Thyroid nodules are a common encounter in clinical practice with a prevalence of up to 50% depending on mode of detection (1-3). For most of these nodules, evaluation with clinical examination, neck ultrasound, thyroid function tests, and, occasionally, fine needle aspiration (FNA) is sufficient to conclude they can be safely observed long term. However, a significant percent of nodules needs a different management plan. This is the case for benign nodules that are growing and causing local compressive symptoms, for toxic nodules, for nodules harboring a malignancy, and occasionally for nodules causing obvious asymmetry over the neck with subsequent esthetic concerns. In these cases, the standard management has been surgery, either a total thyroidectomy or a lobectomy depending on the specifics of the disease. For toxic nodules, radioactive iodine (RAI) is also a treatment option. However, both options, particularly surgery, often result in elimination of more than the affected thyroid parenchyma, leading to the developement of hypothyroidism. Furthermore, surgery has its own undesirable implication of a scar over the neck and the risk of complications (dysphonia and/or hypoparathyroidism). In contrast, RAI does not carry these risks, but it does engender negative reactions in some patients due to concerns about impact on pregnancy, on small children in the household, and potential risk for secondary malignancies.

Therefore, the need for additional therapeutic options is self-evident. Nodular focal ablative therapies have surfaced over the last couple decades. Chemical ablation of thyroid lesions with ethanol is the first such approach to have withstanded the clinical efficacy test. Its principle is that of exposing the targeted cells directly to highly concentrated alcohol and thus affecting their viability. Thermal ablation (TA) of thyroid nodules is a more recent addition to this field. It has many technological facets (radiofrequency ablation [RFA], laser thermal ablation [LTA], microwave ablation [MWA], and high-intensity frequency ultrasound [HIFU]) that are involved in delivering the energy to the target lesion and destroying its constitutive cells (Table 1).

This review will explore the areas where these ablative approaches have been found to be most effective. For this manuscript RAI therapy will not be considered an ablative therapy and will not be discussed further. We will start with case vignettes, discuss the evidence supporting the ablative therapies, review additional considerations tied to these therapies, and conclude with a section on the methodology of ablative procedures, focusing on practical aspects.
Table 1. Minimally invasive techniques for management of thyroid nodules and cysts

| Ablative technique | Principle | Main utilization | Therapy duration | Estimated cost | US presence |
|-------------------|-----------|-----------------|-----------------|----------------|-------------|
| PEI               | Ultrasound-guided transcutaneous injection of ethanol into target lesion | 1. Recurrent, large thyroid cysts 2. Cervical adenopathy from thyroid carcinoma | ~10-15 min | Low | Common |
|                   | Action: direct toxic effect of ethanol on target tissue | | | | |
| RFA               | Ultrasound-guided electrode placed transcutaneously into target lesion | 1. Solid or predominantly solid benign compressive thyroid nodules 2. Toxic thyroid nodules | ~5-60 min* | Moderate | Rare |
|                   | Action: oscillating current generates hyperthermia through frictional agitation in target, leading to cell death via coagulative necrosis | | | | |
| LTA               | Ultrasound-guided optical fiber placed transcutaneously into target lesion | 1. Solid or predominantly solid benign compressive thyroid nodules 2. Toxic thyroid nodules | ~30 min | Moderate | Very rare |
|                   | Action: laser/light energy emitted from optical fiber induces electromagnetic heating, leading to cell death via coagulative necrosis | | | | |
| MWA               | Ultrasound-guided microwave applicator inserted transcutaneously into target lesion | 1. Solid or predominantly solid benign compressive thyroid nodules (limited evidence) | ~30 min | Moderate | Not reported |
|                   | Action: microwave energy generates hyperthermia by increasing molecular kinetic energy, leading to cell death via coagulative necrosis | | | | |
| HIFU              | Ultrasound beams delivered to target tissue through multiple shots after computerized mapping, without skin disruption. | 1. Solid or predominantly solid benign compressive thyroid nodules (limited evidence) | ~60-90 min | Unknown | Not reported |
|                   | Action: ultrasound waves deposit energy in the target resulting in hyperthermia, leading to cell death via coagulative necrosis | | | | |

Abbreviations: PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; LTA, laser thermal ablation; HIFU, high-intensity frequency ultrasound; MWA, microwave ablation. *Time is closely dependent on size of the ablated lesion.

