]; $p = 0.002$) and 6-months (99.82 [98.28–100] vs 91.01 [83.29–92.33]; $p < 0.001$).

Technical considerations

Table 3 presents the results of the technical aspects related to PEI. The mean volume of ethanol injected was 2.25 (2.00–2.50) mL in the total treated nodules (n = 32). The volume of ethanol injected was higher in the subgroup of nodules ≥ 15 mL vs nodules < 15 mL (2.50 [2.50–3.00] mL vs 2 [2–2.50] mL, respectively; $p < 0.001$). On the other hand, the volume of ethanol injected was higher in the subgroup of cyst-dominant mixed nodules vs pure cysts (2.50 [2.50–3.00] mL vs 2 [2–2.50] mL, respectively; $p < 0.001$).

Regarding the number of PEI treatments, 6 patients (18.80%) required 2 PEI sessions, and only 2 (6.3%) required 3 PEI sessions. No case required more than 3 PEI sessions. A total of 100% of the nodules that underwent ≥ 2 PEI sessions had an initial volume ≥ 15 mL. No differences were found between the number of PEI sessions and nodule composition (pure cysts vs cyst-dominant mixed nodules).

Table 2 PEI results according to the characteristics of the nodules treated at Hospital Verge de la Cinta UARNT: comparison between cysts < 15 mL and ≥ 15 mL, and comparison between pure cysts and predominantly cystic mixed nodules.

	Maximum diameter (cm) Median (Q1–Q3)	Volume (mL) Median (Q1–Q3) Initial	1 month	3 months	6 months	VRR (%) Median (Q1–Q3) 1 month	3 months	6 months
Total	3.53 (2.90–4.40)	11.99 (6.44–23.01)	1.17 (0.03–2.62)[a]	0.51 (0.00–1.59)[a]	0.51 (0.00–0.67)[a]	89.92 (79.02–99.67)	96.71 (90.15–100)[b]	98.57 (94.80–100)[b]
Nodular volume < 15 mL	2.95 (2.50–3.10)	7.37 (5.4–9.24)	0.17 (0.00–1.12)[a]	0.00 (0.00–0.49)[a]	0.00 (0.00–0.05)[a]	97.98 (80.35–100)	100 (93.59–100)[b]	100 (99.09–100)[b]
Nodular volume ≥ 15 mL	4.45 (4.00–4.60)	23.91 (20.64–29.08)	2.62 (2.16–12.34)[a]	1.57 (0.55–4.20)[a]	0.55 (0.45–1.50)[a]	85.00 (65–91.07)	91.37 (86.52–96.86)[b]	96.78 (92.21–98.28)[b]
p-Value (Volume < 15 ml vs ≥ 15 ml)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.039	0.011	0.001
Pure cysts	3.20 (2.89–4.40)	10.98 (5.70–22.68)	1.10 (0.00–2.26)[a]	0.19 (0.00–0.78)[a]	0.03 (0.00–0.51)[a]	91.67 (80.00–100)	99.09 (95.98–100)[b]	99.82 (98.28–100)[b]
Predominantly cystic mixed nodules (composition)	4.00 (3.00–4.40)	20.64 (0.23–24.78)	2.28 (1.22–4.62)[a]	1.82 (1.32–2.14)[a]	1.50 (0.54–1.79)[a]	84.67 (64.00–89.78)	90.10 (76.81–90.68)[b]	91.01 (83.29–92.33)[b]
p-Value (Pure cysts vs mixed nodules)	0.424	0.284	0.063	0.006	0.001	0.124	0.002	< 0.001

PEI: ultrasound-guided percutaneous ethanol injection with ethanol aspiration; Q1, Q3: first and third quartiles VRR: volume reduction rate.
[c]Non-parametric Mann-Whitney U test comparing cysts with volume < 15 mL and ≥ 15 mL.
[d]Non-parametric Mann-Whitney U test comparing types based on composition as pure cysts or predominantly cystic mixed nodules.
[a] $p < 0.05$ vs initial volume.
[b] $p < 0.05$ vs VRR at 1 month.

