Minimally Invasive Techniques for the Management of Thyroid Nodules

Chelsey K. Baldwin, MD, ECNU[a,*], Michael B. Natter, MD[a], Kepal N. Patel, MD[b], Steven P. Hodak, MD, ECNU[a]

KEYWORDS

• Thyroid nodule • Thyroid neoplasms • Minimally invasive therapy • Ethanol ablation • Thermal ablation • Radiofrequency ablation • Laser ablation

KEY POINTS

- Data increasingly support the use of minimally invasive techniques (MITs) as nonsurgical options for the treatment of thyroid disease.
- MITs are typically performed in the ambulatory setting under local anesthesia. This facilitates rapid treatment and discharge postprocedure.
- Evidence supports the use of MIT for the treatment of select benign symptomatic and autonomously functional thyroid nodules. Recent literature demonstrates the potential for MIT in the treatment of primary papillary thyroid cancer as well as recurrent disease.
- These techniques require training, practice, and competent understanding of cervical anatomy to minimize risk and produce successful outcomes. When performed by an experienced operator, risks associated with RFA are typically lower than those associated with surgical management creating a favorable risk to benefit ratio.

Thyroid nodules are common and the majority are benign and do not require intervention.[1] A subset of benign thyroid nodules (BTN) may be symptomatic or autonomously functional requiring definitive treatment. Radioactive iodine (RAI) is effective in treating autonomously functional thyroid nodules (AFTN), but can render the patient permanently hypothyroid and presents risks of salivary and lacrimal gland injury as well as potential risks of secondary malignancy. Surgical management is appropriate for BTN and thyroid cancers requiring definitive management. Surgery requires hospital admission, general anesthesia, and even if the procedure is limited to lobectomy up to 23.6% of patients will remain permanently hypothyroid.[2] Surgery also conveys a

[a] Department of Medicine, Diabetes and Endocrinology Section, New York University School of Medicine, 222 East, 41st Street, Floor 23, NY 10016, USA; [b] Otolaryngology and Biochemistry, Division of Endocrine Surgery, Department of Surgery, Division of Endocrine Surgery, New York University School of Medicine, 530 1st Avenue, Floor 12, NY 10016, USA

* Corresponding author.

E-mail address: Chelsey.Baldwin@nyulangone.org

Endocrinol Metab Clin N Am 51 (2022) 323–349
https://doi.org/10.1016/j.ecl.2022.01.001 endo.theclinics.com
0889-8529/22/

small risk of permanent hypoparathyroidism and voice changes. Alternatives to both surgery and RAI are appealing, and recent innovation in MIT for the management of thyroid nodules may provide such an alternative.

MIT uses a variety of ultrasound-guided percutaneous methods performed in the outpatient setting under local anesthesia with the optional addition of a mild sedative. MIT is associated with no or minimal scarring, rapid recovery, and almost never results in hypothyroidism in appropriately selected patients.

The composition, size, and functional status of thyroid nodules dictate both the selection and success of each modality of MIT. The goal of this article is to present the various MIT modalities, discussion of indications, techniques, risks, and outcomes.

MIT MODALITIES

Simple aspiration

Outcomes by indication

Cystic and predominantly cystic nodules. Predominantly cystic nodules are composed of greater than 50% fluid by volume and are overwhelmingly benign[3] but may still produce compressive and cosmetic symptoms. These symptoms can often be immediately relieved by simple aspiration and drainage. However without the use of sclerosing agent (typically 95%–98% dehydrated ethanol) cystic fluid reaccumulation occurs in 58%–81%[4,5] of cases. Despite the relatively high likelihood of fluid reaccumulation, the procedure is low risk and allows the acquisition of diagnostic cytology to confirm benignity before more definitive treatment such as ethanol ablation (EA), thermal ablation, or surgery. Simple aspiration (**Fig. 1**) is, therefore, often a reasonable first step in the management of predominantly cystic nodules.[6]

Technique

Please refer to the included Appendix 1 for the discussion of the technique for simple aspiration of predominantly cystic nodules.

Ethanol ablation

Outcomes by indication

Pure cyst and predominantly cystic nodules. In the case of reaccumulation of a predominantly cystic nodule, ethanol sclerotherapy commonly referred to as EA offers an effective means of therapeutic escalation after negative cytology has been verified[6] (**Fig. 2**). EA may be used as first-line therapy for the initial treatment of purely cystic nodules without confirming benign cytology given the risk of malignancy is less than 1%.[7] Injection of 95% to 99% ethanol into an evacuated cyst causes coagulative and ischemic necrosis of the cyst epithelium and small vessels in contact with ethanol including inducing reactive fibrosis that can prevent the reaccumulation of cystic contents. EA is 85% to 98% effective in pure cysts and 60% to 90% effective in predominantly cystic nodules (>50% cystic).[6] The ability to evacuate all cystic fluid contents before ethanol instillation has been shown to predict higher success rate (93.3%) versus nodules with a lesser degree of cystic fluid evacuation.[4] However it's noteworthy that even when EA sufficiently resolves the cystic component of a complex thyroid nodule, Jang and colleagues reported that patient satisfaction may decline when the initial solid component exceeds 20%.[8]

Autonomously functioning thyroid nodules. EA for AFTN was first proposed in 1990 by Livraghi and colleagues who reported that multiple and serial injections of 1 to 5 mL of 95% ethanol-induced coagulative necrosis leading to the normalization of thyroid function, nodule volume reduction, and normalization of nuclear scintigraphy.[9,10]

Fig. 1. Placement of Needle via transisthmic approach into the lumen of cyst.

Complete responses ranged from 64% to 85% and nodule volumes greater than 15 mL were associated with poor response.[11] Papini and colleagues subsequently suggested that EA might be particularly useful in young patients with nontoxic AFTN in which progression over lifetime is likely, nodules tend to be smaller, and as a way of avoiding hypothyroidism following surgical management or RAI.[12] Papini and colleagues reported EA success rates of greater than 90% in nontoxic AFTN.[11] A newer vascularity targeted ethanol injection technique has been described by Sharma and colleagues which requires fewer ethanol injections and smaller volumes of ethanol (median 0.46 mL/mL nodule volume), resulting in an increase in TSH in 83% of patients and TSH normalization in 61%, n = 18.[13] However, median nodule volume in this study was 5.7 mL and large nodule volume greater than 20 mL was cited as the cause for 2/5 reported procedure failures.

Despite the low rate of malignancy in AFTN we still recommend obtaining benign cytology on one occasion before EA since papillary thyroid carcinoma in these functional thyroid nodules may still rarely occur.[14]

Recurrent papillary thyroid cancer. A growing literature supports the use of EA as a 2nd line intervention for treated recurrent PTC in appropriately selected cases. Though there are no head-to-head comparisons of surgical management and EA, meta-analysis data including 27 studies with a total of 1617 patients that though the surgery was statistically superior to EA rates of posttreatment cervical recurrence as well as complications, both were low and statistically similar for both procedures. However, the authors note that cases in the surgery cohort represented more histologically aggressive PTC recurrence, and patients treated with EA were generally older with more clinically indolent disease underscoring the clinical superiority of surgical management. The authors conclude that though surgical management remains the most definitive management option for recurrent PTC, EA can be effective for treating selected lesions when a “berry picking” approach is reasonable.[15]

Long-term follow-up of patients following EA is relatively scant but Hay and colleagues report over 5 years of mean follow-up for 25 patients with recurrent PTC

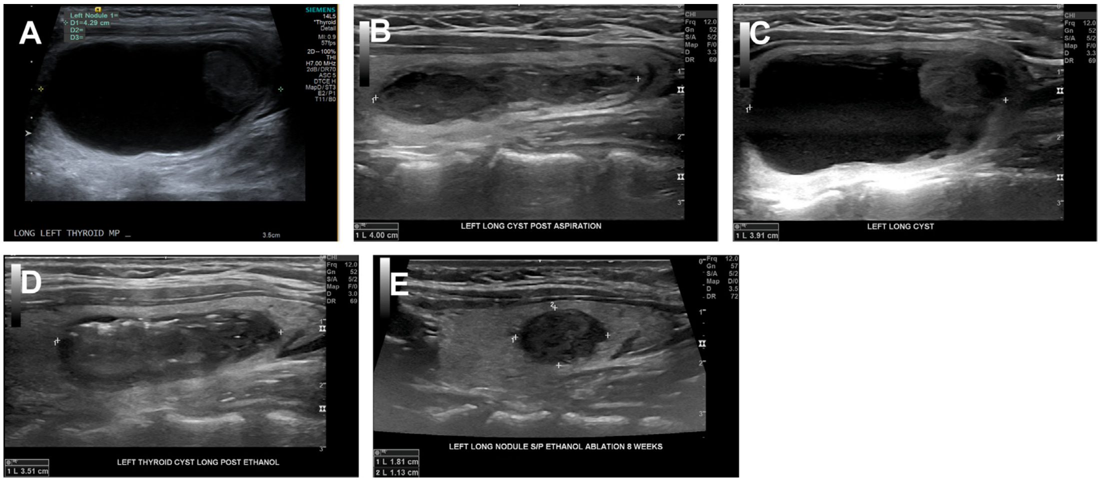

Fig. 2. Case of a 37-year-old female with cosmetic and compressive symptoms due to left-sided predominantly cystic nodule (*A*) Initial ultrasound evaluation (*B*) Status post simple aspiration (*C*) Reaccumulation of cystic fluid at 1-month follow-up (*D*) Immediately post ethanol aspiration (*E*) sustained benefit at 8-weeks post ethanol ablation.

with a total of 37 foci of cervical nodal recurrence.[16] Of 37 treated lesions 35 (95%) demonstrated a decrease in lesion size, 17 (46%) demonstrated complete ultrasonographic resolution, and all lesions seemed avascular by Doppler flow on follow-up. Subsequent disease recurrence at different sites was noted in 6 patients with a total of 18 new lesions of which 15 (83%) were successfully treated with additional EA. The authors further note that EA allowed avoidance of 40 neck reoperations at an aggregate cost savings of more than $61,000.