aVery low cost <$1000; low-cost range is $1000-3000; Moderate-cost range is $3000-10 000; high cost is >10 000$.
Ablative Therapies for Benign Thyroid Nodules
Clinical Case
A 38-year-old woman was referred to the endocrine clinic for re-evaluation of a right thyroid nodule initially diagnosed, biopsied, and found benign 3 years ago. She can now see the nodule and endorses pressure when hugging her children. In the past few months, she also noticed fine tremors, insomnia, and heat intolerance. Her past medical history is otherwise unremarkable. On physical examination she has fine hand tremors, a regular pulse at 82 beats/minute, and there is an easily noticeable right thyroid nodule occupying most of the right lobe. The examination is otherwise unremarkable while the thyroid tests reveal thyrotoxicosis with thyrotropin (TSH) 0.02 mIU/L (0.30-4.20 mIU/L) and normal triiodothyronine and thyroxine. Neck ultrasound showed a 4.2 × 1.9 × 2.8 cm (11.2 mL) solid, isoechoic nodule in the right thyroid lobe with smooth margins and increased vascularity, with normal surrounding parenchyma and no lymphadenopathy (Fig. 1A and 1B). 123I scintigraphy showed a hot right thyroid nodule with suppression of uptake in the surrounding thyroid tissue. She would like to eliminate the local pressure sensation but avoid surgery and RAI due to concerns about hypothyroidism.

Ablation of Benign Nontoxic Thyroid Nodules
In this patient the change in nodule volume over time has made it visible and generated local compressive symptoms. The standard approach would be to treat such a patient with a lobectomy or with RAI therapy in the case of toxic nodules. However, sufficient data indicate that for these cases consideration can also be given to the newly emerging minimally invasive TA modalities (Table 2).

What is the evidence supporting RFA of benign thyroid nodules?
Image-guided TA techniques, the most used being RFA and LTA, have been utilized successfully in Europe and Asia for more than a decade. Most studies have focused on RFA; compared with surgery, RFA is associated with fewer complications and side effects, eliminates the need for hospitalization, and results in higher patient satisfaction (4-7). RFA has also demonstrated good efficacy in reducing nodule volume—the available clinical trials indicate a decrease in volume of 70% to 80% which typically occurs in 6 to 12 months and often persists up to 5 years (8-11). These results have led current guidelines to support RFA use in select patients with benign solid or predominantly solid nonfunctioning thyroid nodules that cause compressive symptoms and/or cosmetic concerns (12, 13). Another category of nodules considered for RFA at some centers are lesions ≥5 mL in volume/≥3 cm in maximum diameter, asymptomatic yet growing (12, 14). Conversely, such treatment is not recommended for asymptomatic, stable, and nontoxic thyroid nodules. This is a position that we also endorse.

What additional considerations are important regarding RFA for benign thyroid nodules?
Defining a thyroid nodule size cut-off for ablation needs to be flexible, as symptoms and cosmetic concerns are influenced by a variety of factors, including nodule location, neck circumference, and cultural norms. Prior to proceeding with RFA, current recommendations advocate for confirmation of benign cytology on 2 consecutive ultrasound-guided FNA biopsies to reduce the risk of a false-negative result (12, 15). Additionally, baseline compressive symptoms (eg, self-evaluated by patients using a visual 10-cm analog scale with grading 0-10 cm) and cosmetic scores (Table 3) should be collected when possible to aid in determining response to treatment following ablation (12). The degree of volume reduction is predicted most consistently by the initial size of the nodule (with nodules <10 mL achieving more percent reduction than larger lesions (16, 17)) and by the amount of energy delivered per unit of nodule volume (9, 18).

What is the safety profile of RFA?
The energy generated by RFA has been a concern, and early operators have reported skin burns and injury to the recurrent laryngeal nerves with voice changes. Fortunately, subsequent series have found that, except for mild pain and local heat sensation present in about 5% of patients, moderate to major complications are extremely rare (19-22), and in a review of 15 studies the overall incidence of hematoma, skin burn, brachial plexus rupture, permanent voice change, hypothyroidism, or thyroiditis were reported in <1% of patients (23). This certainly reflects the increasing skill of the
| Area of concern                        | Thermal ablation                                                                 | RAI ablation                                                                 | Surgery                                                                 |
|---------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Spectrum of therapy                   | Mainly benign, toxic or nontoxic nodules within the reach of ultrasound<sup>a</sup> | Only benign toxic nodules                                                     | All benign or malignant nodules                                        |
| Expertise availability                | Only available at certain tertiary care centers                                  | Covered routinely                                                            | High-volume thyroid surgeons are available at tertiary care centers    |
| Insurance coverage                    | Inconsistent<sup>b</sup>                                                          | Covered routinely                                                            | Covered routinely                                                      |
| Procedural cost<sup>c</sup>           | Moderate                                                                        | Very low/low                                                                | High                                                                   |
| Location                              | Outpatient procedure                                                             | Outpatient procedure                                                         | Inpatient usually                                                      |
| Anesthesia                            | Local or general<sup>d</sup>                                                      | Absent                                                                       | From light sedation to general anesthesia                              |
| Scar                                  | No scar                                                                         | No scar                                                                      | Collar scar                                                            |
| Complications                         | Potential discomfort during procedure                                           | Well-tolerated                                                               | Potential discomfort postprocedure                                      |
|                                       | Minimal complications                                                           | Minimal complications                                                        | 1-2% long-term dysphonia                                               |
| Risk of hypothyroidism                | <1%                                                                             | 20-40%                                                                       | 10-40% for lobectomy<sup>e</sup>                                       |
| Monitoring for regrowth               | Consistent need for ultrasound monitoring                                       | Very rare for toxic nodules                                                  | Absent                                                                 |
| Need for repeat therapy               | 5-10%<sup>f</sup>                                                               | Rare                                                                         | Absent                                                                 |

