Review Article

Current guidelines for the application of radiofrequency ablation for thyroid nodules: a narrative review

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Background and Objective: Thyroid nodules are frequently incidentally found on physical exam or imaging for an unrelated work-up. Although surgery remains the gold standard for treating symptomatic benign and/or malignant thyroid nodules, radiofrequency ablation (RFA) has emerged as a minimally invasive treatment option for high risk patients and those who decline surgery. The novel application of RFA to treat thyroid disease was originally described for symptomatic, benign thyroid nodules. Since then, several studies have tried to expand its indication to treat primary and recurrent well-differentiated thyroid cancer. The high success rates and the low complication profile, has allowed for quick adoption of RFA as a treatment option for well-selected patients with benign thyroid nodules and locoregional recurrent thyroid malignancy. As such, multidisciplinary guidelines and consensus statements were developed to standardize indications, techniques, outcome measures, and follow-up to ensure the best patient care. This article summarizes the current indications and recommendations to help guide clinicians on how best to effectively and safely utilize RFA to treat thyroid disease.

Methods: A PubMed/MEDLINE search between 2000–2022 using a combination of "radiofrequency ablation", "RFA", "thyroid nodule", and "guidelines" was conducted. The inclusion criteria were articles published in English which offered recommendations on RFA use for thyroid nodules.

Key Content and Findings: For symptomatic, benign thyroid nodules, RFA is effective at significantly reducing nodule volume. For large nodules, multiple RFA sessions may be needed to achieve clinically significant volume reduction. Patients undergoing RFA for autonomously functioning thyroid nodules may see symptomatic relief but success rates are variable. RFA may serve a curative or palliative role in recurrent well-differentiated thyroid cancers. There is little data describing the use of RFA for primary well-differentiated thyroid cancer >1 cm and the role of RFA for thyroid microcarcinomas remains controversial.

Conclusions: RFA is a safe minimally invasive technique and may be considered, in appropriate circumstances, a first-line treatment option for benign thyroid nodules. Practices adopting RFA will likely increase as more clinicians become familiar with this technique, highlighting the importance of developing standardized guidelines.

Keywords: Thyroid nodules; radiofrequency ablation (RFA); autonomously functioning thyroid nodules (AFTN); recurrent thyroid cancer

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Introduction

Thyroid nodules are a common incidental finding with an estimated prevalence of 5–7% in the adult population with 19–68% detected by cervical ultrasonography (US) (1,2). While asymptomatic thyroid nodules can frequently be observed, those causing compressive symptoms, poor cosmesis, hyperfunctional, or suspicious for malignancy should be offered treatment. Total thyroidectomy or thyroid lobectomy continues to be the gold standard for definitive management of symptomatic and malignant thyroid nodules (2,3). While the safety and efficacy of thyroid surgery is well documented when performed by high-volume, experienced surgeons, there is a small but real risk of significant complications including: life threatening neck hematoma, recurrent laryngeal nerve injury, and hypoparathyroidism, all of which can severely affect patients' quality of life (4,5). These risks are increased in patients undergoing a reoperation, have Graves' disease, have a large goiter size, and/or if the surgical indication is for malignancy (3,6-8). Furthermore, while it is reported that high-volume endocrine surgeons do a disproportionately larger number of thyroidectomies in the United States, the majority of thyroid surgeries are still being performed by low- and intermediate-volume surgeons which have been shown to have higher complication rates compared to high-volume surgeons (9,10). These risks, as well as the patient's overall fitness for surgery, and the patient's preference must be taken into account when determining the best treatment strategy for thyroid nodules.