In patients with smaller foci of recurrent PTC, EA has been shown to have efficacy similar to the RFA with statistically similar outcomes both for VRR and complete disappearance of the targeted lesion. The rate of complications following RFA and EA were also statistically similar leading the authors to conclude that both RFA and EA are similarly effective interventions for patients with locally recurrent thyroid cancer who are not candidates for surgical management.

We agree that though surgery remains the most definitive method for control of locoregionally recurrent PTC EA may be effective for patients who are not ideal candidates for surgery, especially in the case of pauci-metastatic small volume locoregional recurrence, and may result in considerable cost savings when compared with surgery.

Technique

Please refer to the included Appendix 1 (**Figs. 3–6**) for the discussion of the technique for the EA of cystic lesions and recurrent PTC.

Thermal ablation

Thermal ablation includes a number of methods that generally employ the use of nonionizing electromagnetic energy to produce heat-induced coagulative necrosis of target tissue.

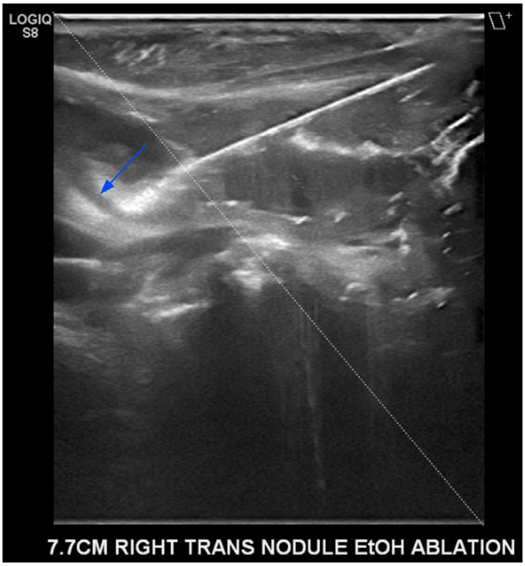

Fig. 3. Hyperechoic artifact of ethanol injection can obscure needle tip. Blue arrow demonstrates ethanol flow from the needle tip.

Fig. 4. Lidocaine 1% applied to anesthetize the thyroid capsule appears as an anechoic band separating the thyroid capsule and anterior lying sternothyroid muscle.

Radiofrequency ablation

Thyroid radiofrequency ablation (RFA) involved the percutaneous insertion of a 19 to 20 G internally water-cooled radiofrequency electrode to deliver electromagnetic energy in the range of 450 to 1200 kHz to cause friction between charged ions resulting in thermal injury and subsequent coagulative necrosis. Initially described for the treatment of hepatocellular disease, RFA was first used for the treatment of thyroid cancer lymph node metastasis in 1998. An early obstacle for thyroid RFA was unintended collateral tissue necrosis of nearby structures around the treatment target due to the distant propagation of heat generated during the procedure. Pivotal breakthroughs in thyroid RFA technique included the 1996 development of internally water-cooled electrodes that minimize thermal propagation,[17] and the transisthmic moving shot technique in 2008[18] which allows improved control of the treatment zone.. Though RFA has been successfully used in Asia and Europe for over a decade [19,20] whereby numerous guidelines have been developed (**Table 1**), FDA approval of RFA for the treatment of soft tissue disease including structural thyroid disease was only granted in 2018 making the procedure still relatively new in the US (RFA Approval

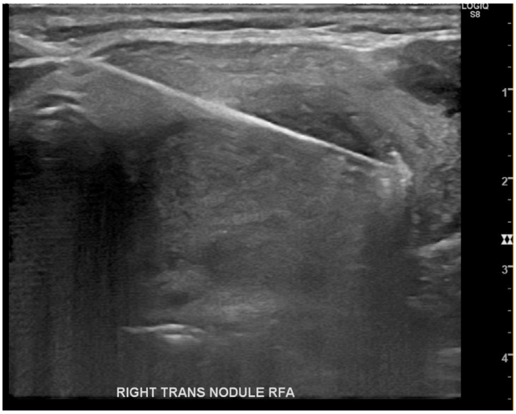

Fig. 5. The marginal vein is punctured and ablated initially by the electrode tip to avoid heat sink and promote peripheral treatment.

Fig. 6. Right-sided thyroid nodule (*A*) before RFA (*B*) immediate post-RFA demonstrating classic hyperechoic changes (*C*) 4-months post-RFA with classic dense hypoechoic appearance.

letter, March 14, 2018, Retrieved May 1, 2021 https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172012.pdf). Additionally, RFA lacks a CPT billing code and is still considered an experimental procedure by most payers within the US limiting reimbursement and therefore access for many patients. Despite an extensive international literature demonstrating the efficacy and safety of RFA, the US experience has remained limited and further published studies using US populations will be needed to support the development of a CPT code that will allow reimbursement for what is now almost exclusively a cash-only procedure.

Outcomes by indication

Benign symptomatic predominantly solid thyroid nodules Benign nodules causing cosmetic or compressive symptoms can be effectively treated with RFA with an expected volume reduction rate (VRR) of 50%–88.2% over the course of 6 to 18 months.[21,22] Patients reported significant improvement in cosmetic scores[23,24] and compressive symptom scores.[25]

Factors impacting efficacy include the feasibility of complete nodule treatment impacted by proximity to high-risk structures, nodule size, and nodule composition. Smaller nodule size and those with larger cystic components are associated with the greatest VRR.[21,26] Though a single competently performed RFA is effective in most cases, multiple treatments may be necessary in nodules greater than 30 mL[25] or in the case of marginal regrowth of previously treated lesions.[27]

Compared with surgical management which is the traditional first-line treatment of symptomatic benign nodules, it is important to educate patients that the benefit of RFA is not immediate, and instead accrues over the course of months. The VRR within the first 3 to 6 months occurs at the most rapid rate with continued but more gradual volume reduction over the following 6 to 18 months, as shown in a prospective single-center Austrian study which demonstrated a VRR of 68% and 82% at 3 and 12 months, respectively.[26] Despite this delay in therapeutic benefit one retrospective study demonstrated the efficacy and safety of RFA (n = 200) compared with patients managed surgically (n = 200) for cytologic benign symptomatic or functional thyroid nodules. RFA treated nodules demonstrated a mean 84.8% volume reduction at 1 year and had a lower risk of complications compared with those managed surgically, 1% versus 6%, $P = .002$.[28] Notably, the risk of postprocedural hypothyroidism was significantly lower after RFA versus surgery, 0.13% versus 71.5%, respectively.[28] Cases of post-RFA hypothyroidism are rarely reported to occur in patients with high titer of TPO or Tg antibodies before RFA.[29,30] Costs of RFA and surgery were similar in this study but the cost of thyroid surgery in China was reported to be $\$2556.95 \pm \$171.88$ compared with an average US Medicare cost of $5784 (https://www.medicare.gov/procedure-price-lookup/cost/60210 accessed 8/7/2021), suggesting that cost–benefit comparison is location dependent.

Bernardi and colleagues[24] compared RFA to hemithyroidectomy for the alleviation of nodule-related symptoms and found that though symptomatic and cosmetic outcomes were not statistically different following patients with RFA experienced significantly less procedure-related pain, hypothyroidism, and complications.