Abbreviations: RAI, radioactive iodine.
<sup>a</sup>Nodules that can be well visualized by ultrasound and treated with ultrasound-guided probe.
<sup>b</sup>Papillary thyroid microcarcinoma can be considered for this approach if they would be considered appropriate for active surveillance.
<sup>c</sup>There is an ongoing process for creating specific Current Procedural Terminology (CPT) codes for insurance reimbursement. Authors’ experience is that insurance coverage is around 60%.
<sup>d</sup>Very low cost <$1000; low-cost range is $1000-3000; moderate-cost range is $3000-10 000; high cost is >$10 000.
<sup>e</sup>Depends on size of lesion, location and operator preference.
<sup>f</sup>Logistical restrictions imposed by radiation safety rules (vary by region).
<sup>g</sup>Rate varies depending on preoperative thyroid function.
<sup>h</sup>Varies widely with protocol utilized and criteria for success/failure. Needs considering in comparison with conversion to surgery.
operators as the series grew larger and it also emphasizes the importance of seeking such expertise for patients interested in this procedure.

What about other TA therapies?
Other TA techniques, LTA, MWA, and HIFU, have been studied less extensively for the treatment of solid benign thyroid nodules and are used less frequently than RFA (24). The efficacy of LTA in solid thyroid nodules has been initially documented in several single-center studies (25, 26) and subsequently confirmed by multicenter prospective randomized trials that demonstrated a 59% to 72% mean nodule volume reduction at 12 months (27, 28). Studies comparing RFA to LTA have shown that both TA techniques result in clinically significant and long-lasting volume reduction of benign thyroid nodules, but there was a lower risk of regrowth and need for retreatment with RFA (9, 29, 30). Given the lower efficacy, higher cost, and limited evidence compared with RFA and LTA, HIFU and MWA are not routinely recommended (13).

When should retreatment or surgery be considered after TA?
Several studies have evaluated risk factors for nodule regrowth to help with the decision for repeat TA (31). However, the decision for repeat TA should be contrasted with that for surgery if nodule volume returns to the preablation value or if compressive symptoms persist or develop de novo. Although repeat TA may be an option, there is no evidence that it will be equivalent to surgery in this population.

Ablation of Toxic Thyroid Nodules
Besides leading to compressive symptoms, the nodule described in the vignette also exhibits autonomous thyroid hormone production, a separate indication for therapy. Toxic nodules account for up to 10% of thyroid nodule cases, with approximately 75% of these patients exhibiting subclinical or overt hyperthyroidism (1, 32). While both radioactive iodine (RAI) therapy and thyroid surgery are considered relatively safe and effective definitive treatment approaches (33) they have several limitations, as discussed earlier. It is, therefore, not surprising that TA therapies have also been studied for this pathology (Table 2).