Chemical and thermal ablation techniques have emerged as promising outpatient minimally invasive procedures for treating select patients with thyroid nodules. Ethanol ablation (EA) involves injecting a sclerosing agent into the nodule to cause volume reduction and prevent recurrence (11). While this technique has been effective in achieving volume reduction in purely or predominately cystic nodules, EA may require several sessions to be effective for large or solid nodules (12). Another minimally invasive treatment option is thermal ablation which utilizes high temperatures to ablate the thyroid tissue and include: laser ablation, high-intensity focused ultrasound, microwave ablation and radiofrequency ablation (RFA). While each technique uses a different approach to deliver heat to the nodule, all result in irreversible cellular damage, leading to nodule shrinkage and have been found to be effective for solid nodules. Of these thermal ablation techniques, RFA and laser ablation are the most studied and available internationally (13).

RFA's low complication rate coupled with the freedom to perform the procedure with only local anesthesia or sedation makes it an attractive option for those who may not be able to tolerate general anesthesia (14). Since it was first described in 2006 as an alternative treatment option for nonfunctional, benign thyroid nodules, subsequent studies have demonstrated potential applications for RFA in treating autonomously functioning thyroid nodules (AFTN) (15-17), primary differentiated thyroid microcarcinomas (18-20), and recurrent well-differentiated thyroid carcinoma (WDTC) (21-23). While this technique is not as frequently used in the United States, RFA is rapidly being adopted in both Asian and European countries, necessitating the development of best practice guidelines. Over the past few years, there have been multiple professional society guidelines and consensus statements developed by surgeons (3,14), endocrinologists (13,24,25), and radiologists (26), to help standardize indications, techniques and follow-up practices. Herein, we discuss the current guidelines for the application of RFA in treating both benign and malignant thyroid disease. We present this article in accordance with the Narrative Review reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-18/rc).

Methods

A comprehensive and systematic literature search was conducted to identify articles that summarized or gave guidance for using RFA to treat benign and malignant thyroid nodules. A PubMed/MEDLINE search between 2000–2022 using a combination of "radiofrequency ablation", "RFA", "thyroid nodule", and "guidelines" was conducted. The inclusion criteria were articles published in English which offered recommendations on RFA use for thyroid nodules. The articles that resulted from the search were reviewed to determine if the recommendations were the result of a thorough literature review and high level evidence. Articles were excluded if the majority of the recommendations were not pertaining specifically to RFA to treat thyroid disease (*Table 1*). In total, seven articles were included to compare current guidelines on RFA in thyroid nodules. These guidelines are summarized in *Table 2*.

RFA technique

When originally described by Kim *et al.* (30) in 2006 as a means to treat thyroid disease, the technique utilized

Table 1 The search strategy summary

Items	Specification
Date of search	January 5, 2023
Databases and other sources searched	PubMed/MEDLINE
Search terms used	A combination of "radiofrequency ablation", "RFA", "thyroid nodule", and "guidelines" was conducted
Timeframe	2000–2022
Inclusion and exclusion criteria	Inclusion criteria: articles published in English which offered recommendations on RFA use for thyroid nodules
	Exclusion criteria: the majority of the recommendations were not pertaining specifically to RFA to treat thyroid disease
Selection process	The authors conducted the selection independently. Each article was discussed regarding their value and relevance to the manuscripts' objective

a single active electrode inserted along the longest axis of the thyroid nodule to create a spherical ablation zone noted by observing a transient hyperechogenic change at the electrode tip on US. While this definition of an ablative zone is frequently used in other studies (18,30), another definition that is described is using a temperature threshold maintained by the probe for a set time period to guarantee thermocoagulation (16). One limitation of creating a spherical ablation zone is that thyroid nodules are frequently ellipsoid, and that the close proximity to other important cervical structures (i.e., the carotid artery, jugular veins, nerves) prevents fully ablated nodular margins. As such, ablation zones were frequently conservative, resulting in the peripheral areas of thyroid nodules being left untreated. The "moving shot" technique was described by Baek *et al.* (15) which conceptually divided the nodule into smaller units in an effort to obtain greater ablative volume while not extending past the nodule margin. These units would typically be smaller at the periphery or when near important cervical structures and larger at the center of the nodule. When tested in animal models (31), this technique proved to achieve a larger ablation volume and is currently the recommended technique when performing RFA to treat thyroid nodules (13,14,26,29).