Table 3 Technical aspects related to IPE: aspirated volume, volume of ethanol used, and number of PEI sessions.

	Volume (mL) Median (Q1–Q3)		PEI (%)	
	Extracted	Ethanol	2nd session	3rd session
Overall group (n = 32)	20.00 (15.00–35.00)	2.25 (2.00–2.50)	6 (18.80%)	2 (6.30%)
Nodular volume				
< 15 mL (n = 18)	15.00 (12.00–20.00)	2.00 (2.00–2.50)	0 (0.00%)	0 (0.00%)
≥ 15 mL (n = 14)	35.00 (23.00–38.00)	2.50 (2.50–3.00)	6 (42.90%)	2 (14.30%)
p	< 0.001[a]	< 0.001[a]	0.002[c]	0.098[c]
Composition				
Pure cysts (n = 25)	20.00 (15.00–35.00)	2.00 (2.00–2.50)	4 (16.00%)	1 (4.00%)
Predominantly cystic mixed nodules (n = 7)	20.00 (16.00–30.00)	2.50 (2.50–3.00)	2 (28.6%)	1 (14.30%)
p	0.963[b]	0.031[b]	0.451[c]	0.320[c]

PEI: ultrasound-guided percutaneous ethanol injection with ethanol aspiration; Q1, Q3: first and third quartiles.
[a] Non-parametric Mann-Whitney U test comparing cysts with initial volume < 15 mL and ≥ 15 mL.
[b] Non-parametric Mann-Whitney U test comparing cysts.
[c] Proportion difference test.

Table 4 Quality of life scores specific to benign thyroid disease (Thy-PRO39es) before and 6 months after treatment with PEI.

	Baseline			6 Months			p-Value [a]
Parameter	Mean	SD	Mode	Mean	SD	Mode	p-Value
Global impact on quality of life (4)	1.28	0.81	1	0.19	0.40	0.00	< 0.001
Goiter (12)	3.75	1.95	4.00	0.53	0.62	0.00	< 0.001
Hyperthyroidism symptoms (16)	0.03	0.18	0.00	0.03	0.18	0.00	0.999
Hypothyroidism symptoms (16)	0.00	0.00	0.00	0.00	0.00	0.00	0.999
Ocular symptoms (12)	0.00	0.00	0.00	0.00	0.00	0.00	0.999
Fatigue (12)	0.50	1.02	0.00	0.38	0.75	0.00	0.046
Cognitive impact (12)	0.19	0.47	0.00	0.13	0.42	0.00	0.157
Anxiety (12)	1.97	2.09	0.00	0.53	0.80	0.00	< 0.001
Depression (12)	0.22	0.79	0.00	0.16	0.57	0.00	0.157
Emotional susceptibility (12)	1.13	1.48	0.00	0.53	0.95	0.00	0.001
Social life impact (12)	0.31	0.78	0.00	0.16	0.45	0.00	0.059
Impact on activities of daily living (12)	0.66	0.94	0.00	0.19	0.47	0.00	0.001
Cosmetic impact (12)	3.44	2.44	1.00	0.09	0.30	0.00	< 0.001

All results are expressed as mean and standard deviation. Each item on the different scales goes from 0 (no impact on quality of life) up to 4 (great impact on quality of life).
SD: standard deviation; PEI: ultrasound-guided percutaneous ethanol injection with ethanol aspiration.
The maximum score that can be obtained is indicated in parentheses after each scale.
[a] Wilcoxon non-parametric test.

Quality of life

Table 4 shows the scores from the quality-of-life questionnaire specific to benign thyroid disease (ThyPRO-39es) in the total group of patients (n = 32) at baseline and 6 months after treatment. Scores on the goiter, fatigue, anxiety, emotional susceptibility, social life impairment, daily life impairment, and cosmetic discomfort scales showed a significant improvement 6 months after PEI treatment. Overall quality of life, scored from 0 (good) up to 4 (poor), significantly improved from 1.28 SD, 0.81 down to 0.19 SD, 0.40 ($p < 0.001$).

