Review Article

A clinical practice review of percutaneous ethanol injection for thyroid nodules: state of the art for benign, cystic lesions

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Abstract: Percutaneous ethanol injection (PEI) is a widely used treatment option for cystic and predominantly cystic thyroid nodules. It has several advantages over other treatment modalities. Compared to surgery, PEI is less painful, can be performed in the outpatient setting, and carries less risk of transient or permanent side effects. Compared to other minimally invasive techniques such as radiofrequency ablation (RFA), PEI is less expensive and does not require specialized equipment. PEI performs well in the context of cystic nodules. PEI does not perform as well as other techniques in solid nodules, so its use as a primary treatment is limited to cystic and predominantly cystic thyroid nodules. However, PEI is also being explored as an adjunct treatment to improve ablation of solid nodules with other techniques. Here, we provide a clinical review discussing the genesis, mechanism of action, and patient selection with respect to ethanol ablation, as well as the procedure itself. Predictors of operative success, failure, and common adverse events are also summarized. Altogether, PEI allows impressive volume reduction rates with minimal complications. Several recent studies have also evaluated the long-term impact of PEI up to 10 years after treatment and revealed maintenance of robust treatment efficacy with no undesirable long-term sequelae. Thus, PEI remains the treatment of choice for benign but symptomatic cystic and predominantly cystic thyroid nodules.

Keywords: Percutaneous ethanol injection (PEI); ethanol ablation; review; benign thyroid nodule

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Introduction

Background

Thyroid nodules are common and detectable in up to 65% of the general population (1). Risk factors for benign thyroid nodules include advanced age, female gender, and iodine deficiency (2). Though the vast majority of thyroid nodules are benign, those which elicit compressive symptoms or functional disease still require treatment.

Non-malignant thyroid nodules can be hyperfunctioning, elicit compressive symptoms, or cause cosmetic concerns. Though symptomatic nodules are less likely to be malignant than incidentally discovered nodules (3), the risk is not zero and treatment is still required (4). Several treatment options may reduce the size of nodules which cause either distressing local compressive symptoms or

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cosmetic concerns, including medical management, surgical intervention, as well as minimally invasive techniques such as simple aspiration, ethanol ablation, or radiofrequency ablation (RFA).

Medical management involves the use of thyrotropin thyroid-stimulating hormone (TSH)-suppressing levothyroxine (LT4) therapy. However, there is limited evidence for the efficacy of LT4 therapy in reducing nodule size. For example, a 2007 randomized controlled trial found no difference in nodule volume when patients were treated with LT4 for 12 months compared to those without treatment (control group) (5). Another work reported similar findings, reporting LT4 treatment to be superior to placebo only when supplemented with iodine, with a volume reduction ratio (VRR) of only −17.3%. However, this result had marked variability, as 26.7% of patients treated with LT4 + iodine had an increase in nodule size (6). A meta-analysis of 2,083 patients concluded limited benefit with LT4 treatment, finding a VRR of >50% in 16% of patients who received LT4 versus 10% of patients who received no treatment or placebo (P=0.03) (7). Though LT4 therapy is typically well tolerated, hyperthyroid symptoms were described in 25% of LT4-treated patients versus 7% of those receiving placebo (7). In all, LT4 therapy may provide slight benefit versus placebo to nodular reduction, however, current guidelines do not recommend LT4 treatment for thyroid nodules (8). Thus, other options are needed for more consistent and substantial volume reduction in patients with significant symptoms or cosmetic concerns.