Benign nodules

Nonfunctional thyroid nodules

Consensus guidelines strongly recommend that the diagnosis of benign thyroid nodules be confirmed with at least two fine-needle aspirations (FNA) prior to RFA treatment (13,14,24,26). Thyroid nodules that are nonfunctional are frequently asymptomatic and can grow to significant sizes before finally being identified. Depending on the size and the location of the nodule in the thyroid, these nodules may cause compressive symptoms (i.e., dysphagia, venous congestion, or dyspnea) and/or become cosmetically undesirable. When describing their initial experience using RFA to treat a heterogenous cohort of 35 solid and cystic benign thyroid nodules, Kim *et al.* (30) found that the residual nodule volume at the first and sixth months after treatment was 53.5%±26.5% and 30.7%±25.0% respectively. Of those that complained of compressive symptoms, 88% reported an improvement of symptoms. Since then, there have been subsequent studies replicating significant volume reduction (50–80%) within the first 6–12 months of treatment in nonfunctioning thyroid nodules (30,32-35).

Currently, debate remains on whether a single RFA session is adequate to achieve the desired volume reduction or if additional RFA sessions are necessary. When prospectively randomizing 30 patients to undergo one or two RFA sessions, Huh *et al.* (36) found that there was no significant difference in volume reduction for patients at their 6-month follow-up. The authors concluded that a single RFA session is appropriate and that additional sessions should be limited to nodules greater than 20 mL as symptoms may persist after a single RFA session in those situations. However, it is important to highlight that the

Table 2 Summary of the published guidelines and consensus statements for the application of radiofrequency ablation in treating thyroid disease

Author (years)	Country	Technique	Benign thyroid nodule			Malignant thyroid nodule	
			Cytology	Nonfunctioning	AFTN	Primary	Recurrent
Dietrich (27), 2018	International	Trans-isthmus, moving shot	US-guided FNA or CNB 1 US-guided FNA if AFTN	Recommended for symptomatic nodules or patients with cosmetic problems	Recommended for toxic or pre-toxic nodules Large AFTN (>20 mL) may be less responsive	Does not address	Recommended in patients with high surgical risk or refuse surgery with curative/palliative intent
Kim (26), 2018	Korean	Trans-isthmus, moving shot	2 US-guided FNA or CNB 1 US-guided FNA if AFTN	Recommended for symptomatic nodules or patients with cosmetic problems	Recommended for toxic or pre-toxic nodules Large AFTN (>20 mL) may be less responsive	No clear indication May have a role in patients with high surgical risk or refuse surgery	Consider in patients with high surgical risk or refuse surgery Curative intent: those with 3–4 local tumors all ≤2 cm Palliative intent: when size reduction may reduce symptoms and improve quality of life
Papini (25), 2019	Italy	Trans-isthmus, moving shot	US-guided FNA or CNB 1 US-guided FNA if AFTN	Recommended as potential first-line for solid, symptomatic nodules or with patients cosmetic problems	Can be a safe alternative if first-line techniques (surgery/RAI) are contraindicated	Does not address	Does not address
Dobnig (28), 2020	Austria	Trans-isthmus, moving shot	US-guided FNA or CNB	Recommended for symptomatic nodules, patients with cosmetic problems, or nodular growth >2 cm	Can be a safe alternative if first-line techniques (surgery/RAI) are contraindicated	No clear indication Mentions that for low risk PTMC where active surveillance is considered, RFA may also be considered	Consider in differentiated, iodine-refractory thyroid carcinoma with local recurrence
Papini (13), 2020	European	Trans-isthmus, moving shot	US-guided FNA or CNB	Recommend against treating asymptomatic lesions Recommended for symptomatic nodules or with patients cosmetic problem who decline surgery	Recommend against as a first-line treatment for large AFTN Consider in young patients with small AFTN	Does not address	Does not address

Table 2 (*continued*)

Table 2 (*continued*)