Safety

The most common complication was mild local pain in most patients. Only 1 patient experienced local inflammation, pain, fever, and hyperthyroidism symptoms within 24 hours after the procedure due to a transient thyroiditis process, which resolved within a week with analgesics and a tapering dose of corticosteroids. No cases of recurrent paralysis, local abscess, or mediastinitis were observed.

Discussion

The management of benign thyroid nodules has undergone significant changes since the implementation of minimally invasive techniques, such as PEI and RFA, as an alternative to surgery in patients with symptomatic nodular thyroid disease.[2,6,7,12]

At the end of the 1990s, the first experiences of PEI for the treatment of cystic thyroid nodules as an alternative to surgery began to be reported. The group led by Zingrillo et al. was one of the first to report the results of 20 patients with cystic thyroid nodules indicated for surgery due to compressive symptoms (nodule volume > 10 mL with tracheal displacement) who underwent PEI, showing an 85% up to 90% reduction at the 6-month follow-up.[14] In Spain, Reverter et al. were the first to report the results of 30 patients undergoing PEI, demonstrating the safety and efficacy of the treatment, achieving a VRR of 70% up to 90% at the 12-month follow-up.[15]

In our study, the median VRR was clinically significant (reduction of > 50% of nodule volume) in 100% of the patients who underwent PEI at 1-, 3-, and 6 months.

Currently, despite the extensive experience with PEI in the treatment of cystic thyroid nodules, controversies surround the PEI procedure, particularly concerning the volume of ethanol and whether the administered ethanol should be aspirated.

Regarding the volume of ethanol administered, early studies suggested injecting an amount of ethanol relative to 50% of the total aspirated material volume.[16,17] Cho et al. reported excellent results with injections of < 5 mL of ethanol in 60 patients with cystic nodules treated with PEI, achieving a VRR of 70% up to 88.5% at the 7-years follow-up.[18] In Spain, Reverter et al. reported similar results with a maximum injection of 2 mL of ethanol.[15] Although there is no defined protocol for selecting a specific ethanol volume, there is currently a consensus that the injected volume should not exceed 10 mL.[19]

Regarding the technique used (ethanol aspiration vs ethanol retention), a retrospective study by Kim et al. found a higher rate of intracystic hemorrhage at the follow-up in patients undergoing PEI with ethanol aspiration (due to sudden pressure changes inside the thyroid nodule that caused the rupture of pericapsular vessels), suggesting that ethanol retention was associated with a lower rate of complications.[20]

In contrast, in a prospective study of more than 200 patients, Park et al. described a higher rate of local complications (local pain) in the group of patients undergoing PEI with ethanol retention, concluding that PEI with ethanol aspiration should be considered the technique of choice.[21] On the other hand, rare but serious PEI-related complications with ethanol retention, such as skin necrosis, venous thrombosis, and mediastinitis, have been reported.[22]

In this regard, our protocol has opted for PEI with ethanol aspiration with small volumes (< 5 mL) as the first-line therapy for cystic or predominantly cystic thyroid nodules. Overall, we inject volumes of 2 mL for nodules < 15 mL and 3–4 mL volumes for nodules > 15 mL.

Another aspect to consider when evaluating the efficacy of PEI is the initial volume of the thyroid nodule and its composition.

There seems to be a clear association between initial volume and the success rate of the procedure, such that nodules with higher initial volumes (>15–20 mL) have higher recurrence rates.[23] In our study, we found significant differences between initial volume and treatment response, showing a higher 6-month VRR in nodules with initial volumes < 15 mL vs those with volumes ≥ 15 mL.