What is the evidence supporting RFA of toxic thyroid nodules?
Available studies have focused on patients with toxic nodules who declined RAI and surgery or for whom these procedures were contraindicated (20, 34-37). However, there is no consensus among professional societies on the use of TA therapies in this clinical scenario (12, 13, 33, 38, 39). The main consideration of using ablative techniques for toxic nodules is the higher potential for preservation of thyroid function compared with RAI or surgery, while achieving significant nodule volume reduction and resolution or amelioration of symptoms of hyperthyroidism (15, 20, 34, 40). Several studies, albeit heterogeneous, have shown that RFA and LTA can achieve normalization of thyroid function tests with an average volume reduction of 70% to 80% at 12 to 24 months and singled out nodules <12 mL as having excellent results (41, 42). A prospective study of 30 patients with mean nodule diameter of 3.9 cm found that a single RFA session reduced nodule volume by 75% with significant improvement in local discomfort and cosmetic score, and with 50% of patients achieving long-standing euthyroidism at 12 months (34). In a randomized prospective trial, a single session of LTA, while equally effective at volume reduction, resulted in only 50% of patients achieving normal TSH, compared with 100% of those treated with RAI (43). Some have performed repeat RFA for large toxic nodules unresponsive to initial ablation, and documented 79% of patients having concomitant nodule volume reduction and resolution of hyperthyroidism without any major complications (20). Additionally, one can follow RFA with RAI therapy for the nodules that remain toxic after RFA. In this case, there will be a significant reduction in the dose of RAI and likely, through decrease in nodule size, also a considerable improvement in health-related quality of life compared with RAI alone (37, 44).

What additional considerations are important regarding thyroid function?
It is reassuring to see that the studies in this area have rarely identified patients developing hypothyroidism after TA. One study (22) indicates only 1 such case in a patient with preexistent anti-thyroglobulin and anti-thyroid peroxidase (TPO) antibodies. Some authors render patients euthyroid with antithyroid drugs before TA (34, 35). We are pursuing that for couple weeks before therapy in patients with more severe hyperthyroidism or with large toxic nodules (>10 mL). This is based on our experience (manuscript in preparation) that suggests a possibly significant, albeit transient, increase in thyroid hormone levels after TA.

Is there a need for FNA prior to TA for toxic thyroid nodules?
In general, since toxic nodules very rarely harbor malignancy, FNA biopsy is typically not recommended (3). Yet some experts recommend 1 benign cytology prior to TA unless there are sonographic concerning features, in which case 2 cytological assessments are deemed necessary (12, 15, 45).

What about the other thermal ablative therapies for toxic thyroid nodules?
Currently there are insufficient data to recommend use of HIFU or MWA for the treatment of toxic nodules.

How is RFA Performed for Treatment of Benign Thyroid Nodules?
TA of benign symptomatic thyroid nodules is performed with the intention of treating as much of the nodule as possible while avoiding extrathyroidal extension of the ablation zone. This approach maximizes safety by protecting extrathyroidal structures from nontarget ablation, but also means that these ablations may be subtotal, with some untreated benign nodular tissue along the nodule’s periphery. The treatment is performed on an outpatient basis, most commonly under local anesthesia, but moderate sedation or even general anesthesia

| Appearance                                      | Cosmetic score |
|-------------------------------------------------|----------------|
| No palpable mass                                | 1              |
| Mass not visible but palpable                   | 2              |
| Mass visible with swallowing only               | 3              |
| Easily visible mass at all times                 | 4              |

Table 3. Physician-assessed cosmetic score
may be appropriate depending upon patient and target lesion characteristics (14, 46-48). For example, larger lesions which require more time to treat may warrant higher levels of sedation. After skin preparation, a dermatotomy is made, and the ablation applicator is advanced into the target lesion under real-time sonographic guidance. Needle path planning is done under ultrasound guidance and aims to avoid blood vessels and produce a trajectory that allows optimal electrode placement and movement during ablation. If possible, lesions are treated with a single puncture, but multiple entry sites may be needed for larger nodules. A trans-isthmic approach is preferred when possible to minimize unwanted electrode migration during patient swallowing and to avoid leakage of heated fluid from the ablation target (13, 48, 49). Thyroid RFA commonly uses the moving shot technique, where each zone is ablated until the tissue becomes transiently hyperechoic or impedance becomes high enough that energy is no longer being deposited (49).

Because ablative techniques result in gas production which obscures deeper structures from sonographic visualization, the deeper zones are treated first, sequentially moving superficially. Once 1 sonographic plane has been treated, the next adjacent sonographic plane is treated in a similar manner until the nodule has been treated as thoroughly as possible. The appropriate length of exposed tip radiofrequency electrode or laser filament is selected to produce the desired ablation volume based upon nodule size, shape, and adjacent structures. Ablation zones are typically more aggressive in the center of the nodule, with smaller ablations performed along the nodule and thyroidal margins to enhance safety (48). After the ablation, ultrasound images are obtained to assess for completeness and complications. Undertreated areas may be identified based on the presence of Doppler flow or relatively increased echogenicity compared with treated tissue (following the initial hyperechoic change that occurs during TA, the treated zone may become hypoechoic). Adjunct maneuvers (cyst aspiration, hydrodissection, leveraging of the nodule with the electrode, etc.) may enhance the safety and technical success of thyroid TA.