Author (years)	Country	Technique	Benign thyroid nodule			Malignant thyroid nodule	
			Cytology	Nonfunctioning	AFTN	Primary	Recurrent
Orloff (14), 2022	International	Trans-isthmus, moving shot	2 US-guided FNA or CNB 1 US-guided FNA if AFTN	Recommended as first-line alternative for symptomatic nodules or patients with cosmetic problems	Can be a safe alternative if first-line techniques (surgery/RAI) are contraindicated	Not first-line treatment May be considered in patients with primary PTMC if: 1. Unifocal 2. Cytologically confirmed PTC without aggressive subtype 3. No metastatic lymphadenopathy 4. High risk/refuse surgery	Consider in patients with high surgical risk or refuse surgery Curative intent: those with 3–4 local tumors all ≤1.5–2 cm Palliative intent: when size reduction may reduce symptoms and improve quality of life
Ha (29), 2021	Asia	Trans-isthmus, moving shot	2 US-guided FNA or CNB 1 US-guided FNA if AFTN	Recommended as first-line alternative for symptomatic nodules or patients with cosmetic problems	Can be a safe alternative if first-line techniques (surgery/RAI) are contraindicated	Does not address	Does not address

AFTN, autonomously functioning thyroid nodules; US, ultrasonography; FNA, fine-needle aspiration; CNB, core-needle biopsy; RAI, radioactive iodine; PTMC, papillary thyroid microcarcinoma; RFA, radiofrequency ablation; PTC, papillary thyroid carcinoma.

timing of the second RFA session was one month after the initial session which may be too early to observe the full volume reduction potential of the initial RFA session. It is possible that if the second RFA session occurred one year after the index RFA session to allow for maximum volume reduction, that the study results may be different.

In an effort to study the long-term benefits of additional RFA sessions, Kim *et al.* (37) retrospectively grouped 90 nodules into 3 groups: those that met the criteria for additional RFA and underwent additional sessions, those that met the criteria but did not undergo additional sessions, and those that did not meet the criteria for additional sessions. At the 5-year follow-up, they found that patients who underwent additional RFA sessions had a larger reduction of volume compared to those that met the criteria for more RFA sessions but did not undergo additional sessions. Furthermore, they found that compared to nodules that did not meet the criteria for additional sessions, nodules that had additional RFA sessions presented with larger index nodule sizes but were able to achieve similar percent volume reductions, supporting the recommendation that larger nodules may need multiple RFA sessions to achieve peak volume reduction. Regardless of whether a patient receives one or multiple sessions of RFA, recent longitudinal studies have shown that RFA results in long lasting nodule volume reduction (67–93.4%) along with improvement in compressive symptoms when followed at 2-, 4- and 5-year post treatment (33,38-40). These studies have reported a low recurrence rate (4.1–5.6%), all of which were secondary to the regrowth from undertreated peripheral margins. When these recurrences were reevaluated with FNA, all were confirmed to be benign.

When compared to observation alone, thyroid nodules treated with RFA significantly decreased in volume with improvement in symptom scores at the 6-month follow-up visit (34,41,42). A retrospective study comparing patients treated with thyroidectomy versus those treated with RFA found that patients who underwent surgery had higher postoperative complications (6% *vs.* 1%, P=0.02) and needed longer hospitalization (6.6±1.6 *vs.* 2.1±0.9 days, P<0.01) (43). These findings are supported by a meta-analysis which also showed comparable symptom improvement in patients treated with thyroidectomy or RFA, but found that those who underwent RFA had lower incidences of hoarseness, hypothyroidism, pain, and hospitalization time (44). Recently, Jin *et al.* (45) randomized patients with benign thyroid nodules to thyroidectomy or thermal ablation to compare patient satisfaction and quality of life (QoL). They found that those treated with thermal ablation reported higher Thyroid-specific QoL, total social well-being and total psychological well-being scores at last follow-up. Additionally, patients who were treated with thermal ablation were more likely to recommend the therapy method than those who underwent surgery (94% *vs.* 32%, P<0.0001). In light of these positive findings, there is unanimous agreement among published guidelines and consensus statements that RFA is indicated in patients who have compressive and/or cosmetic symptoms from nonfunctional, benign thyroid nodules (*Table 2*) (13,14,26,28,29).