Nodules causing compressive symptoms or functional disease traditionally have been treated surgically. However, surgery is expensive, invasive, and associated with risks of complications, including bleeding, infection, recurrent laryngeal nerve injury, hypothyroidism, and hypoparathyroidism (9), the latter three which may be permanent. Open thyroid surgery can also result in noticeable neck scarring, which can be distressing for patients (10,11). Robot-assisted minimally invasive surgery has been used as a method for minimizing scarring (12,13), but there have been reports of increased risks of other adverse effects (14). Radioactive iodine ablation (RAI) is another option for patients with hyperfunctioning "hot" nodules, also referred to as autonomously functioning thyroid nodules (AFTN), that may minimize some of the adverse effects associated with surgery. However, its use is typically limited to hot nodules and is not without risk, including post-procedure hypothyroidism (15) and other drawbacks associated with radiation such as its linear dose-response risk of solid cancer mortality (8,16). Of note, RAI and the anti-thyroid medication of choice, methimazole, are contra-indicated in pregnancy (17). Given the limited indications for treatment, RAI may not be an optimal treatment for pregnant patients or those with large thyroid nodules.

To address the lack of suitability of non-surgical management and to offer an alternative to surgery, minimally invasive ablative techniques have been explored for treatment of thyroid nodules. For benign cystic or predominantly cystic thyroid nodules, several such approaches have been explored. Simple cyst aspiration may be carried out, though recurrence rates can be as high as 60% (18). To improve outcomes, chemical and thermal techniques have been developed. Thermal techniques include laser ablation (LA) (19), high intensity focused ultrasound (HIFU) (20), microwave ablation (MWA) (21), and RFA (22,23). While effective, thermal techniques are more expensive and require the use of specialized equipment. Chemical ablation techniques typically involve percutaneous ethanol injection (PEI) (24), and less commonly polidocanol injection (25). PEI is relatively inexpensive, requires no specialized equipment, and is generally carried out in an outpatient setting with only local anesthesia. Furthermore, the effect of ethanol in simple cysts is limited to the nodule, providing superior specificity to thermal techniques, and avoiding disruption of surrounding structures (26). Thus, PEI has emerged as the treatment of choice for benign cystic nodules.

History and mechanism of action

Based on prior experience with hepatocellular and parathyroid carcinomas, ethanol ablation was first used to treat benign cysts in 1985 (27) and to treat AFTN in 1990 (28). Ultrasound-guided PEI has since become a mainstay of treatment for benign cystic thyroid nodules (8,24) and has been reported to produce VRRs as high as 90% in functional nodules and 100% in cystic nodules (29,30). PEI is thought to induce ablation by a combination of coagulative necrosis via dehydration and ischemic necrosis by means of endothelial injury and thrombosis (31,32). Importantly, no evidence has suggested PEI to induce tumorigenesis or increase the risk of malignancy. As these mechanisms are mediated by direct contact, PEI is less useful in circumstances where ethanol can leak or diffuse out of the target region (33). PEI is also less useful in cysts with a solid component of over 20% (34-36), likely due to a reduction in direct contact with the center of the solid component.

More recently, PEI has been used to treat thyroid papillary microcarcinoma (37) and local recurrent metastases of well-differentiated thyroid carcinoma (38,39). PEI has also been suggested as an alternative for thyroid cancer recurrence when tissue fibrosis from previous surgery limits normal approaches (40). However, surgery and radiation remain first line treatments for these circumstances and PEI should be considered only as an adjunct therapy or in the case of contraindications to surgery (8,24).

Rationale and knowledge gap

Recent advances have led to increased usage of minimally invasive techniques to treat thyroid nodules. However, clinical practice guidelines from major societies are often slow to update and there is a need for updated summaries of recent research (24,41,42). Since the most recent guidelines have been updated, there have been new data published on long-term outcomes after PEI (43,44) and meta-analyses with data on efficacy and factors influencing treatment success (45,46). Compared to other recent reviews (45,46), this work will provide a higher-level and accessible summary of current literature and clinical practice together with context on the historical use of PEI on thyroid nodules.

Objective

Our objective is to collate and summarize recent research in the use of percutaneous ethanol ablation of thyroid nodules for consideration in clinical decision making.