Back to Our Patient

After reviewing all options, she elected to proceed with RFA given the progressive nature on her compressive symptoms as well as the presence of thyrotoxicosis. Within the first month after RFA the tremors disappeared and around 2 months after the procedure she noticed that the nodule was less visible, and she no longer had local pressure. The TSH value was 0.8 mIU/L at 3 months postprocedure while the nodule shrank to 4.5 mL (60% volume reduction). At 1-year after RFA TSH was 0.6 mIU/L and the nodule decreased to 2.6 mL (80% volume reduction) but showed persistent vascularity at its periphery (Fig. 2A and 2B). She is very pleased with the results (invisible nodule and absent local pressure) but understands the need for follow-up which will guide the discussion about the need for additional therapy (see “What About Other TA Therapies?”).

Nonsurgical Management of Thyroid Cysts

Clinical Case

A 27-year-old man presents for evaluation of an enlarging thyroid lesion detected 3 years ago. Imaging at that time revealed a right thyroid cyst measuring 5.2 × 4.3 × 3.9 cm (44 mL). No intervention was deemed necessary as he was asymptomatic. Two years later the lesion was larger and was pursued with FNA (benign cystic content) and drained (10 mL). Five months later the patient again noticed slow enlargement of this lesion, causing swallowing challenges and anxiety related to the rate of growth. The ultrasound showed a cystic nodule (Fig. 3A and 3B) that occupies most of the right thyroid lobe and measures 9.3 × 5.5 × 6.8 cm (174 mL). While the patient is euthyroid and the FNA is unremarkable, surgery was recommended due to compressive symptoms. He is interested in alternative therapeutic options to avoid a surgical scar and minimize the risk of hypothyroidism.

Ethanol Ablation for Cystic Thyroid Nodules

This case illustrates 1 of the 10% of thyroid lesions that are purely cystic and in which the risk of malignancy is negligible (<1%). However, despite their low malignancy risk, cystic nodules can become rather large due to fluid accumulation and result in compressive symptoms or cause esthetic concerns due to the appearance of a bulging mass in the neck. When symptoms are present, cyst aspiration is recommended for symptom relief (13). However, it is estimated that in 60% to

Figure 2. (A) Transverse ultrasound view of solid thyroid nodule 1 year after RFA. (B) Longitudinal ultrasound view with Doppler color flow of solid nodule 1-year after RFA.
What is the evidence supporting PEI for thyroid cysts?
The first studies documenting the safety and efficacy of PEI for treating recurring and symptomatic cystic nodules came from Japan (52), followed shortly thereafter by various reports from Italy (53, 54). A double-blind randomized study (N = 66) compared instillation of 99% ethanol vs isotonic saline into the cyst, followed by complete emptying. At 6 months postprocedure, 82% of patients treated with ethanol were cured (ie, cyst volume was ≤1 mL at the end of follow-up) compared with 48% of patients treated with saline, with the chance of success decreasing with higher number of previous aspirations and larger baseline cyst volume (51). Complications included transient pain and in 1 patient transient dysphonia. In 2018 Inguez-Ariza et al. published the first PEI study in the United States (55). After a median follow-up of 2 years, 89% of treated patients reported no compressive symptoms and 75% had >50% reduction in nodule volume. Four patients (20%) reported mild and transient symptoms (mild pain, a vasovagal reaction, and bleeding into the cyst) but none were deemed serious. A recently published systematic review and meta-analysis evaluated a total of 1667 nodules with up to 10 years of follow up (56). They noted volume reductions of 81% at 12 months, 74% at 5 years, and 69% at 10 years, along with significant reductions in compressive symptoms and cosmetic concerns.

What are the local complications and the risk of recurrence?
The meta-analysis by Cesareo et al. (56) identified no permanent complications in these studies and, reassuringly, the thyroid function was unaffected in all patients. However, early postprocedure complications include mild to moderate pain or local burning sensation, transient dysphonia, vasovagal reaction, and bleeding into the cyst (55). The risk of recurrence is quite low, compared with cyst drainage alone, and has been reported to range between 7% and 38% (57, 58). It is highest in nodules with larger initial volume (>20 mL) and higher vascularity (grade >1). In such cases repeat PEI may be helpful.

