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Long-term efficacy and safety of percutaneous ethanol injection (PEI) in cystic thyroid nodules: A systematic review and meta-analysis

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Abstract

Background: Percutaneous ethanol injection (PEI) is used for the treatment of benign cystic thyroid nodules. This systematic review and meta-analysis aimed to obtain strong evidence of its long-term efficacy and safety.

Methods: PubMed, CENTRAL, Scopus and Web of Science databases were searched until November 2020 for studies reporting data on volume reduction rate (VRR), compressive symptoms and cosmetic concerns. Associated complications were assessed. A random-effects model was designed to pool the data.

Results: Out of 385 papers, nine studies evaluating 1667 nodules were finally included. Overall, VRR at 6, 12, 24, 36, 60 and 120 months was 77%, 81%, 72%, 68%, 74% and 69%, respectively. Significant reductions in the compressive symptoms and cosmetic concerns were observed. No permanent complications were observed.

Conclusions: The present meta-analysis showed that PEI could significantly reduce the volume of benign cystic thyroid nodules. This reduction was already effective at 6 months post-treatment, and the effect was stable over time.

Roberto Cesareo and Gaia Tabacco are equally contributed.

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KEYWORDS
cystic thyroid nodules, meta-analysis, percutaneous ethanol injection, volume reduction rate

1 | INTRODUCTION

Thyroid nodules are commonly found as palpable lesions in about 5% of women and 1% of men from iodine-sufficient regions. However, its incidence increases up to 70% in the general population when detected by ultrasound (US).[1–3] The management of thyroid nodules depends on the risk of malignancy, the presence of symptoms and thyroid function (the presence of thyrotoxicosis). Malignancy is mainly assessed using US risk stratification systems and fine-needle aspiration (FNA) cytology. Factors including medical history, physical examination, laboratory results and findings from other imaging modalities, such as radionuclide thyroid scan, should always be considered too.[4] In case of the absence of malignancy risk, patients with thyroid nodules can be managed differently. Asymptomatic, benign nodules generally require no treatment, and patients are asked for clinical follow-ups. On the other hand, patients complaining of compressive symptoms or cosmetic concerns specifically correlated with goitre may require specific treatment.[5–7] Three main treatment options are available: surgery, radioactive iodine and image-guided thyroid ablation.[8–11]

In patients with symptomatic cystic thyroid nodules, the first line of treatment is via simple aspiration.[4] The recurrence rate following this treatment ranges from 10% to 90% depending on the number of aspirations and cyst volume.[12,13] Therefore, in cases with recurrent cystic thyroid nodules, other strategies should be considered.[4] Surgery has been the traditional treatment, though it is associated with the recognized risks of general anaesthesia and a 2%–10% possibility of perioperative complications such as hypothyroidism, hypoparathyroidism and recurrent laryngeal nerve injury. Additionally, surgery is expensive and may not be appropriate for a surgically high-risk individual.[11] On the other hand, there is no indication for radioactive iodine in euthyroid subjects with a single cystic nodule, and this technique is usually considered in subjects with autonomously functioning thyroid nodules.[14]

Among image-guided thyroid ablations, percutaneous ethanol injection (PEI) has been the most widely used method in patients with symptomatic cystic thyroid nodules. PEI is associated with improved outcomes compared with simple aspiration or saline injection and has similar efficacy and safety but higher simplicity and lower costs compared with other ablations.[4,15,16] To date, data on the results of PEI have been limited to the first few months of follow-up in the majority of the reports. In addition, different criteria have been used to assess its efficacy. Obtaining more robust evidence on the durability of results over time by using consistent methods could allow a better estimation of the role of PEI compared with surgery in symptomatic patients with benign cystic thyroid nodules. With this aim, we conducted a systematic review of the literature on PEI use in these patients to evaluate its technical and clinical efficacy. The endpoints of the meta-analysis were changes in the volume reduction rate (VRR), compressive symptoms, cosmetic concerns and associated complications.