Methods

PubMed and Google Scholar were used to search for the publications on PEI of thyroid nodules from January 1990 to September 2022. The search was conducted using the key terms "percutaneous ethanol injection", "ethanol ablation", "thyroid nodules", "complications", "efficacy", and "safety". The search was conducted using variable combinations of the keywords. Articles were included if they provided data on the efficacy and safety of percutaneous ethanol injection for treatment of thyroid nodules.

Patient selection

Though PEI is a cost-effective attractive management modality which is scarless and obviates the need for anesthesia, a certain criteria excludes patients from its treatment (47). For example, patients with thyroid nodules which are near the "danger triangle" (deep and paratracheal, in close proximity to the typical course of the recurrent laryngeal nerve) are poor candidates for PEI, regardless of nodule composition. Furthermore, the inability to localize the thyroid nodule on preoperative assessment disqualifies ultrasound-guided PEI as a feasible management option.

PEI is indicated primarily for relapsing symptomatic, benign cystic, and predominantly cystic thyroid nodules. In cases of cystic nodule recurrence following simple aspiration, PEI is the suggested first line treatment for cysts with a solid component of less than 20% (46). For nodules with a greater solid component, thermal ablation is recommended. Cytologic analysis of fluid acquired from simple aspiration may be used to confirm if the nodule is benign prior to PEI. For pure cysts, PEI may be carried out even in the absence of cytologic confirmation given the low likelihood of malignancy. For partially cystic nodules, one or two benign fine-needle aspiration (FNA) results are needed depending on the ultrasound features of the nodule (48). Ultrasound features indicating a benign nodule may include (8):

(I) Spongiform appearance;
(II) Colloid-containing predominantly cystic nodule (comet-tail sign);
(III) Regular peripheral nodule calcification ("eggshell" calcifications) with no focal discontinuity;

In the absence of these features, two benign FNA results should be acquired prior to PEI. Additionally, the presence of malignancy-associated ultrasonographic features warrants further investigation. Malignant features include a hypoechoic, solid nodule with (8):

(I) Microcalcifications/Macrocalcifications;
(II) Taller than wide shape;
(III) Irregular margins or extrathyroidal extension;

It should be noted that calcifications are commonly present in nodules previously treated with PEI and do not represent suspicious findings in this context. Generally, thyroid function tests (TFTs) should be obtained prior to PEI, and coagulation studies may be performed for patients at higher risk for bleeding (24).

In patients with recurrent thyroid carcinoma, PEI may be performed if there are contraindications for surgery. Prior to PEI, FNA should be performed to confirm recurrence of the malignancy. TFTs and calcitonin levels should also be assessed. However, RFA may be a superior option and yield a lower rate of recurrence on subsequent follow up (48,49), limiting the utility of PEI for recurrent carcinoma. There is little evidence for use of PEI in the case of primary thyroid carcinoma, and thus is not recommended in this context (50). PEI may also be used effectively for hyperfunctioning nodules (51,52). However, efficacy may be greater for smaller nodules with fewer locules (50).

Course of treatment

PEI requires only a 16-to-20-gauge needle, a syringe, 95–99% ethanol, and ultrasound. A local anesthetic such as lidocaine may also be used (24). The cyst is typically aspirated prior to ethanol injection. Viscous colloid material may require aspiration with a larger needle or a pigtail catheter and suction pump (53). Irrigation of the cyst with normal saline followed by aspiration can also be used to reduce the viscosity of the cyst contents (54). Subsequently, ethanol is injected into the center of the cyst (24). There is no consensus on the amount of ethanol to be injected, but 50% of the aspirate volume has been suggested (24). This volume can be scaled up depending on the individual cyst and if the ethanol will be subsequently removed. Kim *et al.* found that leaving ethanol in the cyst for a period of 2 minutes prior to aspiration is sufficient for effective treatment (36). Aspiration of ethanol at the end of the procedure can improve patient satisfaction as it results in an immediate reduction of cyst size. Ethanol removal may also minimize unwanted side effects due to leakage from the tissue, though reports of similar complications rates (ethanol aspiration *vs.* retention groups) have been suggested (55). Complaints of pain during PEI may be due to ethanol leakage from the cyst and is an indication for leakage evaluation using ultrasound followed by aspiration of ethanol to help minimize pain.