Regarding nodule composition, there also seems to be an association between a higher proportion of the solid component and a lower VRR. This is because the solid component is more resistant to ethanol, and blood vessels present in the solid component drain ethanol from within the lesion, reducing its efficacy.[24] Some authors suggest that PEI with ethanol retention is superior to PEI with ethanol aspiration in mixed nodules as it allows vessel coagulation in the solid component.[24] Other authors suggest that to improve the ablation efficacy of mixed nodules, a combination of PEI for the cystic component plus RFA for the solid component should be used.[25] In our study, the only nodule that did not show a clinically significant reduction of more than 50% was a mixed nodule with a predominant cystic component and an initial volume of 37.48 mL (16% reduction after 3 PEI sessions). In this case, given the benign nature of the solid component (confirmed by 2 FNA biopsies with a Bethesda II result), treatment with RFA was offered.

A larger initial volume and a greater solid component are the main predictors for the need to perform > 1 PEI session.[26] There is no defined consensus on the criteria for conducting a new PEI session. In our protocol, following the recommendations of Deandrea et al.[8] and Leet et al.,[26] we perform a new PEI in cases in which a significant VRR is not observed in the subsequent check-ups (at 1-, 3-, and 6-months). Only 6 out of 32 patients underwent 2 PEI sessions, and 2 out of 32 patients underwent 3 PEI sessions. We found significant differences between nodule volume and the number of PEI sessions, with a higher number of PEI sessions in patients with nodules having an initial volume > 15 mL.

In our study, we aimed to assess the impact of MITs on the HRQoL of patients with thyroid nodules. HRQoL does not seem to improve in patients with nodular thyroid disease who undergo surgery.[27] In a prospective study led by a group of German surgeons, HRQoL worsened in 14% of the patients and showed no change in 56% of the patients.[28] In contrast, Jeong et al. demonstrated a significant improvement in all HRQoL items assessed using the ThyPRO questionnaire in 86 patients treated with MITs (PEI and RFA).[9] In our study, the overall quality of life of the patients significantly improved with the application of MIT.

The main limitations of this study are the limited number of patients and the lack of a control group (PEI with ethanol retention) to assess the efficacy of PEI with ethanol aspiration vs PEI with ethanol retention and the complication rates associated with both procedures. The high proportion of nodules with an initial volume < 15 mL and purely cystic possibly overestimates the efficacy of PEI. The objective of our study was to evaluate the safety, efficacy, and

impact on the HRQoL of PEI within the first year of operation of the UARNT at our center, with the aim of including it in the service portfolio of the endocrinology and nutrition department.

Conclusions

PEI is a simple and effective alternative that can be performed outpatiently, with a low complication rate. PEI is associated with a clinically significant VRR, along with the improvement of symptoms and quality of life. HRQoL is one of the most important considerations when deciding on clinical management for patients with thyroid lesions. MITs, such as PEI, are an effective tool for improving HRQoL.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.endien.2024.11.003.