2 | METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

2.1 | Search strategy

A comprehensive search on PubMed, CENTRAL, Scopus and Web of Science was performed until 20 November 2020. The complete search used for PubMed was thyroid[Title/Abstract] AND cyst*[Title/Abstract] AND ethanol[Title/Abstract]. References of the studies obtained from the search were further screened for additional studies. No language or time restrictions were adopted.

2.2 | Study selection

Studies reporting data of patients with benign cystic thyroid nodules treated with PEI and later followed up for at least 6 months were included in this systematic review. The exclusion criteria were as follows: (a) articles not within the field of interest of this review; (b) studies evaluating PEI treatment for cases involving benign solid nodules, malignant lesions or metastases; (c) studies with less than 6-month follow-up; (d) studies on cases with less than 50 cystic nodules undergoing PEI treatment; (e) studies with overlapping data; and (f) review articles, editorials, letters, comments or case/series reports. Two investigators (GT and AMN), independently and in duplicate, searched papers, screened titles and abstracts of the retrieved articles, reviewed the full texts, and finally selected articles for their inclusion. All disagreements were resolved by consensus.

2.3 | Data extraction

The following information was extracted independently and in duplicate by the two investigators (GT and AMN) in a pilot form: (1) general information on the study such as author details, publication year, country, study type, follow-up duration, number of patients and number of nodules; (2) PEI procedure; (3) VRR at 6, 12, 24, 36, 48, 60 and 120 months; (4) number of nodules achieving technical efficacy and criteria to define this endpoint; (5) compressive symptom score; (6) cosmetic problem score; and (7) complications. The VRR was defined as $\left[(\text{initial volume-final volume}) \times 100\right]/(\text{initial volume})$.[9]

According to a recent proposal, technical efficacy should be defined as a 50% volumetric reduction at one year. Since this criterion was heterogeneously adopted in the literature, data on the study-specific VRR cut-off and assessed follow-up were extracted.[9] For those studies adopting different time points, data were extracted in the closest follow-up time among the evaluated ones (e.g., data at 14 months were reported in the 12-month follow-up). The main paper and supplementary material were searched; if data were missing, the corresponding author was contacted. Data were cross-checked, and discrepancies if any were discussed.

2.4 | Study quality assessment

The risk of bias for the included studies was assessed independently by two reviewers (GT and AMN) through the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Studies.[18]

2.5 | Statistical analysis

The primary outcome was VRR at 6, 12, 24, 36, 48, 60 and 120 months after PEI therapy. Endpoints were analysed as continuous variables and were summarized as weighted means with 95% confidence intervals (CIs). In the case of a missing mean value in a study for a specific outcome, it was calculated from the median according to Hozo et al.[19] If standard deviation was missing in a study for a specific outcome, it was calculated from standard error, 95% CI or interquartile range; if none of these data were available, the largest among the other studies was reported. Meta-regression of VRR based on the baseline nodule volume was attempted. Concerning technical efficacy, complications, change in compressive symptom score and cosmetic problem score from baseline to the last available follow-up, we collected data and listed in tables, given the heterogeneous reporting (e.g., missing data were not interpreted as evidence of non-occurrence of a specific complication). Heterogeneity between studies was assessed using the I^2 statistic, with 50% or higher being regarded as high. Publication bias was assessed using Egger's test, and the trim-and-fill method was used to estimate its effect. All analyses were carried out using Prometa 3.0 (Internovi) with a random-effect model; significance was set at $p < .05$.

3 | RESULTS

In total, 385 papers were found, of which 117 were from PubMed, 18 from CENTRAL, 146 from Scopus and 104 from Web of Science. After removing 222 duplicates, 163 articles were analysed for title and abstract; 135 reports were excluded (guidelines, meta-analysis, review, survey, consensus, case report, case series, conference paper, letter, follow-up <6 months, less than 50 cystic nodules undergone PEI, mixed treatments [e.g., PEI and radiofrequency ablation], not within the field of the review [e.g., pancreatic cysts, parathyroid cysts]). The full text of the remaining 28 papers was retrieved, and nine studies were finally included in the meta-analysis (Figure 1).[20–28] No additional studies were retrieved from the references of the included studies.