For recurrent thyroid cancer, a slightly modified procedure is possible. In this case, a slightly smaller needle may be used (22–25 G) followed by initiating injection of ethanol at the peripheral area of the tumor and working towards the center of the tumor (24). Injection will progressively turn the tumor echogenic and should be continued until the entire tumor has been treated. Injection should be terminated if there is observed leakage outside the tumor or severe pain (24).

Post-operatively, patients should be discharged after a short observation period. Follow-up ultrasound is typically performed between 1-6 months post-operatively (24). If inadequate volume reduction or cyst growth is observed, additional sessions of PEI may be performed. After 3 PEI sessions, alternate treatments should be considered (56). For AFTN, measurement of TFTs should be performed to assess normalization of thyroid function (50). Radioisotope scans may also be considered for AFTN (57).

Efficacy and safety

Overall performance

PEI has been found to be highly effective in reducing cyst size and symptoms for predominantly cystic thyroid nodules. In a recent meta-analysis, the pooled VRR at 1, 6, and 12 months were 70.01% (95% CI: 62.62–77.40%), 90.75% (95% CI: 84.02–97.49%), and 84.97% (95% CI: 79.08–90.85%), respectively (41). The meta-analysis also found that ethanol ablation had a higher success rate, defined by more than 50% volume reduction, than aspiration alone [standard mean difference (SMD), 0.72; 95% CI: 0.29–1.14, P<0.001] (46). PEI also had similar success rates to RFA (SMD, 0.170; 95% CI: −0.367 to 0.708, P=0.53) (58,59) and policosanol sclerotherapy (SMD, −0.171; 95% CI: −0.410 to 0.068; P=0.16) (60). In one study with very long follow-up, median VRR after PEI continued to increase over a period of 10 years, indicating substantial treatment efficacy (43).

Predictors of success

A consistent predictor of success is the cystic nature of the nodule. Studies show greater VRR in cysts than predominantly cystic thyroid nodules (89.7% *vs.* 78.2%, P<0.001) (36). The association of ethanol volume and its retention or aspiration is less well understood. Retention of less than 50% of ethanol increased the success rate in some studies (46) but larger injected volume of ethanol was correlated with VRR in cystic nodules in other studies (36). Still, others works report no significant difference in VRR between ethanol aspiration and retention groups (61). One study of 217 thyroid nodules found smaller initial volume (P=0.011) and less nodular vascularity (P=0.001) to be independent predictors of success in predominantly cystic thyroid nodules yet found no predictive factors (of operative failure or success) in cystic nodules (36). Expectedly, numbers of treatment sessions correlates with VRR. For example, Negro *et al.* reported that the VRRs in thyroid cysts after the first, second, and third ethanol ablation sessions were 66.0%, 74.4%, and 79.4%, respectively (62). Some predictors of failure include large initial volume

(>20 mL), increased vascularity, >20% of solid component, and low amount of cystic fluid aspirated prior to ethanol injection (46).

Side effects and adverse events

Mild pain is the most common complaint after PEI which is passively treated and reduced by lower volume retention. The most common major complication is transient dysphonia, reported with a frequency of 0.53% (6/1,136 cases) (46). Attractively, no permanent recurrent laryngeal nerve damage secondary to PEI has been reported in the literature. In contrast, RFA has been reported to cause permanent recurrent laryngeal nerve paralysis (63) and has a slightly higher rate of transient dysphonia (0.97%, 15/1,543) (64). Interestingly, one study reported drunkenness with a frequency of 10.4% in patients undergoing PEI (60). Of note, the remnant of the nodule after ethanol ablation can mimic malignancy on subsequent US and can lead to unnecessary biopsies if the patient is under surveillance (65).