AFTN

Definitive management of thyrotoxicosis from AFTN has traditionally been with radioactive iodine (RAI) or with a hemi- or total thyroidectomy (46). However, some patients may have comorbidities that would make surgery prohibitively high risk, while others may have contraindications for RAI therapy (i.e., pregnancy) or may decline surgical intervention. When observed over a year, Cervelli *et al.* (47) found that RFA had similar nodule volume reduction rates, similar rates of euthyroid restoration, and decreased rates of clinical hypothyroidism (0% *vs.* 20%, P<0.05) compared to a fixed dose of RAI (15mCi of ^{131}I). Similar to nonfunctional thyroid nodules, AFTN nodule volume significantly decreased (50–86%) after RFA treatment (15-17,48-50). However, other studies suggest that RFA may have a less predictable response on reducing thyroid hormone hypersecretion. Studies in Korea suggest that RFA improves mean thyroid stimulating hormone (TSH), total triiodothyronine (T3) and free thyroxine (fT4) levels (15,48). When evaluating the patients with ^{99m}Tc pertechnetate scintigraphy, only 45–80% had inactive thyroid nodules after RFA treatment. Italian studies similarly found improvement in TSH, T3 and fT4 levels after RFA therapy (16,49-51). In their population, they found that 24–86% of patients treated with antithyroid medication prior to RFA maintained a euthyroid state after withdrawal of the antithyroid medication post RFA treatment. One reason for the wide range of hormonal normalization rates is hypothesized to be secondary to the incomplete ablation of the nodule margins which may still be functional. Suspecting that the varying response rates may be related to the pre-treatment AFTN size, Cesareo *et al.* (50) compared treatment response for small (<12 mL) and medium (>12 mL) AFTNs and found that the number of patients achieving a euthyroid state was greater in

those with small AFTNs, suggesting that the preoperative nodule volume may be a predictive factor on the efficacy of RFA. This supports the theory that insufficient nodule ablation may be the reason that some patients are unable to achieve euthyroidism as smaller nodules typically respond with greater nodule volume reduction. Indeed, while not reaching statistical significance (P=0.08), Bernardi *et al.* (49) observed that patients who achieved euthyroidism had an average nodule volume reduction of 81% compared to 68% in patients who did not achieve a hormonal response after a single RFA session after 12 months. However, this remains controversial as a meta-analysis by Kim *et al.* (52) did not find an association between TSH normalization and preoperative nodule volume. Due to the variable response rates in treating AFTN, current guidelines cautiously recommend RFA as a therapeutic alternative when first line therapies (RAI or surgery) are contraindicated (*Table 2*). While there are no definitive size cutoffs, all recommendations specifically acknowledge that RFA may be less effective in large AFTNs.

Primary malignant disease

The standard of care for patients diagnosed with well-differentiated thyroid cancer is partial or total thyroidectomy. Currently, there is little data on the role of RFA for the curative treatment of primary malignant disease greater than 1 cm. While current guidelines do not recommend RFA for use of malignant lesions greater than 1 cm, an international consensus statement by Orloff *et al.* (14) suggests that if the treatment intent is palliative, patients with larger tumors may be candidates for RFA to relieve compressive symptoms.