The sustainability of nodule volume reduction after RFA treatment was illustrated in a study of 111 patients with benign, nonfunctional thyroid nodules that demonstrated a mean volume reduction of 93.4% maintained over 3 years of follow-up with only a 5.6% rate of recurrence (increase of >50% of volume) attributed peripheral regrowth.[31]

Autonomous functioning thyroid nodules In 2008, Baek and colleagues[32] published the first case report of the successful use of RFA for AFTN. Subsequent studies

Table 1
Current RFA pre procedure requirements and indication by guidelines

Guidelines	Pre - Procedure Work up	First-Line Indications	Second-Line Indications
KSThR 2017	Two benign FNA/CNB Exception: One benign FNA/CNB in AFTN or K-TIRADS 2	Compressive or cosmetic symptomatic nonfunctional predominantly solid nodule Toxic or pretoxic AFTNs	Cystic/predominantly cystic nodule (after failed EA) Primary or recurrent thyroid neoplasms in patients refusing or unable to undergo surgery
AACE/ACE/AME 2016	Two benign FNA/CNB	Compressive or cosmetic symptomatic nonfunctional predominantly solid nodule	
NICE 2016	Two benign FNA/CNB	Compressive or cosmetic symptomatic benign thyroid nodules	
MITT group 2019	Two benign FNA/CNB Exception: One benign FNA/CNB in AFTN or EU-TIRADS 2, 3 Repeat FNA after initial RFA, before re-treatment in the setting of regrowth	Compressive or cosmetic symptomatic nonfunctional predominantly solid nodule	Cystic/predominantly cystic nodule (after failed EA) Dominant nodule in nontoxic MNG refusing surgery AFTN in patient refusing surgery or RAI Small AFTN in patients prioritizing sparing thyroid tissue and >80% of nodule ablation expected
Austrian professional associations 2019	Two benign FNA/CNB	Compressive or cosmetic symptomatic benign thyroid nodules Unifocal AFTN <15 mL	

(*continued on next page*)

Table 1 (*continued*)

Guidelines	Pre - Procedure Work up	First-Line Indications	Second-Line Indications
ETA 2020	Two benign FNA/CNB Exception: One benign FNA/CNB of spongiform or pure cystic lesions	Compressive or cosmetic symptomatic predominately solid benign thyroid nodules well defined dominant nodule of MNG Small AFTN and incomplete suppression of the perinodular thyroid issue	Cystic or predominantly cystic nodules that failed EA Large AFTN in patients who decline surgery or RAI Large AFTN with compressive symptoms may consider concurrent RAI and TA (RFA or LTA) for more rapid therapeutic response

Abbreviations: AACE/ACE/AME, American Association of Clinical Endocrinology/American College of Endocrinology/Associazione Medici Endocrinologi; AFTN, autonomous functioning thyroid nodule; CNB, Core needle biopsy; EA, ethanol ablation; ETA, European Thyroid Association; EU-TIRADS- European thyroid imaging reporting, and data system; FNA, fine needle aspiration; KSThR, Korean Society of Thyroid Radiology; K-TIRADS, Korean thyroid imaging reporting and data system; LTA, laser thermal ablation; MITT, minimally invasive treatment of thyroid; MNG, multinodular goiter; NICE, National Institute for Health and Care Excellence; RAI, radioactive iodine; TA, thermal ablation.

have reported variable efficacy of RFA for the treatment of AFTN with the improvement of thyroid function tests, discontinuation of antithyroidal medication, and scintigraphic evidence of response in66.7%–100%,[30,33,34] 22.7%–78.6%,[22,34–36] and44.4%–79.5%[30,34] of cases, respectively.

Cesareo and colleagues published a prospective study that demonstrated that RF outcomes for AFTN were dependent on nodule size: nodules less than 12 mL had larger VRR, greater increases in TSH, and significantly higher cure rate.[37] Additionally, they showed higher pretreatment AFTN volume was a negative predictor for the normalization of thyroid function.[38] This is consistent with the Austrian guidelines that support the use of RFA in AFTN less than 15 mL.[39]

Controversy still exists over whether initial nodule volume and the number of RFA treatments is accurate predictors of outcome as these findings have not been consistently significant.[40] Bernardi and colleagues reported that following RFA of patients with AFTN with complete normalization of thyroid function had an average of 81% volume reduction versus 68% volume reduction in those with only a partial response whereby thyroid function did not fully normalize,[36] suggesting that the ability to deliver complete treatment to the target nodule and not just initial nodule size is the critical factor impacting treatment outcome. This has been recognized by the Italian minimally invasive treatment of the thyroid group (MITT) group that recommends the consideration of RFA as a second-line intervention for AFTN when projected treated volume reduction will be at least 80%.[19]

Sung and colleagues demonstrate in a retrospective multi-institution study of 44 patients, that repeat sessions of RFA may be necessary for adequate response TSH normalization occurred in 81.7% of patients with AFTN with a mean initial nodule volume of 18.5 mL $\pm$ 30.1 mL. Treatment required a mean of 1.8 $\pm$ 0.9 sessions but up to 6 RFA sessions were necessary for the complete treatment of AFTN with attention to the adequate treatment of the marginal zones that could otherwise result in neoplastic regrowth of unabated tissue.[34]

Pretoxic nodules, defined as AFTN that do not suppress surrounding thyroid tissue on scintigraphy may respond to RFA better than more overtly functional thyroid nodules; Spiezia and colleagues reported 100% of patients with pretoxic nodules were able to discontinue antithyroid drugs following RFA versus 53% with toxic nodules.[35] Because of these findings, the European Thyroid Association 2020 guideline supports the first-line use of RFA for the treatment of pretoxic AFTN.[41]

Radioactive iodine (RAI) and surgery are the most commonly recommended first-line treatments for AFTN, though RFA is now recognized as a reasonable second-line option. There are a few studies in which RFA has been compared with these standards of care. To our knowledge, only a single retrospective study of 50 nodules compares RAI and RFA for the treatment of AFTN. Nodules were treated with fixed dose of 15 mCi of RAI (n = 25; mean pretreatment volume 11.0 mL) or 1 session of RFA (n = 25; mean pretreatment volume 14.3 mL).[33] The study demonstrated 100% efficacy restoring euthyroid function in both groups however RFA demonstrated a significantly larger VRR of 76.4% compared with RAI VRR of 68.4% (P > .05). Hypothyroidism occurred in 20% of patients treated with RAI and none of the patients treated with RFA leading the study authors to suggest that RFA may be a preferable option for the treatment of AFTN.

A 2014 retrospective study by Bernardi and colleagues comparing RFA to surgical management of thyroid nodules included a small subset of AFTN treated by RFA versus Surgery (n = 12; n = 20, respectively). Not surprisingly, the cure rate following thyroidectomy was 100% compared with only 33% of patients whose hyperthyroidism resolved following RFA.[24]

Predominantly cystic nodules (cystic component 50%–90%) Ethanol ablation of predominantly cystic nodules has demonstrated superior volume reduction compared with RFA, with a mean volume reduction of 81.1% versus 70.8%, respectively.[42] And Baek and colleagues did not demonstrate the superiority of RFA to EA in predominantly cystic nodules when superiority was defined as greater than 13% difference in VRR. Data suggest that EA is preferable first-line intervention for predominantly cystic nodules.[43] However, RFA may be considered as a second-line option after the failure of EA.[19,41,44] In 2011, Jang and colleagues showed that approximately a third of patients with predominantly cystic nodules, typically those with solid component greater than 20%, could be effectively treated with subsequent RFA leading to significant improvement in cosmetic and symptom scores as well as significant volume reduction of 92%, $P > .001$.[8]

Combined and simultaneous use of sclerotherapy and RFA has also been proposed. Shen and colleagues studied 119 patients with mixed solid cystic nodules treated with a combination of RFA for solid portions and polidocanol sclerotherapy in cystic portions resulting in VRR of 91.08%,[45] however the study is limited by lack of comparison to RFA or sclerotherapy only control groups.

Thyroid neoplasms Radiofrequency ablation (RFA) is also emerging as a useful tool for the management of small primary papillary thyroid cancers, follicular neoplasm, and locoregionally recurrent papillary thyroid cancer. Limited data do not support the use of RFA for the treatment of more aggressive thyroid carcinomas such as anaplastic carcinoma and medullary thyroid cancer.

Papillary thyroid cancer: The safety and efficacy of RFA for the treatment of papillary thyroid micro-carcinoma (PTMC) has been well demonstrated,[46,47] suggesting that in addition to observational management RFA may be another useful nonsurgical alternative for management. Complete or near-complete resolution of micro-PTC has been repeatedly demonstrated[47–49] including the treatment of bilateral PTMC foci.[50] Emerging data also show the efficacy of RFA treatment of larger primary tumors up to T1bN0.[51] These studies generally include cytologically confirmed solitary papillary thyroid carcinomas without aggressive clinical and ultrasonographic features in patients not otherwise suitable for surgical intervention.[46] Though literature is limited and additional studies are necessary, it still seems that RFA can be a useful alternative to surgery for small and otherwise low-risk papillary thyroid cancers.