Declaration of competing interest

None declared.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 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. Thyroid. 2016;26:1–133.
2. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: a review. JAMA. 2018;319:919–24.
3. Alexander EK, Doherty GM, Barletta JA. Management of thyroid nodules. Lancet Diabetes Endocrinol. 2022;10:540–8.
4. 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:R133–46.
5. Nixon IJ, Angelos P, Shaha AR, Rinaldo A, Williams MD, Ferlito A. Image-guided chemical and thermal ablations for thyroid disease: review of efficacy and complications. Head Neck. 2018;40:2103–15.
6. Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, et al. 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: executive summary of recommendations. Endocrine Practice. 2010;16:468–75.
7. Moon W-J, Baek JH, Jung SL, Kim DW, Kim EK, Kim JY, et al. Ultrasonography and the ultrasound-based management of thyroid nodules: consensus statement and recommendations. Korean J Radiol. 2011;12:1.
8. Deandrea M, Trimboli P, Creanza A, Garino F, Mormile A, Bertolino S, et al. Long-term follow-up of cystic thyroid nodules treated with percutaneous ethanol injection (PEI) using two different approaches. Eur J Endocrinol. 2020;183:489–95.
9. Jeong SY, Ha EJ, Baek JH, Kim TY, Lee Y-M, Lee JH, et al. Assessment of thyroid-specific quality of life in patients with benign symptomatic thyroid nodules treated with radiofrequency or ethanol ablation: a prospective multicenter study. Ultrasonography. 2022;41:204–11.
10. Boronat M, González-Lleó A, Rodríguez-Pérez C, Feldt-Rasmussen U, López-Plasencia Y, Rasmussen ÅK, et al. Adaptation and cross-cultural validation of the Spanish version of the thyroid-related quality-of-life patient-reported outcome questionnaire. Endocrinol Diabetes Nutr. 2018;65:500–7.
11. Watt T, Hegedüs L, Groenvold M, Bjorner JB, Rasmussen ÅK, Bonnema SJ, et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol. 2010;162:161–7.
12. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European Thyroid Association Clinical Practice Guideline for the use of image-guided ablation in benign thyroid nodules. Eur Thyroid J. 2020;9:172–85.
13. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS committee. J Am Coll Radiol. 2017;14:587–95.
14. Zingrillo M, Torlontano M, Ghiggi MR, D'Aloiso L, Nirchio V, Bisceglia M, et al. Percutaneous ethanol injection of large thyroid cystic nodules. Thyroid. 1996;6:403–8.
15. 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 percutaneous ethanol injection as first-line treatment in symptomatic thyroid cysts. BMC Endocr Disord. 2015;15:73.
16. Valcavi R, Frasoldati A. Ultrasound-guided percutaneous ethanol injection therapy in thyroid cystic nodules. Endocrine Practice. 2004;10:269–75.
17. Yasuda K, Ozaki O, Sugino K, Yamashita T, Toshima K, Ito K, et al. Treatment of cystic lesions of the thyroid by ethanol instillation. World J Surg. 1992;16:958–61.
18. Cho W, Sim JS, Jung SL. Ultrasound-guided ethanol ablation for cystic thyroid nodules: effectiveness of small amounts of ethanol in a single session. Ultrasonography. 2021;40:417–27.
19. Hahn SY, Shin JH, Na DG, Ha EJ, Ahn HS, Lim HK, et al. Ethanol ablation of the thyroid nodules: 2018 consensus statement by the Korean Society of Thyroid Radiology. Korean J Radiol. 2019;20:609.
20. 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? AJNR Am J Neuroradiol. 2005;26:2122–7.
21. 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.
22. Mauz P, Stiegler M, Holderried M, Brosch S. Complications of ultrasound guided percutaneous ethanol injection therapy of the thyroid and parathyroid glands. Ultraschall Med. 2005;26:142–5.
23. Suh CH, Baek JH, Ha EJ, Choi YJ, Lee JH, Kim JK, et al. Ethanol ablation of predominantly cystic thyroid nodules: evaluation of recurrence rate and factors related to recurrence. Clin Radiol. 2015;70:42–7.
24. Kim YJ, Baek JH, Ha EJ, Lim HK, Lee JH, Sung JY, et al. Cystic versus predominantly cystic thyroid nodules: efficacy of ethanol ablation and analysis of related factors. Eur Radiol. 2012;22:1573–8.
25. Jang SW, Baek JH, Kim JK, Sung JY, Choi H, Lim HK, et al. How to manage the patients with unsatisfactory results after ethanol ablation for thyroid nodules: role of radiofrequency ablation. Eur J Radiol. 2012;81:905–10.
26. Lee SJ, Ahn I-M. Effectiveness of percutaneous ethanol injection therapy in benign nodular and cystic thyroid diseases: long-term follow-up experience. Endocr J. 2005;52:455–62.

27. Promberger R, Hermann M, Pallikunnel SJ, Seemann R, Meusel M, Ott J. Quality of life after thyroid surgery in women with benign euthyroid goiter: influencing factors including Hashimoto's thyroiditis. Am J Surg. 2014;207:974–9.

28. Schmitz-Winnenthal FH, Schimmack S, Lawrence B, Maier U, Heidmann M, Buchler MW, et al. Quality of life is not influenced by the extent of surgery in patients with benign goiter. Langenbecks Arch Surg. 2011;396:1157–63.