3.1 | Qualitative analysis (systematic review)

The characteristics of the included articles are summarized inTable 1.[20–28] The studies were published between 2002 and 2020 and had sample sizes ranging from 58 to 432 nodules. Among the nine studies, four were

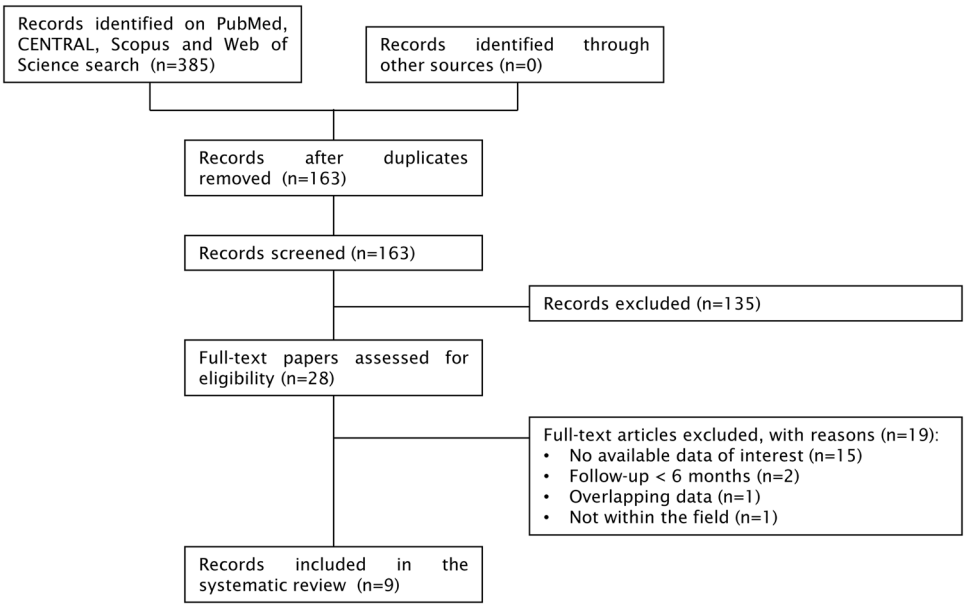

FIGURE 1 Flow chart of the systematic review

TABLE 1 Characteristic of included studies and availability of data

First Author, year	Country	Study design	Number of nodules	Population	Nodule volume (ml)[a]	Cystic component cut-off (%)	Previous FNA	6-month assessment	12-month assessment	24-month assessment	36-month Assessment	48-month assessment	60-month assessment	120-month assessment
Del Prete, 2002[28]	Italy	PCS	98	recurrent simple cystic nodules >10 ml, causing pressure symptoms, refusal or ineligibility for surgery. Euthyroidism and normal calcitonin	35.2 ± 20.1	90	Two benign		x	x	x	x	x	x
Guglielmi, 2004[27]	Italy	-	58	recurrent cystic nodules causing pressure symptoms or cosmetic problems	13.7 ± 14.0	-	Benign						x	
Valcavi, 2004[26]	Italy	RCT	135	cystic nodules >2 ml causing pressure symptoms or cosmetic problems. Euthyroidism and normal calcitonin	19.0 ± 19.0	50	Benign		x					
Lee, 2005[25]	South Korea	-	432	complex cysts. Euthyroidism	15.6 ± 12.6	-	Benign	x	x	x	x			
Basu, 2014[24]	India	-	60	simple or complex cystic nodules with at least 2 ml cystic component, no or one malignant feature on US. Euthyroidism	8.5 ± 5.6	50	Benign or non-diagnostic	x						
Gong, 2017[23]	China	RCS	135	cystic nodules causing pressure symptoms or cosmetic problems, no malignant features on US. Euthyroidism	15.2 ± 18.7	50	Benign or non-diagnostic		x					
Halenka, 2019[22]	Checz Republic	RCS	200	recurrent or symptomatic cystic nodules, refusal or ineligibility for surgery. Euthyroidism	8.5 [5.5 - 16.0]	60	Benign or non-diagnostic	x	x					