Recurrent papillary thyroid cancer: A retrospective study by Choi and colleagues compared RFA and repeat surgical management for the treatment of patients with fewer than 3 foci of recurrent PTC. There was no statistically significant difference in recurrence-free survival between groups; however, there was a significantly higher risk of both hypocalcemia and overall complication rate among the patients managed with surgery.[52]

Chung and colleagues published a retrospective single institution study examining long-term outcomes among 29 patients with a total of 46 recurrent foci of PTC treated with RFA all of whom had a minimum of 5 years of posttreatment follow-up. Complete resolution was noted in 91% of cases. Though new locoregional recurrence and distant metastasis developed in 8 of 29 (28%), and 2 of 29 (7%) patients, respectively, 19 of 29 (66%) patients remained disease free with no long-term complications due to RFA at a mean of 80-months follow-up.[53]

Chung and colleagues also performed a meta-analysis including 24 studies, 2421 patients, and 2786 thyroid nodules to determine the safety of RFA for the treatment of benign nodules and recurrent thyroid cancers. Not surprisingly, complications occurred more frequently following the treatment of recurrent cancer compared with benign nodules. The authors suggest that the absence of normal thyroid tissue surrounding BTN and operator inexperience which could not be determined in the meta-analysis may explain the outcome differences. They nonetheless conclude that despite a slightly great risk of complication compared with the treatment of benign nodules, RFA is still a relatively safe and effective treatment of recurrent PTC.[54]

Follicular neoplasm: Surgery remains the standard of care for follicular neoplasms as only histologic examination can confirm the presence or absence of capsular and vascular invasion that distinguishes follicular thyroid carcinoma (FTC) from benign follicular neoplasm. However, as most of the follicular neoplasms are histologically benign great interest in less invasive methods such as RFA despite a generally sparse and controversial literature.[55] The use of RFA for follicular adenomas was discouraged by Dobrinja and colleagues who reported treatment of 6 ultrasonographically bland follicular neoplasms ranging in size from 2 to 40 mL. Of 6 treated nodules greater than 20 mL at the time of initial treatment regrew at 6 and 24 months of follow-up and were proven to be FTC following surgical excision. They conclude that RFA may delay surgical management for patients harboring follicular thyroid cancer and question whether RFA itself might induce neoplastic transformation.[56] Conversely, Ha and colleagues reported successful management of 1 to 2 cm nodules cytologic follicular neoplasms in 10 patients who refused surgery. Outcomes included 99.5% mean volume reduction, with 8/10 nodules completely disappearing, and no recurrence by final follow averaging more than 5 years.[57] Lesion size may be the critical factor differentiating the outcomes in these 2 small studies: Histologically follicular neoplasms greater than 4 cm have been shown to have a malignancy rate of 31% versus 13% for lesions less than 4 cm ($P = .05$)[58] and Machens and colleagues previously showed that the risk of all metastasis from FTC was nearly zero in tumors < 2 cm.[59] The noted differences in size may, therefore, explain the differences in outcomes noted by Dobrinja and Ha and colleagues and may suggest that for smaller follicular neoplasms that are very unlikely to have undergone malignant transformation RFA may be effective.

Though RFA is an alluring alternative for minimally invasive treatment of smaller follicular neoplasms, data remain extremely limited, and far more study is needed before an adequately supported recommendation can be made.

Device and techniques. Please refer to the included Appendix 1 for the discussion of the technique for RFA of thyroid nodules.

Laser ablation

Laser is a highly columnated, coherent, monochromatic energy source uniquely suited for thermal ablation because it can precisely deliver energy to an intended treatment target via an optical fiber. The feasibility of percutaneous laser ablation (LA) for the treatment of thyroid nodules was initially proposed by Pacella in 2000.[60]

Device and technique. Please refer to the included Appendix 1 for the discussion of the technique for LA of thyroid nodules.

Summary of clinical outcomes. A multicenter retrospective review by Pacella demonstrated that LA may be effectively and reproducibly provided in an ambulatory setting (n = 1531 patients) with a mean nodule volume reduction of 72% $\pm$ 11% (range 48%–96%), significant improvement in both compressive and cosmetic symptoms, and a low complication rate of 0.9%.[61]

Clinical outcomes following LA and RFA have also been compared with determine whether one method is conclusively superior. A large meta-analysis by Trimboli included 12 studies using RFA and an additional 12 studies using LA for the treatment of thyroid nodules.[62] Though a greater VRR was demonstrated with RFA the authors note that marked heterogeneity in the size and type of nodules limit the ability of the study to conclude RFA is a superior method. A more recent 6-month, single-center, randomized, open-label, parallel trial compared outcomes among 60 patients with nonfunctional benign thyroid nodules (NFBTN) randomly assigned to receive either a single session of RFA or LA. A successful procedure was defined as a >50% reduction in nodule volume at 6-month and both RFA and LA demonstrated statistically identical success rates of 86.7% and 66.7%, respectively (P = .13). Both methods also achieved similar reductions in compressive symptoms and cosmetic score; however, RFA demonstrated a statistically superior VRR of 64.3% compared with 53.2% for LA (P = .02).[63]

One group of authors has found that LA is more common in Europe but RFA is more widely used in Asia.[62] Our experience is that clinicians that routinely offer thermal ablation treatments for thyroid nodules are increasingly migrating away from LA in favor of RFA because of its superior VRR and relative ease of use. Nonetheless, LA remains a widely used and effective thermal ablation method.

High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) is a form of thermal ablation first introduced in the 1940s when it was observed that focusing high-power ultrasound beams at a distance from a source could cause complete necrosis of tissues lying within the focus.[64] It is a noninvasive modality that uses sound waves to cause intense vibrations which, in turn, generates frictional heat to cause necrosis within the target. For the thyroid gland, the first clinical report described the successful ablation of a 1 cm toxic adenoma that became cystic 2 weeks after the application.[65] Biochemical euthyroidism was attained within 3 months and maintained for up to 18 months. The target nodule also shrank and became a tiny hypoechoic scar with no demonstrable Doppler flow. The authors concluded that HIFU might be a safe and effective treatment of small-sized toxic thyroid adenomas.

Device and technique. Please refer to the included Appendix 1 for the discussion of the technique for HIFU of thyroid nodules.

Advantages and disadvantages of high-intensity focused ultrasound. One of the major advantages of HIFU ablation is that it is truly noninvasive. There is no skin or nodule puncture making infection and bleeding extremely rare. This benefit is particularly important for patients who are anticoagulated and HIFU ablation is reportedly safe to perform without withholding any of these agents before the procedure.[66] The major disadvantage of HIFU ablation is that the treatment efficacy is less predictable when compared with other forms of MITs. This is because the acoustic energy needs to propagate through multiple tissue layers before reaching the thyroid. As a result, the energy can become attenuated by the tissue layers on top of the target. HIFU ablation is less suited in patients with thick necks or deep-seated nodules because of energy attenuation. Unwanted prefocal heating to the skin, subcutaneous tissues, and muscles can also occur and both cause discomfort and reduce treatment efficacy. This is likely the main reason that treatment outcomes are variable in the literature. Fortunately, with currently available HIFU technology the frequency of skin burns has declined to 1%.[67–69]

Summary of clinical outcomes. HIFU lacks data from high-quality prospective studies. Two systematic reviews of HIFU for benign nonfunctional nodules reported pooled volume reductions of 45% to 70% ranging from 3 to 24 months of follow-up.[70] As with other thermal ablation techniques, there is an inverse correlation between initial nodule size and final volume reduction.[71,72] Thyroid function is rarely affected by HIFU treatment of an isolated nodule.[73]

Microwave ablation

Microwave ablation uses electromagnetic waves in the microwave energy spectrum (300 MHz to 300 GHz) to produce tissue-heating effects. The oscillation of polar molecules produces frictional heating, ultimately generating tissue necrosis within solid tumors.[74] Because an electromagnetic field is used instead of an electrical current, electrical conduction is not necessary. The effectiveness and safety of MWA has been demonstrated in many articles.[75–78]

Device and technique. Please refer to the included Appendix 1 for the discussion of the technique for MWA of thyroid nodules.

Advantages and disadvantages of Microwave ablation. Compared with RFA, MWA uses higher frequency waves and thus has higher speed of temperature rise and smaller ablation zones. The reduction in treatment time may be more valuable when treating larger tumors. The restricted ablation zone could help avoid injury to critical structures around the tumor. However, as a result of rapid temperature rise, the carbonization of tumor may be more severe than RFA and may block heat transmission. As a result, a moving-shot ablation technique should be used in large tumors.

Summary of clinical outcomes. A meta-analysis of 7 studies of MWA for BTN (1146 subjects and 1226 nodules) showed a pooled VRR of 63% (CI: 84.0%–100.6%, I2 = 24%) at 12 months postablation.[75] Symptom and cosmetic scores were significantly lower postablation with pooled mean differences of 1.50 (CI: −0.4, 3.42) and 1.20 (CI: 0.87, 1.52), respectively. In addition, the overall complication rate was low (0%–4.6%) with voice change and hematoma being the most common major complication. A more recent meta-analysis comparing MWA and RFA for BTN demonstrated a pooled VRR of 80.0% (CI: 76.6%–83.5%, I^2 = 74.1%) at 12 months postablation, and noted that VRR was not statistically different at 3 and 6 months, but was lower at 12 months when compared with RFA (80.0 vs 86.2%, P = .036).[76]

Complications and risks of minimally invasive techniques

The confines of neck anatomy and the numerous proximate critical structures such as the trachea, esophagus great vessels, nerve plexi, recurrent laryngeal nerves (**Fig. 7**), and parathyroid glands (**Fig. 8**) require the operator to have an understanding of the mechanism by which each MIT treatment is delivered as well as expertise with cervical ultrasound anatomy to avoid potentially serious complications.

A meta-analysis of randomized control trials of MIT modalities for the treatment of BTN found no significant difference in the rate of complications among the various modalities.[42] However, some complications, for example, rare reports of inebriated sensation after EA or transient hyperthyroidism after the treated of AFTN are unique to the modality and target lesion, respectively. **Table 2** summarizes the side effects of MIT by modality.