How is PEI performed?
Patients are positioned supine, possibly with the head turned away from the targeted side, potentially with a cervical support to accentuate neck extension. Sonographic evaluation of the targeted cyst is performed with a high-frequency linear transducer; then an approach is selected which avoids blood vessels and critical structures. A path that traverses thyroid parenchyma is preferred as it minimizes the potential for ethanol to leak into nontarget areas. After the skin has been prepared in sterile fashion, local anesthesia is delivered to the skin and the intervening tissues under sonographic guidance. Next, under sonographic guidance, a needle or catheter is placed into the target cyst. The authors prefer to place a centesis catheter because of the ease with which it can aspirate even complex fluid or blood. A 3-way stopcock is connected to the needle or catheter and the contents aspirated as completely as possible. Closing the 3-way stopcock prior to disconnecting the aspirating syringe will prevent air from entering the cystic nodule, which would compromise sonographic visualization. Additionally, this allows a single puncture, as opposed to repeated punctures for aspiration, injection, and re-aspiration. Next, high-purity ethanol (95-99%) is instilled through the indwelling needle or catheter and allowed to percolate. Dwell time for ethanol is variable based on practice, with some advocating for times as short as 2 minutes, while others employ 10 to 25 minutes (55, 59, 60). While the volume of ethanol to be instilled can be estimated preprocedurally by performing volumetric calculations based upon the cyst dimensions, practically it can be determined based on the volume aspirated. It is not necessary to completely fill the cyst with the maximal volume of ethanol, rather a volume sufficient to contact every surface of the cyst walls is needed, typically 50% of the aspirate. Instilling a lower than maximal volume also decreases the chances that the cyst is pressurized and could leak ethanol into nontarget tissues. After the percolation period, the entire volume of ethanol is reaspirated. During the percolation period, patients remain motionless and supine so as to not dislodge the indwelling needle or catheter and to not expel the ethanol. Patients are attended during this period to ensure they remain asymptomatic.
Table 4. Comparison of nonsurgical vs surgical management of thyroid cysts

| Area of concern     | Simple aspiration                                                                 | Aspiration and ethanol sclerosis                                      | Surgery (lobectomy)                                    |
|---------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------|
| Spectrum of therapy | Cysts within the reach of ultrasound<sup>a</sup>                                   | Cysts within the reach of ultrasound<sup>a</sup>                        | All cysts                                              |
| Expertise availability | Common                                                                             | Mainly at tertiary care centers                                       | High-volume thyroid surgeons are available at tertiary care centers |
| Insurance coverage | Covered routinely                                                                | Covered routinely                                                      | Covered routinely                                      |
| Procedural cost<sup>b</sup> | Very low                                                                          | Low                                                                    | High                                                  |
| Location            | Outpatient procedure                                                              | Outpatient procedure                                                  | Inpatient usually                                      |
| Anesthesia          | Local                                                                              | Local                                                                  | From light sedation to general anesthesia             |
| Scar                | No scar                                                                           | No scar                                                                | Collar scar                                            |
| Complications       | Well-tolerated                                                                    | Potential discomfort during procedure                                  | Potential discomfort postprocedure                     |
|                     | Minimal complications                                                             | Minimal complications                                                 | 1-2% long-term dysphonia                               |
| Risk of hypothyroidism | Absent                                                                           | Absent                                                                 | 10-40% for lobectomy<sup>c</sup>                      |
| Cyst recurrence rate | High (>60%) possibility of regrowth of treated cyst necessitating repeat intervention or conversion to surgery | Very low possibility of regrowth of treated cyst necessitating repeat intervention or conversion to surgery | Absent                                                |

<sup>a</sup>Cysts that can be well visualized by ultrasound and treated with ultrasound-guided probe.

<sup>b</sup>Very low cost <$1000; low-cost range is $1000-3000; moderate-cost range is $3000-10 000; high cost is >$10 000.

<sup>c</sup>Rate varies depending on preoperative thyroid function.
Back to Our Patient
He is referred to our interventional radiology for consideration of ethanol ablation. The cyst is again aspirated (162 mL of clear fluid) and 5 cc of 99% ethanol is injected. Seventeen months postprocedure he achieved 97% reduction in volume and resolution of compressive symptoms. (Fig. 4A and 4B).

Ablative Therapies for Papillary Thyroid Carcinoma
Clinical Cases

Case 1
A 52-year-old man presents with an isolated 0.9 × 0.4 × 0.9 cm (0.170 mL) irregular thyroid nodule detected on a neck computed tomography scan performed after a motor vehicle accident. He was evaluated with ultrasound, and biopsy 4 months earlier confirmed the nodule to be papillary thyroid carcinoma (Fig. 5A and 5B). There were no abnormal appearing lymph nodes and no other thyroid nodules. He chose observation but now is no longer comfortable with that plan. He is also interested in avoiding surgery due to concerns about hypothyroidism and inquired about ablative therapies for this papillary thyroid microcarcinoma (PTMC).