TABLE 1 (Continued)

First Author, year	Country	Study design	Number of nodules	Population	Nodule volume (ml)[a]	Cystic component cut-off (%)	Previous FNA	6-month assessment	12-month assessment	24-month assessment	36-month Assessment	48-month assessment	60-month assessment	120-month assessment
Park, 2019[21]	Korea	RCS	221	cystic nodules causing pressure symptoms or cosmetic problems, no malignant features on US. Euthyroidism and normal calcitonin	18.1 ± 24.3	50	Two benign		x					
Deandrea, 2020[20]	Italy	RCS	328	recurrent cystic nodules causing pressure symptoms or cosmetic problems, without calcification, fibrosis or substernal extension. Euthyroidism	23.1 ± 23.7	50	Benign or non-diagnostic	x	x	x			x	x

Abbreviations: -, not reported; FNA, fine-needle aspiration; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; US, ultrasound; x, retrieved data.

[a]Data are reported as mean ±standard deviation or median [interquartile range].

retrospective cohorts, one was a prospective cohort, and one a randomized controlled study. The study design was not clearly stated in three of the studies.[24,25,27] The participants were generally represented by euthyroid outpatients with a benign cystic or predominantly cystic thyroid nodule, causing compressive symptoms or cosmetic concerns. Benignity was defined according to one to two separate FNA; Bethesda I or TIR1C (non-diagnostic-cystic) was allowed in four studies.[20,22–24] Basu et al in their study mentioned that FNA was performed only on those nodules showing one or more high-risk features of malignancy on US.[24] The cystic component cut-off ranged from 50% to 90%. Four of the nine studies included only recurrent nodules, three studies included subjects with normal calcitonin only, and two studies included subjects refusing or not eligible for surgery only. The technical aspects of the PEI are reported in Table 2. Overall, 1667 nodules were treated with PEI. The nodule volume at baseline was 18 ± 18 ml.

3.2 | Quantitative analysis (meta-analysis)

The primary outcome was VRR at 6, 12, 24, 36, 48, 60 and 120 months. There was not enough data for a meta-analysis to be performed at 48 months. Concerning the other time points, PEI was found to be associated with a VRR of 77%, 81%, 72%, 68%, 74% and 69%, at 6, 12, 24, 36, 60 and 120 months, respectively. No statistically significant differences were found between VRR at each follow-up with the previous one (Table 3). These data were confirmed when the technical efficacy was assessed: a VRR of at least 50% was reported in approximately 80% of treated nodules, irrespective of the time of assessment (Table 4). Both compressive symptoms and cosmetic problem scores showed improvement from baseline to the last available follow-up. Of note, data were available from a limited number of studies and each outcome was evaluated using different scales (e.g., for compressive symptoms, a three-score arbitrary scale vs. a visual analog scale). Nevertheless, this did not result in an inconsistency in the findings, and PEI was always associated with better scores (Table 5). The list of reported complications is provided in the Supplementary Material. The most common side effect was transient local pain. Transient dysphonia was reported in four patients, hematoma in two and fever in six. None of the studies reported any permanent vocal cord palsy, change in thyroid function or other major side effects.

Overall, high heterogeneity was found in the meta-analyses of VRR at the assessed time points (Table 3). To investigate this, a meta-regression using nodule volume at baseline as the explanatory variable and the 12-month VRR as the outcome variable was performed, showing a significant interaction (p = .019) (Figure 2). No publication bias was observed (Supplementary Material).