Anticoagulation and procedure-related bleeding complications

Retrospective studies have led to general agreement that conventional anticoagulation/antiplatelet therapy (AC/AP) including agents such as aspirin, clopidogrel, cilostazol, or warfarin both as monotherapy and in combination may be safely continued before FNA with no statistically significant difference in the rate of postprocedural hematoma, bleeding, nondiagnostic aspirates, or other complication.[79–83] A single report

Table 2
Reported risks of MIT by treatment modality (implied rates were not included)

Risks	Simple Aspiration	Ethanol Ablation • Cystic nodules • AFTN	RFA • Benign predominantly solid nodules • AFTN • Parathyroid • primary PTC • Recurrent PTC	Laser Ablation • Benign predominantly solid nodules • primary PTC • Recurrent PTC	HIFU • Benign predominantly solid nodules • Parathyroid	Microwave Ablation • Benign predominantly solid nodules • Cystic nodules • Parathyroid • primary PTC
Overall	1%[86]	8.2% -29%[87,88] 90% -100%[11,13]	3.3%[29] 2.4% - 100%[34,38] 0% -10%[89–91] 3.0% - 8.5%[47,50] 10.4%[52]	0% - 15%[35,92–94] 91.9%[95] 8.3%[96]	0% – 31.8 %[69,97] 25%[98]	0% -36.3%[74,99] 10.3%[100] 28.6%[77] 5.2%[78]
Minor complications	1%[86]	19% -29%[10,88] 90% -100%[11,13]	1.9%[29] 100%[34] 2.3 - 4.1%[47,48]	0% - 1.6%[92,93] 91.9%[95] 4.2%[96]	0% – 31.8 %[69,97]	0% -36.3%[74,99] 10.3%[100] 22.9%[77] 0.6%[78]
Pain[a]		19% -29%[10,88] 90% -100%[11,13]	2.6%[b,29] 100%[34] 8.5%[50]	91.9%[95]		
Extra-thyroidal hematoma		0.8% - 3.9%[11,101]	0% – 2.1%[18,28] 1.6% - 2.7%[47,48]	0%[95]	0%[c 66]	36.3%[74]
Intra-nodular/ thyroid hemorrhage /hematoma	1%[86]	6.5%[87]	5%[8]		0%[c 66]	10.3%[100]
Vomiting			0.09% – 0.6%[29,31]		8%[68]	
Skin burns			0.3%[29] 0.8 - 1.4%[47,48]	0%[92] 4.2%[96]	0% - 31.8%[67–69]	0% -10%[74,99]

Fever		6.0%[d 35] 0.02% - 8%[10,11]	0.3%[29]	2.7%[95]		27.3%[74]
Transient hyperthyroidism		0% -3.8%[88,102] 0% – 38%[10,11]	1.3% -2.7%[18,24]	1.6%[93]		
Vasovagal reaction			0.3%[29]			
Drunken sensation		1.6%[103]				
Development of thyroid autoantibody			2.3%[e,34]			
Major complications	0%[86]	0% - 3.4%[89,104] 3.2%[101]	1.4 %[29] 0% - 1.4%[8,30,34,35,38] 0% -10%[89–91] 0.8 - 1.4%[47,48] 3%[f,52]	0% - 15%[35,92–94] 0%[95] 4.2%[96]	0% - 3.9%[67,68,105] 25%[98]	0% - 9.1%[74,99,106] 5.7%[77] 4.6%[78]
Diffuse glandular hemorrhage or airway compromising hematoma	Case reports[107,108]					
Hypoparathyroidism			0%[28] 0%[52]			
Edema requiring steroid			9.1%[22]	15%[92]		
Nodule Rupture			0.2% - 0.5%;[28,29] 0.07% requiring surgical intervention [g,29]			Case series of 3[109]
Hypothyroidism		0%[88]	0% – 0.3%;[26,28,29,h] 0%[34] 0%[110]	1.6%[i,93]	0% - 1.4%[73,111]	

(*continued on next page*)

Table 2 (*continued*)

Transient voice change		0% -3.4%[9,87,112] 0% - 3.9%[11,13]	0.5% - 2.7%[18,24,28] 0% -10%[89–91] 0.8% - 1.4%[47,48] 8.3 %[52]	0% - 8.3%[92–94] 0%[95] 4.2%[96]	0% - 3.9%[67,68,105] 25%[98]	0% - 9.1%[74,99,106] 5.7%[77] 4.6%[78]
Permanent voice change		0%[87]	0% - 0.09%[28,31] 0%[52]	0%[92–94] 0%[95] 0%[96,113]	0%[67,105]	0%[74,99,106] 0%[77] 0%[78]
Brachial plexus injury			0% - 0.09%[28,31]			
Wound infection / abscess		0%[87] 0.8%[101]	0.3%[26]	0%[95]		
Arrhythmia		1.6%[87]	TC[i]	0.82%[93]		
Thrombus of Jugular Vein		0.23%[11]				
Carotid a. injury			TC	TC	TC	TC
Tracheal injury		TC	AR	TC	TC	TC[114]
Esophageal injury	TC	TC	TC	TC	TC	TC[114]
Spinal Accessory n. injury			TC	TC	TC	TC[114]
sympathetic chain injury			TC		Case report[115]	

Abbreviations: AR, anecdotal risks are nonpublished risks but are known to have occurred; TC, theoretic complications have not yet been reported in literature nor known to have occurred but thought to be possible by expert opinion.

[a] The reporting of pain between studies is highly variable, ranging from reporting of all cases of intraprocedural pain regardless of severity to only pain requiring the discontinuation of procedure.

[b] Pain has been reported at ablation site or radiates to head, ear, teeth, shoulder, and chest.

[c] All patients in the study underwent HIFU while continuing anticoagulation or antiplatelet agent therapy.

[d] Study provided combined data for cold and pretoxic/toxic nodules.

[e] 1/44 patients treated with RFA for AFTN developed Tg Ab without hypothyroidism.

[f] Choi and collegues only considered voice change a major complication if persistent greater than 1 mo, leading to a discrepancy between the reported frequency of voice change and major complications.

[g] Patient had an associated abscess formation.

[h] Patient was noted to have TPO or Tg positivity before thermal ablation.

[i] RF current passes through the heart use of monopolar electrode making cardiac electrical events a theoretic concern.

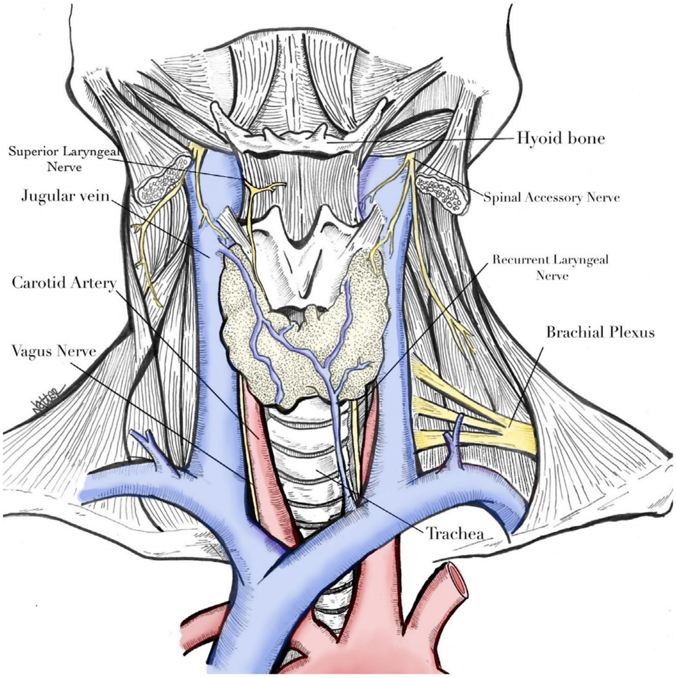

Fig. 7. At-risk structures of the neck during MIT. *(Courtesy of* Michael B. Natter, MD, New York, NY)

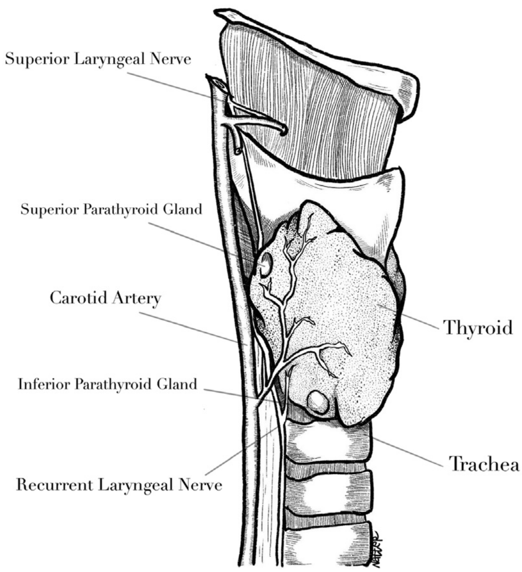

Fig. 8. Posterior view of the thyroid demonstrating at-risk structures of the neck. *(Courtesy of* Michael B. Natter, MD, New York, NY)

Table 3
Timeline for the cessation of AC/AP/NOACs[44,85] for RFA, LA or other MIT in which increased risk of bleed is perceived

Stop Before Procedure	Restart Medication Postprocedure
ASA, clopidogrel 7–10 d	24 h
warfarin 3–5 d	12 h
4–6 h for heparin	2–6 h
NOACs 3 d	24–48 h

that makes a notable exception to these generally positive findings is a retrospective study by Khan and colleagues that found that the rate of nondiagnostic aspirates among 47 patients receiving aspirin monotherapy was approximately double that of 500 patients receiving no AC/AP: 34% and 16%, respectively.[84]

We are not aware of studies that address procedure-related bleeding and nondiagnostic aspirate rates for patients treated with novel oral anticoagulants (NOACs) including dabigatran, rivaroxaban, and apixaban. However, Lyle and colleagues suggested that as the rate of bleeding complications associated with NOACs is similar to that of more conventional AC/AP for minor procedures such as dental and other minor surgeries which do not require the discontinuation of these agents, they are as safe as AC/AP and also do not require discontinuation before FNA.[85] We also agree that in routine cases, AC/AP/NOACs may be safely continued before FNA. For patients treated with warfarin, we prefer an INR of 2.5 or lower and will usually defer FNA in the case of supratherapeutic INRs.