Discussion

Prior to the development of minimally invasive techniques such as PEI, surgery was the mainstay of treatment for thyroid nodules. However, PEI has some distinct advantages to surgery for the treatment of cystic nodules. PEI causes minimal discomfort and can be performed with only or even without local anesthetic, improving treatment options for high-risk surgical patients (29). PEI also has a shorter recovery period and avoids the formation of scars which may be distressing to patients (10,11). There is also a reduced risk of perioperative complications as compared to surgery (46,66).

PEI remains the suggested first-line treatment modality for benign cystic thyroid nodules. However, RFA has been gaining popularity rapidly in the United States, with several large academic centers recently starting to offer RFA (22). Comparisons of retrospective studies demonstrate that RFA may allow improved VRRs in cysts with a greater solid component (45,67). However, one randomized trial by Baek *et al.* comparing efficacy between RFA and PEI in partially cystic thyroid nodules (cystic component from 50–90%) found no significant difference in efficacy (68). The study did report treatment failure in 50% of patients with a highly vascular solid component in the PEI group (2/4) versus 0% of patients with a highly vascular solid component in the RFA group (0/3). Two other trials by Sung *et al.*, limited to cystic nodules, found little difference between PEI and RFA (58,59). No other trials have directly compared RFA to PEI, and additional research is needed to elucidate the relative strengths of each procedure.

Traditionally, thermal ablative strategies such as LA, MWA, and RFA are recommended for the treatment of benign solid nodules. One study found only 13.7% of benign nodules to have a cystic component >75%, limiting the broader application of PEI versus thermal ablative techniques (69). Recently however, Zhu *et al.* reported that PEI injection into solid benign thyroid nodules immediately prior to RFA shortened the procedure time, reduced the power used, and increased patient comfort when compared to RFA alone. The authors reported similar overall therapeutic success rates (EA + RFA: 90.9% *vs.* RFA: 86.4%, P=0.869) and posit the strategy to allow enhanced thermal conduction (70). These results suggest a possible role for PEI in the treatment of solid benign thyroid nodules and warrant further study.

Other important factors worth consideration before PEI recommendation include patient selection, patient anxiety, and cost. Patients with a single, well-localized cystic or predominantly cystic thyroid nodule are the most appropriate candidates for PEI. As a local ablation strategy, PEI is not well-suited for the treatment of multinodular AFTN, multinodular goiter, or other non-localized disease (41). One other limitation of PEI is that it prevents the determination of specimen pathology. When using PEI, results from aspiration cytology or FNA in addition to ultrasound must be used to evaluate the possibility of malignancy. In some cases, results may be inconclusive or falsely benign, leading to surgical intervention after PEI for a continuously growing nodule. One study from Monzani *et al.* noted that surgical excision after PEI was not complicated by special technical issues and that previous PEI did not interfere with histopathologic analysis (71). From a financial standpoint, PEI may be the most attractive of the minimally-invasive treatment as it obviates the need for special equipment (72). Additionally, PEI is more commonly accepted by insurance providers (72), highlighting the importance of discussing costs and benefits of different treatment modalities with patients.

Strengths and limitations of this review

This review summarizes the most relevant recent literature on PEI of thyroid nodules and offers commentary on the applicability of recent studies to clinical practice. The strengths of this review include collation of the most important recent research in this topic in one place for easy access, as well as some discussion of relevant conclusions drawn by the authors of recent works. This review also provides an overview of the current state of the field and outlines the research suggesting the best use cases and limitations for PEI of thyroid nodules.

This review is not a systematic literature review or meta-analysis, but a clinical practice review and there is therefore a risk for bias in selection of studies to discuss. We attempted to minimize bias by careful searching and thoughtful discussion, but recognize this is a limitation of the study. To limit the risk of such bias impacting our work, we limited conclusions drawn in our discussion to statements well-supported by multiple high-quality studies.

Conclusions

Given its low-risk, cost-effectiveness, and impressive VRRs, PEI continues to be an acceptable and preferred treatment option for the management of symptomatic cystic or predominantly cystic thyroid nodules.

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Footnote

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