3.3 | Study quality assessment

The risk of bias of the included studies is shown in Supplementary Material. Statement of the study question, patients' selection against eligibility criteria, description and delivery of the intervention,

TABLE 2 Details of the PEI procedure

First Author, year	Needle (G)	Ethanol volume	Ethanol removal	Anaesthesia	Number of treatments
Del Prete, 2002[28]	20-22	0.7-1.5 ml/ml of the initial nodular volume, not exceeding 15 mL	left in the cyst	no	1.8 ± 1.3
Guglielmi, 2004[27]	22	25% of the volume of the aspirated fluid, not exceeding 10 mL	left in the cyst	intracystic	2.2 ± 1.3
Valcavi, 2004[26]	18-22	50%-70% of the volume of aspirated fluid	left in the cyst	no	1-3
Lee, 2005[25]	23	40%-100% of the volume of the aspirated fluid	removed after 2 minutes	no	2.3 ± 1.2
Basu, 2014[24]	18-22	50%-100% of the volume of the aspirated fluid	left in the cyst	-	1 or 2
Gong, 2017[23]	18-20	50% of the volume of aspirated fluid	removed after 10 minutes	-	-
Halenka, 2019[22]	18-20	1-10 ml in the first session, or 20% of the residual fluid volume in the following ones	left in the cyst	no	1.7 ± 1.0
Park, 2019[21]	16-18	50% of the volume of the aspirated fluid	left in the cyst or removed after 2-5 minutes	skin anaes-thesia	-
Deandrea, 2020[20]	18-21	30%-50% of the volume of the aspirated fluid	left in the cyst	intracystic	2 ± 1

Abbreviations: -, not reported; PEI, percutaneous ethanol injection.

TABLE 3 Volume reduction rate of cystic thyroid nodules following PEI according to follow-up

	Number of nodules (number of studies)	VRR (95% CI) (%)	I^2
6-month assessment	894 (4)	77 (62 to 92)	99
12-month assessment	1354 (7)	81 (71 to 91)	99
24-month assessment	617 (3)	72 (64 to 79)	91
36-month assessment	473 (2)	68 (57 to 79)	99
48-month assessment	-	-	-
60-month assessment	324 (3)	74 (59 to 89)	91
120-month assessment	145 (2)	69 (53 to 86)	86

Note: $p > .05$ versus previous assessment for all comparisons.

Abbreviations: CI, confidence interval; PEI, percutaneous ethanol injection; VRR, volume reduction rate.

TABLE 4 Technical efficacy following PEI

First Author, year	Cut-off (%)	Time of assessment (months)	Number of nodules achieving technical efficacy/nodules undergone PEI (%)
Guglielmi, 2004[27]	75	60	50/58 (86%)
Lee, 2005[25]	50	36	343/432 (79%)
Gong, 2017[23]	50	12	122/135 (90%)
Halenka, 2019[22]	50	12	200/200 (100%)
Park, 2019[21]	50	12	184/221 (83%)
Deandrea, 2020[20]	50	120	42/52 (81%)

Abbreviation: PEI, percutaneous ethanol injection.

TABLE 5 Changes in compressive symptom and cosmetic problem scores following PEI

	Compressive symptoms			Cosmetic problems		
First Author, year	Scale	Baseline	Follow-up	Scale	Baseline	Follow-up
Del Prete, 2002[28]	0 = absent, 1 = moderate, 2 = severe, attributed to each symptom	2.3 ± 0.6	0.2 ± 0.3	-	-	-
Gong, 2017[23]	Visual analog scale (from 0 to 10)	4.2 ± 1.5	0.9 ± 1.2	1 = no palpable mass; 2 = a palpable mass but no cosmetic problem; 3 = a cosmetic problem on swallowing only; 4 = a readily detected cosmetic problem	3.5 ± 0.5	1.4 ± 0.7
Park, 2019[21]	Visual analog scale (from 0 to 10)	3.3 ± 2.1	0.5 ± 0.9	1 = no palpable mass; 2 = a palpable mass but no cosmetic problem; 3 = a cosmetic problem on swallowing only; 4 = a readily detected cosmetic problem	3.9 ± 0.7	1.7 ± 1.0
Deandrea, 2020[20]	0 = absent, 1 = moderate, 2 = severe, attributed to each symptom	2.1 ± 0.3	0.2 ± 0.5	-	-	-

Abbreviation: PEI, percutaneous ethanol injection.