For procedures using 19 to 21G CNB we consider the discontinuation of AC/AP/NOAC when feasible (Table 3) and when discontinuation is not considered high-risk based on the underlying indication for AC/AP/NOAC treatment. For procedures that involve repeated large bore needle insertion and movement through the target lesion such as LA and RFA AC/AP/NOACs must always be discontinued as small procedure-related hematoma in these cases is fairly common and in rare cases, clinically significant hematoma can occur. In this setting, we discontinue all AC/AP/NOACs for at least 3 days and in the select case of warfarin treatment ensure the INR is ~1. In all cases, when the discontinuation of AC/AP/NOAC is required, we request direction from the AC/AP/NOAC prescriber to advise the patient regarding specific instructions for medication discontinuation.

SUMMARY

The use of MITs for the treatment of thyroid disease is an exciting and rapidly developing field. These techniques offer attractive alternatives to surgical management and RAI and are changing the treatment paradigms for thyroid disease.

As with any novel technology, proper training, familiarity and experience are necessary to minimize serious complications. In appropriately selected patients, MITs offer advantages over the traditional surgical and medical management of patients with benign and malignant thyroid disease.

CLINICS CARE POINTS

- FNA documenting benign cytology x 2 before MIT
- The presence of antithyroid antibodies before RFA is a risk factor for postprocedure hypothyroidism

- 1% lidocaine infused along the pericapsular space provides adequate local anesthesia. General anesthesia and deep sedation are not necessary and may lead to inadvertent injury by preventing the patient from reporting pain associated with procedure-related thermal and mechanical injury.
- Postprocedural ultrasound at 1, 6, and 12 months should be performed to evaluate procedural outcomes.

DISCLOSURE

The authors have nothing to disclose.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.pmr.2016.04.003.

REFERENCES

1. Mazzaferri EL. Management of a solitary thyroid nodule. N Engl J Med 1993;328(8):553–9.
2. Lee DY, Seok J, Jeong WJ, et al. Prediction of thyroid hormone supplementation after thyroid lobectomy. J Surg Res 2015;193(1):273–8.
3. Frates MC, Benson CB, Doubilet PM, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006;91(9):3411–7.
4. In HS, Kim DW, Choo HJ, et al. Ethanol ablation of benign thyroid cysts and predominantly cystic thyroid nodules: factors that predict outcome. Endocrine 2014;46(1):107–13.
5. Miller JM, Zafar SU, Karo JJ. The cystic thyroid nodule. Recognition and management. Radiology 1974;110(2):257–61.
6. Hahn SY, Shin JH, Na DG, et al. Ethanol ablation of the thyroid nodules: 2018 consensus statement by the Korean Society of Thyroid Radiology. Korean J Radiol 2019;20(4):609–20.
7. Kanematsu R, Hirokawa M, Higuchi M, et al. Risk of malignancy and clinical outcomes of cyst fluid only nodules in the thyroid based on ultrasound and aspiration cytology. Diagn Cytopathol 2020;48(1):30–4.
8. Jang SW, Baek JH, Kim JK, et al. How to manage the patients with unsatisfactory results after ethanol ablation for thyroid nodules: role of radiofrequency ablation. Eur J Radiol 2012;81(5):905–10.
9. Guglielmi R, Pacella CM, Bianchini A, et al. Percutaneous ethanol injection treatment in benign thyroid lesions: role and efficacy. Thyroid 2004;14(2):125–31.
10. Monzani F, Goletti O, Caraccio N, et al. Percutaneous ethanol injection treatment of autonomous thyroid adenoma: hormonal and clinical evaluation. Clin Endocrinol (Oxf) 1992;36(5):491–7.
11. Lippi F, Ferrari C, Manetti L, et al. Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. J Clin Endocrinol Metab 1996;81(9):3261–4.
12. Papini E, Pacella CM, Verde G. Percutaneous ethanol injection (PEI): what is its role in the treatment of benign thyroid nodules?. Thyroid 1995;5(2):147–50.

13. Sharma A, Abraham D. Vascularity-targeted percutaneous ethanol injection of toxic thyroid adenomas: outcomes of a feasibility study performed in the USA. Endocr Pract 2020;26(1):22–9.
14. Mon SY, Riedlinger G, Abbott CE, et al. Cancer risk and clinicopathological characteristics of thyroid nodules harboring thyroid-stimulating hormone receptor gene mutations. Diagn Cytopathol 2018;46(5):369–77.
15. Heilo A, Sigstad E, Fagerlid KH, et al. Efficacy of ultrasound-guided percutaneous ethanol injection treatment in patients with a limited number of metastatic cervical lymph nodes from papillary thyroid carcinoma. J Clin Endocrinol Metab 2011;96(9):2750–5.
16. Hay ID, Lee RA, Davidge-Pitts C, et al. Long-term outcome of ultrasound-guided percutaneous ethanol ablation of selected "recurrent" neck nodal metastases in 25 patients with TNM stages III or IVA papillary thyroid carcinoma previously treated by surgery and 131I therapy. Surgery 2013;154(6):1448–55 [discussion 1454-5].
17. Lorentzen T. A cooled needle electrode for radiofrequency tissue ablation: thermodynamic aspects of improved performance compared with conventional needle design. Acad Radiol 1996;3(7):556–63.
18. Jeong WK, Baek JH, Rhim H, et al. Radiofrequency ablation of benign thyroid nodules: safety and imaging follow-up in 236 patients. Eur Radiol 2008;18(6): 1244–50.
19. Papini E, Pacella CM, Solbiati LA, et al. Minimally-invasive treatments for benign thyroid nodules: a Delphi-based consensus statement from the Italian minimally-invasive treatments of the thyroid (MITT) group. Int J Hyperthermia 2019;36(1): 376–82.
20. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules - 2016 Update Appendix. Endocr Pract 2016;22:1–60.
21. Kim YS, Rhim H, Tae K, et al. Radiofrequency ablation of benign cold thyroid nodules: initial clinical experience. Thyroid 2006;16(4):361–7.
22. Deandrea M, Limone P, Basso E, et al. US-guided percutaneous radiofrequency thermal ablation for the treatment of solid benign hyperfunctioning or compressive thyroid nodules. Ultrasound Med Biol 2008;34(5):784–91.
23. Jawad S, Morley S, Otero S, et al. Ultrasound-guided radiofrequency ablation (RFA) of benign symptomatic thyroid nodules - initial UK experience. Br J Radiol 2019;92(1098):20190026.
24. Bernardi S, Dobrinja C, Fabris B, et al. Radiofrequency ablation compared to surgery for the treatment of benign thyroid nodules. Int J Endocrinol 2014; 2014:934595.
25. Guang Y, He W, Luo Y, et al. Patient satisfaction of radiofrequency ablation for symptomatic benign solid thyroid nodules: our experience for 2-year follow up. BMC Cancer 2019;19(1):147.
26. Dobnig H, Amrein K. Monopolar radiofrequency ablation of thyroid nodules: a prospective Austrian Single-Center Study. Thyroid 2018;28(4):472–80.
27. Sim JS, Baek JH. Long-term outcomes of thermal ablation for benign thyroid nodules: the issue of regrowth. Int J Endocrinol 2021;2021:9922509.
28. Che Y, Jin S, Shi C, et al. Treatment of benign thyroid nodules: comparison of surgery with radiofrequency ablation. AJNR Am J Neuroradiol 2015;36(7): 1321–5.