Case 2
A 42-year-old woman with history of hypothyroidism secondary to Hashimoto’s thyroiditis (levothyroxine 75 µg daily) complained of neck pressure. Neck ultrasound revealed a 0.9 × 0.6 × 0.6 cm (0.160 mL) suspicious thyroid nodule (Fig. 6A and 6B), positive for PTC on FNA cytology. After reviewing surgical therapy and active surveillance, she elected RFA as part of a research protocol.
Ablation of PTMC

Active surveillance is a valid approach to management for a subgroup of PTMC (3, 61), yet the rate of delayed surgeries is not trivial at 3.4% to 32% (62-64). Most of these interventions are driven by patients' anxiety that develops while monitoring an untreated cancer lesion (65). Therefore, interest in alternative treatment options has increased in recent years. There are currently 2 reported modalities for ablating PTMC: PEI and TA (RFA, LTA and MWA). PEI and RFA have the most supportive evidence, are the most widespread in practice, and will be discussed here in more detail.

What is the evidence supporting PEI for PTMC?

PEI therapy of thyroid carcinoma was first reported by Goletti et al. (66) and it has found a niche as a nonsurgical treatment modality of isolated cervical node metastasis from differentiated thyroid carcinoma and medullary thyroid carcinoma (67, 68). However, its sustained efficacy over the years has led some academic centers to use this approach also for initial therapy of PTMC (69). In their paper, Hay et al. (68) reported that of 17 PTMC treated with PEI; 8 disappeared after a median follow-up of 10 months while the other 9 had a median volume reduction of 82%, without new foci of carcinoma or lymph node metastases.

What is the mechanism of action of PEI for PTMC?

The principle of action of ethanol ablation is based on the toxic effect of concentrated alcohol on the cells, leading to dehydration and protein denaturation in parallel with the toxic effect on small blood vessels causing thrombosis with subsequent ischemia of the subservient territory. This leads to fibrosis of the thyroid lesion, which in time becomes smaller and, in some cases, disappears completely (68-70).

How is PEI for malignant lesions different than the approach for benign thyroid cysts?

Alcohol’s penetration in a solid nodule (as opposed to its free movement in a cyst) is partly based on needle positioning and technique and partly based on free diffusion between the malignant cells. This can be heterogeneous and thus the cytotoxic impact can be uneven. The approach taken at our institutions is to perform a second PEI session 24 hours after the first one and look to retreat areas with residual vascularity based on Doppler flow signal.

What is the evidence supporting TA for PTMC?

TA has been employed for the therapy of PTMC for more than a decade and a few studies are now available to summarize the data. In the systematic review of Choi and Jung (71) TA was followed by a tumor volume reduction of >98% and lymph node metastasis of 0.4% (2 cases, both after LTA) but fortunately without local recurrence or distant metastasis as noted in another systematic review (72). In absolute terms these results appear better than active surveillance, where progression to clinical disease was noted in 4% of patients (63) and lymph node involvement developed in 2% of patients over 5 years (65). However, so far, no trial has directly compared the 2 approaches. The efficacy comparison provided by the meta-analysis contrasting the different TA modalities (71) indicates that RFA is superior in volume reduction at 99.3% compared with MWA (95.3%), while LTA is least effective (88.6%). While this result has probably multiple explanations, it is important to consider that RFA is the dominant TA approach currently in use (both for benign and malignant lesions). Given the indolent nature of PTC 1 of the RFA, pioneering groups led by Baek reported recently the results of a minimum 5-year follow-up of RFA for PTMC (73) and noted that additional ablations were needed in 13/84 tumors (when the initial RFA did not fully ablate the margin of the tumor) for an average of 1.2 RFA sessions per tumor. With this approach the volume reduction was >98% at 24 months after the procedure and no tumors were visible at 5 years. Furthermore, there was no evidence for lymph node involvement or distant metastases during this extended follow-up.

Does TA have a role for larger thyroid malignancies?

TA was rarely studied for ablation of macro PTC (>10 mm diameter) and is unlikely to yield results as attractive as those described for PTMC. One paper utilizing surgical pathology indicated that after TA such lesions still had residual cancer and subsequently presented lymph node metastasis (74). Thus, we endorse the concept that TA at the present time should be considered only for PTMC.

How is RFA for malignant lesions different than the approach for benign thyroid nodules?