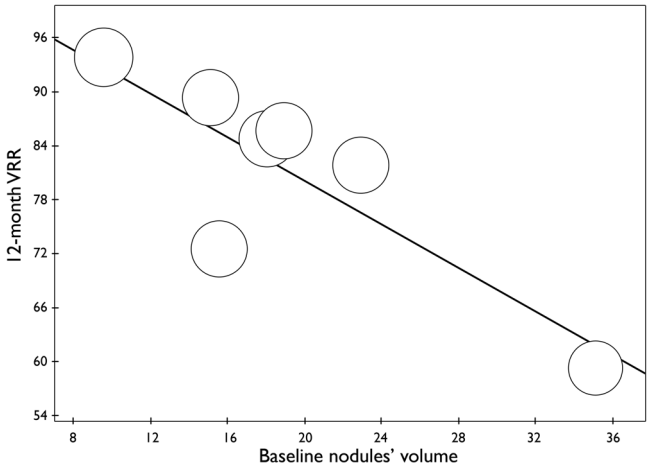

FIGURE 2 Meta-regression on volume reduction rate at the 12-month assessment based on the baseline nodule volume

definition of outcome measures, statistical methods and duration of follow-up were adequate in all. Eligibility criteria were not clearly described in two of the studies (e.g., the cut-off of the cystic component was not reported)[25,27]; additionally, patients included in the study by Del Prete et al.[28] might not be considered as representatives eligible for PEI given that only nodules of at least 10 ml were treated. Sample size justification was not described in any study, and researchers assessing the outcomes were not blinded to the intervention. The loss to follow-up after baseline was higher than 20% in one study, according to the 10-year follow-up.[20] Changes in VRR were reported at different time points in five studies.[20,22,24,25,28]

4 | DISCUSSION

This study aimed to provide robust evidence on the efficacy of PEI to reduce the volume of benign cystic thyroid nodules and their correlated symptoms over time. To our knowledge, this is the first meta-analysis of this topic. Nine studies were found, including 1667 thyroid nodules. The main result of the systematic review is that although PEI is commonly used in clinical practice, only sparse data on its long-term performance have been reported in the literature. Acknowledging this limitation, the overall results of our meta-analysis showed that PEI therapy was effective in reducing nodule size, with effects stable for up to 10 years. Improvements in compressive symptoms and cosmetic concerns have also been demonstrated. Based on our results, we have derived several considerations.

Adequate patient selection is a key factor for PEI treatment strategy. Specifically, the included subjects were generally diagnosed with a benign cystic or predominantly cystic thyroid nodule causing compressive symptoms or cosmetic problems. Benignity was diagnosed on the basis of reports of US and FNA, even if only three studies had specifically reported the absence of malignant ultrasonographic features. We have previously reported that all the five most commonly used thyroid imaging reporting and data systems (TI-RADS) have an appropriate performance in selecting malignant thyroid nodules for FNA, with some differences.[29,30] The correlation

between US presentation and cytological diagnosis, as well as the performance reports of all the main systems for thyroid cytology stratifying the risk of malignancy, was acknowledged.[31–34] Therefore, only nodules with an unsuspicious presentation on US and Bethesda I, TIR1C or benign FNA should be considered for PEI.

The cystic component was generally >50% of the nodule volume. This characteristic was relevant for predicting the overall PEI efficacy. Deandrea et al.[20] reported that the nodules with a cystic component of 50% to 75% achieved a 10-year VRR of 79%, compared with that with a cystic component above 90% achieving the 10-year VRR of 98%. In addition, the overall nodule volume was found to play a relevant role, with smaller nodules associated with improved outcomes, as confirmed in the meta-regression and already reported for other ablations.[8] This finding is in agreement with a previous study showing that pretreatment of cyst influences the chance of success of PEI since large cysts may contain areas of necrosis, haemorrhage and/or calcification that may limit ethanol penetration.[13] The presence of pressure symptoms and/or cosmetic problems specifically correlated with goitre should be assessed before PEI. Indeed, for a subject having an asymptomatic nodule with a low risk of cancer, no treatment would be needed.