29. Baek JH, Lee JH, Sung JY, et al. Complications encountered in the treatment of benign thyroid nodules with US-guided radiofrequency ablation: a multicenter study. Radiology 2012;262(1):335–42.
30. Baek JH, Moon WJ, Kim YS, et al. Radiofrequency ablation for the treatment of autonomously functioning thyroid nodules. World J Surg 2009;33(9):1971–7.
31. Lim HK, Lee JH, Ha EJ, et al. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. Eur Radiol 2013;23(4): 1044–9.
32. Baek JH, Jeong HJ, Kim YS, et al. Radiofrequency ablation for an autonomously functioning thyroid nodule. Thyroid 2008;18(6):675–6.
33. Cervelli R, Mazzeo S, Boni G, et al. Comparison between radioiodine therapy and single-session radiofrequency ablation of autonomously functioning thyroid nodules: a retrospective study. Clin Endocrinol (Oxf) 2019;90(4):608–16.
34. Sung JY, Baek JH, Jung SL, et al. Radiofrequency ablation for autonomously functioning thyroid nodules: a multicenter study. Thyroid 2015;25(1):112–7.
35. Spiezia S, Garberoglio R, Milone F, et al. Thyroid nodules and related symptoms are stably controlled two years after radiofrequency thermal ablation. Thyroid 2009;19(3):219–25.
36. Bernardi S, Stacul F, Michelli A, et al. 12-month efficacy of a single radiofrequency ablation on autonomously functioning thyroid nodules. Endocrine 2017;57(3):402–8.
37. Cesareo R, Naciu AM, Iozzino M, et al. Nodule size as predictive factor of efficacy of radiofrequency ablation in treating autonomously functioning thyroid nodules. Int J Hyperthermia 2018;34(5):617–23.
38. Cesareo R, Palermo A, Benvenuto D, et al. Efficacy of radiofrequency ablation in autonomous functioning thyroid nodules. A systematic review and meta-analysis. Rev Endocr Metab Disord 2019;20(1):37–44.
39. Dobnig H, et al. Radiofrequency ablation of thyroid nodules: "Good Clinical Practice Recommendations" for Austria : An interdisciplinary statement from the following professional associations: Austrian Thyroid Association (ÖSDG), Austrian Society for Nuclear Medicine and Molecular Imaging (OGNMB), Austrian Society for Endocrinology and Metabolism (ÖGES), Surgical Endocrinology Working Group (ACE) of the Austrian Surgical Society (OEGCH). Wien Med Wochenschr 2020;170(1–2):6–14.
40. Kim HJ, Cho SJ, Baek JH, et al. Efficacy and safety of thermal ablation for autonomously functioning thyroid nodules: a systematic review and meta-analysis. Eur Radiol 2021;31(2):605–15.
41. Papini E, Monpeyssen H, Frasoldati A, et al. 2020 European Thyroid Association Clinical Practice Guideline for the Use of Image-Guided Ablation in Benign Thyroid Nodules. Eur Thyroid J 2020;9(4):172–85.
42. He L, Zhao W, Xia Z, et al. Comparative efficacy of different ultrasound-guided ablation for the treatment of benign thyroid nodules: Systematic review and network meta-analysis of randomized controlled trials. PLoS One 2021;16(1): e0243864.
43. Baek JH, Ha EJ, Choi YJ, et al. Radiofrequency versus Ethanol Ablation for Treating Predominantly Cystic Thyroid Nodules: A Randomized Clinical Trial. Korean J Radiol 2015;16(6):1332–40.
44. Kim JH, Baek JH, Lim HK, et al. 2017 Thyroid Radiofrequency Ablation Guideline: Korean Society of Thyroid Radiology. Korean J Radiol 2018;19(4):632–55.

45. Shen R, Cheng R, Zhou H, et al. Ultrasonography-guided radiofrequency ablation combined with lauromacrogol sclerotherapy for mixed thyroid nodules. Am J Transl Res 2021;13(5):5035–42.
46. Tufano RP, Pace-Asciak P, Russell JO, et al. Update of Radiofrequency Ablation for Treating Benign and Malignant Thyroid Nodules. The Future Is Now. Front Endocrinol (Lausanne) 2021;12:698689.
47. Lim HK, Cho SJ, Baek JH, et al. US-Guided Radiofrequency Ablation for Low-Risk Papillary Thyroid Microcarcinoma: Efficacy and Safety in a Large Population. Korean J Radiol 2019;20(12):1653–61.
48. Cho SJ, Baek SM, Lim HK, et al. Long-term follow-up results of ultrasound-guided radiofrequency ablation for low-risk papillary thyroid microcarcinoma: more than 5-year follow-up for 84 tumors. Thyroid 2020;30(12):1745–51.
49. Zhang C, Yin J, Hu C, et al. Comparison of ultrasound guided percutaneous radiofrequency ablation and open thyroidectomy in the treatment of low-risk papillary thyroid microcarcinoma: A propensity score matching study. Clin Hemorheol Microcirc 2021;80(2):73–81.
50. Yan L, Zhang M, Song Q, et al. The Efficacy and Safety of Radiofrequency Ablation for Bilateral Papillary Thyroid Microcarcinoma. Front Endocrinol (Lausanne) 2021;12:663636.
51. Xiao J, Lan Y, Yan L, et al. [Short-term Outcome of T1bN0M0 Papillary Thyroid Cancer after Ultrasonography-guided Radiofrequency Ablation]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2020;42(6):771–5.
52. Choi Y, Jung SL, Bae JS, et al. Comparison of efficacy and complications between radiofrequency ablation and repeat surgery in the treatment of locally recurrent thyroid cancers: a single-center propensity score matching study. Int J Hyperthermia 2019;36(1):359–67.
53. Chung SR, Baek JH, Choi YJ, et al. Longer-term outcomes of radiofrequency ablation for locally recurrent papillary thyroid cancer. Eur Radiol 2019;29(9): 4897–903.
54. Chung SR, Suh CH, Baek JH, et al. Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis. Int J Hyperthermia 2017;33(8):920–30.
55. Gulcelik NE, Gulcelik MA, Kuru B. Risk of malignancy in patients with follicular neoplasm: predictive value of clinical and ultrasonographic features. Arch Otolaryngol Head Neck Surg 2008;134(12):1312–5.
56. Dobrinja C, Bernardi S, Fabris B, et al. Surgical and Pathological Changes after Radiofrequency Ablation of Thyroid Nodules. Int J Endocrinol 2015;2015: 576576.
57. Ha SM, Sung JY, Baek JH, et al. Radiofrequency ablation of small follicular neoplasms: initial clinical outcomes. Int J Hyperthermia 2017;33(8):931–7.
58. Paramo JC, Mesko T. Age, tumor size, and in-office ultrasonography are predictive parameters of malignancy in follicular neoplasms of the thyroid. Endocr Pract 2008;14(4):447–51.
59. Machens A, Holzhausen HJ, Dralle H. The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. Cancer 2005;103(11):2269–73.
60. Pacella CM, Bizzarri G, Guglielmi R, et al. Thyroid tissue: US-guided percutaneous interstitial laser ablation-a feasibility study. Radiology 2000;217(3):673–7.
61. Pacella CM, Mauri G, Achille G, et al. Outcomes and Risk Factors for Complications of Laser Ablation for Thyroid Nodules: A Multicenter Study on 1531 Patients. J Clin Endocrinol Metab 2015;100(10):3903–10.

62. Trimboli P, Castellana M, Sconfienza LM, et al. Efficacy of thermal ablation in benign non-functioning solid thyroid nodule: a systematic review and meta-analysis. Endocrine 2020;67(1):35–43.
63. Cesareo R, Pacella CM, Pasqualini V, et al. Laser ablation versus radiofrequency ablation for benign non-functioning thyroid nodules: six-month results of a randomized, parallel, open-label, trial (LARA Trial). Thyroid 2020;30(6):847–56.
64. Lynn JG, Zwemer RL, Chick AJ. The biological application of focused ultrasonic waves. Science 1942;96(2483):119–20.
65. Esnault O, Rouxel A, Le Nestour E, et al. Minimally invasive ablation of a toxic thyroid nodule by high-intensity focused ultrasound. AJNR Am J Neuroradiol 2010;31(10):1967–8.
66. Lang BH, Woo YC, Chiu KW. High intensity focused ultrasound (HIFU) ablation of benign thyroid nodule is safe and efficacious in patients who continue taking an anti-coagulation or anti-platelet agent in the treatment period. Int J Hyperthermia 2019;36(1):186–90.
67. Lang BH, Woo YC, Wong CKH. High-intensity focused ultrasound for treatment of symptomatic benign thyroid nodules: a prospective study. Radiology 2017;284(3):897–906.
68. Lang BHH, Woo YC, Chiu KW. Two sequential applications of high-intensity focused ultrasound (HIFU) ablation for large benign thyroid nodules. Eur Radiol 2019;29(7):3626–34.
69. Esnault O, Franc B, Ménégaux F, et al. High-intensity focused ultrasound ablation of thyroid nodules: first human feasibility study. Thyroid 2011;21(9):965–73.
70. Lang BH, Wu ALH. High intensity focused ultrasound (HIFU) ablation of benign thyroid nodules - a systematic review. J Ther Ultrasound 2017;5:11.
71. Sennert M, Happel C, Korkusuz Y, et al. Further Investigation on High-intensity Focused Ultrasound (HIFU) Treatment for Thyroid Nodules: Effectiveness Related to Baseline Volumes. Acad Radiol 2018;25(1):88–94.
72. Lang BH, Woo YC, Chiu KW. Single-Session High-Intensity Focused Ultrasound Treatment in Large-Sized Benign Thyroid Nodules. Thyroid 2017;27(5):714–21.
73. Lang BHH, Woo YC, Chiu KW. High-intensity focused ablation (HIFU) of single benign thyroid nodule rarely alters underlying thyroid function. Int J Hyperthermia 2017;33(8):875–81.
74. Feng B, Liang P, Cheng Z, et al. Ultrasound-guided percutaneous microwave ablation of benign thyroid nodules: experimental and clinical studies. Eur J Endocrinol 2012;166(6):1031–7.
75. Cui T, Jin C, Jiao D, et al. Safety and efficacy of microwave ablation for benign thyroid nodules and papillary thyroid microcarcinomas: a systematic review and meta-analysis. Eur J Radiol 2019;118:58–64.
76. Guo DM, Chen Z, Zhai YX, et al. Comparison of radiofrequency ablation and microwave ablation for benign thyroid nodules: A systematic review and meta-analysis. Clin Endocrinol (Oxf) 2021;95(1):187–96.
77. Zhuo L, Zhang L, Peng LL, et al. Microwave ablation of hyperplastic parathyroid glands is a treatment option for end-stage renal disease patients ineligible for surgical resection. Int J Hyperthermia 2019;36(1):29–35.
78. Cao XJ, Liu J, Zhu YL, et al. Efficacy and Safety of Thermal Ablation for Solitary T1bN0M0 Papillary Thyroid Carcinoma: A Multicenter Study. J Clin Endocrinol Metab 2021;106(2):e573–81.
79. Abu-Yousef MM, Larson JH, Kuehn DM, et al. Safety of ultrasound-guided fine needle aspiration biopsy of neck lesions in patients taking antithrombotic/anticoagulant medications. Ultrasound Q 2011;27(3):157–9.