Methodologically RFA for PTMC is somewhat different than the approach utilized for a benign lesion. Since PTMC
lesions are smaller and will require less treatment time, the need for anesthetic support is diminished. On the other hand, malignant lesions are treated with curative intent so ablative margins beyond the nodule are necessary, a factor that is considered during patient selection and procedure planning. Lim et al. reported obtaining minimum margins of 2 mm during RFA of mPTC (75). This is particularly important during follow-up when the volume of the ablated lesions will initially be larger than the volume of the PTMC and this must be interpreted carefully.

What are the potential complications of TA and PEI?
The rate of major complication related to TA is low at 0.7% and all were related to voice changes (71). The overall complication rate was 3.2% and included small hematomas, skin burn (mild), and temporary pain. Of note, MWA did have a higher proportion of both major (2.5%) and minor (5%) complications compared with RFA and LTA, while also being the least utilized. PEI may be followed by transient neck discomfort, typically mild, and occasional transient hoarseness (if posterior nodules). However, none of the PEI-treated PTMC had any long-term complications from therapy (69).

What are the contraindications to ablative therapies for PTMC?
The major contraindications include presence of extrathyroidal extension, presence of cervical adenopathy, genetic basis for thyroid malignancy (eg, Cowden syndrome, familial adenomatous polyposis, Carney complex), and limited visualization by ultrasound. Whether a subcapsular location of the tumor is a contraindication to ablation is debatable and depends on the experience of the operator with hydrodissection techniques. Additional concerns are raised by limited neck mobility, prior surgical scars over the area or prior radiation therapy.

Back to Our Patients
Case 1
The nodule was treated in 2 sessions, on 2 consecutive days, with 0.4 and 0.2 mL of ethanol respectively. Its size decreased gradually over time from 0.169 mL to 0.006 mL at 36 months after procedure (Fig. 7A and 7B). His TSH remained normal but to keep it <2.0 mIU/L he was treated with 50 µg of levothyroxine daily for the first 2 years and then discontinued. His TSH is now 2.8 mIU/L, the nodule is barely visible, and he has no complaints at 4 years from PEI.

Case 2
RFA was preceded by hydrodissection to separate the thyroid from the trachea (15 mL of dextrose solution were used). Thereafter the nodule was ablated using a 1-cm exposed tip with a total ablation time of 2 minutes. She tolerated the procedure well and continued the same dose of levothyroxine. Over the next year she had normal thyroid levels, did not report any local complaints over the thyroid bed, and the nodule was found to be 0.072 mL (0.6 × 0.4 × 0.6 cm) at 13 months after RFA (Fig. 8A and 8B), after an initial increase to 0.280 mL at 6 months of follow-up.

Summary and Conclusions
Summary for TA of Benign Thyroid Nodules
The dominant TA approach is RFA, with most data reflecting that methodology. The main targets for these procedures are compressive and/or toxic thyroid nodules. Conversely, we endorse the opinion that asymptomatic and nontoxic thyroid nodules, without significant esthetic concerns, should not be offered such unnecessary therapy (76, 77). For nontoxic nodules, benign cytology should be documented twice prior to TA, while this is less important for toxic nodules, given their extremely low likelihood of malignancy. TA can decrease the volume of these nodules by about 75% while also controlling hyperthyroidism in most toxic nodules. Repeat TA is likely to increase the rate of response, but adding surgery or RAI might still be needed in some cases.

Summary for PEI of Thyroid Cysts
Purely or predominantly cystic (>80% cystic component) nodules, with associated compressive symptoms that recur after simple aspiration are the ideal target for PEI. Compressive symptoms, along with volume reduction, are durably eliminated in >80% of patients.

Summary for TA/PEI of PTMC
TA and PEI for PTMC have been studied for cases at very low risk for extrathyroidal spread. For that group of patients, the
results, particularly with RFA and PEI, are very encouraging. However, the data remain limited for both approaches and further evaluation is needed before a clear recommendation can be made on this indication, particularly as the penetration of these methods in the United States remains quite low. Ideally, a study comparing active surveillance with TA, PEI, and the standard surgical approach with outcome focused on disease control, quality of life, and the economics of each approach for a minimum of 3-5 years would be most informative for guiding the future of the practice.

For all these thyroid procedures the appropriate selection of patients, along with the availability of a skilled operator, are essential elements needed to reproduce the success rates described here while minimizing the risk of complications. The authors’ approach is to use the team in Interventional Radiology given their familiarity with PEI and TA. Regardless of the local setup, it is important to keep in mind that there is a learning curve for these procedures and the volume of procedures performed will likely, like classic thyroid surgery, play a significant role in both the procedures’ success and complication rates.

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Disclosure Summary

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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