Several protocols for PEI are available, and they mainly differ in terms of the injected ethanol volume and its retention. The ethanol volume ranged from 25% to 100% of the aspirated volume, with one study using up to 1.5 ml/ ml of the initial nodular volume.[24,25,27,28] The systematic review did not find any significant difference favouring higher ethanol volumes; ethanol being potentially associated with the necrosis of adjacent structures, it would be reasonable to inject the lowest effective volume. Concerning the latter aspect, ethanol was found to be left in the cyst after the treatment in the majority of the studies. Whether this was associated with more favourable outcomes is unclear. Indeed, one study directly comparing ethanol retention and aspiration techniques did not find any difference in terms of VRR, compressive symptoms or cosmetic problem scores, while subjects who were treated according to the retention technique were more likely to experience pain after treatment.[21] The last technique variant represented by the single vs. double alcohol injection during the same session was reported in a recent study with a 10-year follow-up but it did not show any difference in outcomes for the majority of the nodules.[20]

A single session of PEI may not be sufficient for several nodules. Indeed, approximately two treatments per nodule were performed in the studies analysed. Retreatment was generally performed 4 weeks after the first session when the effect of a previous session was judged unsuccessful. However, there was no agreement concerning this definition. Indeed, Basu et al planned a new treatment in subjects with <20% reduction in cyst volume, while Deandrea et al and Lee et al up to the complete disappearance of liquid content of the nodule.[20,24,25] Predictors for the need for multiple sessions included a larger nodule volume and a multilocular structure.[22,24,27,28] PEI is a simple and inexpensive technique that is not time-consuming. Its efficacy can be verified by following for just 2–4 weeks for any possible recurrence.[35] The treatment is generally well tolerated, and the complications are minor and transient (e.g., mild local pain). In line with this, the studies analysed reported all sessions being performed in an outpatient setting. Therefore, a new treatment session could be scheduled every time it was needed, supporting the role of PEI as an alternative to surgery to be considered for selected subjects for the management of benign cystic thyroid nodules.[20] In case of inadequate treatment, a surgical approach such as lobectomy or thyroidectomy could be planned, as reported among 13 non-responders in the study by Deandrea et al.[20]

There are some limitations of the present meta-analysis. First, a limited number of papers with heterogeneous reporting were found. Characteristics other than the nodule volume at baseline might be associated with a different VRR (e.g., number of treatments). Second, the inclusion of studies with at least 50 cystic nodules that had undergone PEI resulted in the exclusion of some randomized control trials on the topic.[13,16,36] Nevertheless, the follow-up of these studies was limited to the first 6 months; therefore, the main result of the present meta-analysis, showing the long-term efficacy of PEI, was not affected. Third, even if the duration of follow-up of the two studies was significant, the nodules that could be included at each follow-up differed. Lastly, data on technical efficacy were missing for some studies, and compressive symptoms and cosmetic concerns were unevenly reported. Following standardized reporting in future studies should be useful for future reviews.[8]

5 | CONCLUSIONS

In conclusion, a sufficient number of studies with heterogeneous reporting are available in the literature on the long-term performance of PEI for the management of benign cystic or predominantly thyroid nodules causing pressure symptoms or cosmetic problems. A significant VRR was recorded, and both compressive symptoms and cosmetic concerns were significantly improved with PEI treatment. As a relevant novelty for clinical practice, these results were stable over time, for up to 10 years following treatment. Thus, PEI therapy should be considered an effective and safe strategy in patients with recurrent symptomatic cystic or predominantly cystic thyroid nodules.

CONFLICT OF INTEREST

All the authors participating in the study have nothing to disclose.

AUTHOR CONTRIBUTIONS

RC, GT, AP and MC conceived the meta-analysis. FR provided medical librarian expertise and supported GT and AMN in developing the search strategy, selection criteria and data extraction criteria. GT and MC drafted the manuscript. GT and AMN developed the risk of bias assessment strategy. All authors read, provided feedback and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors. Analyses were performed on data extracted from published papers.

COMPLIANCE WITH ETHICAL STANDARDS

Authorship confirmation statement: The authors confirm that the research meets the ethics guidelines, including adherence to the legal requirements of the country where the study was performed.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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