80. Khadra H, Kholmatov R, Monlezun D, et al. Do anticoagulation medications increase the risk of haematoma in ultrasound-guided fine needle aspiration of thyroid lesions? Cytopathology 2018;29(6):565–8.
81. Denham SL, Ismail A, Bolus DN, et al. Effect of Anticoagulation Medication on the Thyroid Fine-Needle Aspiration Pathologic Diagnostic Sufficiency Rate. J Ultrasound Med 2016;35(1):43–8.
82. Kwon JH, Kim DB, Han YH, et al. Contributory Factors to Hemorrhage After Ultrasound-Guided Fine Needle Aspiration of Thyroid Nodules with an Emphasis on Patients Taking Antithrombotic or Anticoagulant Medications. Iran J Radiol 2018;15(2):e57231.
83. Cordes M, Schmidkonz C, Horstrup K, et al. Fine-needle aspiration biopsies of thyroid nodules. Nuklearmedizin 2018;57(6):211–5.
84. Khan TS, Sharma E, Singh B, et al. Aspirin Increases the Risk of Nondiagnostic Yield of Fine-Needle Aspiration and Biopsy of Thyroid Nodules. Eur Thyroid J 2018;7(3):129–32.
85. Lyle MA, Dean DS. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in patients taking novel oral anticoagulants. Thyroid 2015;25(4):373–6.
86. Galvan G, Manzl M, Balcke C, et al. [Therapy of thyroid cysts with fine needle aspiration]. Schweiz Med Wochenschr 1982;112(26):926–30.
87. Cho W, Sim JS, Jung SL. Ultrasound-guided ethanol ablation for cystic thyroid nodules: effectiveness of small amounts of ethanol in a single session. Ultrasonography 2021;40(3):417–27.
88. Halenka M, Karasek D, Schovanek J, et al. Safe and effective percutaneous ethanol injection therapy of 200 thyroid cysts. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2020;164(2):161–7.
89. Hussain I, Ahmad S, Aljammal J. Radiofrequency Ablation of Parathyroid Adenoma: A Novel Treatment Option for Primary Hyperparathyroidism. AACE Clin Case Rep 2021;7(3):195–9.
90. Korkusuz H, Wolf T, Grünwald F. Feasibility of bipolar radiofrequency ablation in patients with parathyroid adenoma: a first evaluation. Int J Hyperthermia 2018;34(5):639–43.
91. Khandelwal AH, Batra S, Jajodia S, et al. Radiofrequency Ablation of Parathyroid Adenomas: Safety and Efficacy in a Study of 10 Patients. Indian J Endocrinol Metab 2020;24(6):543–50.
92. Papini E, Guglielmi R, Bizzarri G, et al. Ultrasound-guided laser thermal ablation for treatment of benign thyroid nodules. Endocr Pract 2004;10(3):276–83.
93. Valcavi R, Riganti F, Bertani A, et al. Percutaneous laser ablation of cold benign thyroid nodules: a 3-year follow-up study in 122 patients. Thyroid 2010;20(11):1253–61.
94. Spiezia S, Vitale G, Di Somma C, et al. Ultrasound-guided laser thermal ablation in the treatment of autonomous hyperfunctioning thyroid nodules and compressive nontoxic nodular goiter. Thyroid 2003;13(10):941–7.
95. Ji L, Wu Q, Gu J, et al. Ultrasound-guided percutaneous laser ablation for papillary thyroid microcarcinoma: a retrospective analysis of 37 patients. Cancer Imaging 2019;19(1):16.
96. Mauri G, Cova L, Ierace T, et al. Treatment of Metastatic Lymph Nodes in the Neck from Papillary Thyroid Carcinoma with Percutaneous Laser Ablation. Cardiovasc Intervent Radiol 2016;39(7):1023–30.
97. Kovatcheva RD, Vlahov JD, Stoinov JI, et al. Benign Solid Thyroid Nodules: US-guided High-Intensity Focused Ultrasound Ablation-Initial Clinical Outcomes. Radiology 2015;276(2):597–605.

98. Kovatcheva RD, Vlahov JD, Shinkov AD, et al. High-intensity focused ultrasound to treat primary hyperparathyroidism: a feasibility study in four patients. AJR Am J Roentgenol 2010;195(4):830–5.
99. Khanh HQ, Hung NQ, Vinh VH, et al. Efficacy of Microwave Ablation in the Treatment of Large (≥3 cm) Benign Thyroid Nodules. World J Surg 2020;44(7):2272–9.
100. Dong S, Sun L, Xu J, et al. Intracystic Hemorrhage and Its Management During Ultrasound-Guided Percutaneous Microwave Ablation for Cystic Thyroid Nodules. Front Endocrinol (Lausanne) 2020;11:477.
101. Tarantino L, Francica G, Sordelli I, et al. Percutaneous ethanol injection of hyperfunctioning thyroid nodules: long-term follow-up in 125 patients. AJR Am J Roentgenol 2008;190(3):800–8.
102. Antonelli A, Campatelli A, Di Vito A, et al. Comparison between ethanol sclerotherapy and emptying with injection of saline in treatment of thyroid cysts. Clin Investig 1994;72(12):971–4.
103. Yasuda K, Ozaki O, Sugino K, et al. Treatment of cystic lesions of the thyroid by ethanol instillation. World J Surg 1992;16(5):958–61.
104. Kim YJ, Baek JH, Ha EJ, et al. Cystic versus predominantly cystic thyroid nodules: efficacy of ethanol ablation and analysis of related factors. Eur Radiol 2012;22(7):1573–8.
105. Lang BHH, Woo YC, Chiu KW. Vocal cord paresis following single-session high intensity focused ablation (HIFU) treatment of benign thyroid nodules: incidence and risk factors. Int J Hyperthermia 2017;33(8):888–94.
106. Yue W, Wang S, Wang B, et al. Ultrasound guided percutaneous microwave ablation of benign thyroid nodules: safety and imaging follow-up in 222 patients. Eur J Radiol 2013;82(1):e11–6.
107. Noordzij JP, Goto MM. Airway compromise caused by hematoma after thyroid fine-needle aspiration. Am J Otolaryngol 2005;26(6):398–9.
108. Roh JL. Intrathyroid hemorrhage and acute upper airway obstruction after fine needle aspiration of the thyroid gland. Laryngoscope 2006;116(1):154–6.
109. Tian P, Du W, Liu X, et al. Ultrasonographic characteristics of thyroid nodule rupture after microwave ablation: Three case reports. Medicine (Baltimore) 2021;100(9):e25070.
110. Ding M, Tang X, Cui D, et al. Clinical outcomes of ultrasound-guided radiofrequency ablation for the treatment of primary papillary thyroid microcarcinoma. Clin Radiol 2019;74(9):712–7.
111. Korkusuz H, Sennert M, Fehre N, et al. Localized Thyroid Tissue Ablation by High Intensity Focused Ultrasound: Volume Reduction, Effects on Thyroid Function and Immune Response. Rofo 2015;187(11):1011–5.
112. Negro R, Colosimo E, Greco G. Outcome, Pain Perception, and Health-Related Quality of Life in Patients Submitted to Percutaneous Ethanol Injection for Simple Thyroid Cysts. J Thyroid Res 2017;2017:9536479.
113. Spartalis E, Karagiannis SP, Plakopitis N, et al. Percutaneous laser ablation of cervical metastatic lymph nodes in papillary thyroid carcinoma: clinical efficacy and anatomical considerations. Expert Rev Med Devices 2021;18(1):75–82.
114. Yang YL, Chen CZ, Zhang XH. Microwave ablation of benign thyroid nodules. Future Oncol 2014;10(6):1007–14.
115. Ben Hamou A, Monpeyssen H. Horner's Syndrome During High-Intensity Focused Ultrasound Ablation for a Benign Thyroid Nodule. AACE Clin Case Rep 2021;7(3):164–8.