Recently, there have been increasing detection rates of papillary thyroid microcarcinomas (PTMC), defined as papillary thyroid carcinoma (PTC) less than 1 cm, which has sparked debate on whether the risk of surgery outweighs the benefit of the immediate removal of this indolent, low risk cancer. Indeed, the work by Ito *et al.* (53,54) has shown that patients with PTMC without clinical evidence of unfavorable features (proximity to trachea/recurrent laryngeal nerve, clinical nodal disease or high grade "suspicious" features on biopsy), may be managed with *active surveillance*, where patients are serially monitored with US for progression of disease. If disease progression was identified on surveillance imaging, studies found no increased risk of morbidity or mortality when interval surgery was performed (54). While these dichotomous treatment strategies have allowed for individualized management plans, the success of RFA in treating benign and recurrent malignant thyroid disease has presented some with a potential third strategy.

A prospective study by Zhang *et al.* (55) found that of 98 PTMC ablated, 10.2% completely resolved within 6 months (median follow-up of 7.8 months) without evidence of short-term recurrence or metastatic lymph node development. This was supported by Lim *et al.* (19) who looked at 152 PTMCs over a mean follow-up period of 39 months and found complete disappearances in 91.4% of RFA ablated tumors with an overall complication rate of 3%. A subsequent subanalysis on this same cohort of patients with more than 5-year follow-up found a complete disappearance rate of 100% at the 60-month follow-up with a complication rate of 1.4% (20). Although four new thyroid cancers formed during the study period, they were all successfully re-ablated. Most recently, a meta-analysis on the safety and efficacy of RFA for primary PTMC found a pooled complete sonographic disappearance rate of 79% over a mean follow-up time of 33 months. Overall tumor progression was seen in 26 patients (1.5%) with 3 patients (0%) having major complications (56). Currently, both the Task Force Committee of the Korean Society of Thyroid Radiology (KSThR) RFA guidelines (26) and an international multidisciplinary consensus statement (14) cautiously recommend RFA as a treatment strategy in well-selected patients with low-risk PTMC who refuse or are otherwise unfit to undergo surgery and do not want to undergo active surveillance (*Table 2*). Additionally, the international consensus statement by Orloff *et al.* (14) specifically highlights that primary PTMC candidates must be: (I) unifocal and confined to the thyroid gland; (II) cytologically confirmed to be malignant without aggressive subtype; (III) without evidence of metastatic lymphadenopathy.

Recurrent malignant disease

Local regional recurrence rates of WDTC can vary, going as high as 55% depending on tumor size, presence or absence of somatic mutations, and lymphovascular invasion on pathology (2). When locally recurrent disease is identified, resection with RAI remains the standard of care. As previously mentioned, the risk of complications (life threatening neck hematoma, recurrent laryngeal nerve injury) increases in reoperation cases which must be discussed with patients prior to pursuing surgery. Similar to

primary PTMC, studies have suggested that RFA may have a role as a minimally invasive treatment option in patients with local regional recurrences of WDTC.

RFA for treating local recurrence in WDTC was first described by Dupuy *et al.* (21) in 2001 as a small case series of eight patients. With a mean follow-up of 10.2 months, six patients had no evidence of tumor after RFA treatment on US and/or repeat FNA. Subsequent studies found RFA sessions caused disappearance and/or significant volume reduction of metastatic lymph node deposits as well as decrease in serum thyroglobulin levels at last follow-up (22,23,57). Specifically, Kim *et al.* (23) retrospectively looked at patients with recurrent WDTC less than 2 cm who were treated with RFA or surgery and found comparable 3-year recurrence-free rates at 92.6% and 92.2% respectively. Additionally, a meta-analysis found the pooled proportion of patients with complete disease disappearance after RFA treatment to be 68.8%, the pooled serum thyroglobulin reduction of 71.6% and the complication rate of 5.8% (58). It is also important to highlight that RFA may have a role in recurrent disease even if radiological complete ablation is not possible. Park *et al.* (59) evaluated patients with inoperable, symptomatic local regional disease, and found that 63.6% of patients had symptom relief after volume reduction from RFA therapy. In regards to recurrent malignant thyroid disease, current recommendations agree that RFA may be considered in well-selected patients with recurrent WDTC who are not amenable to or unable to tolerate surgery (*Table 2*) (14,26,27). However, the consensus statement by Orloff *et al.* (14) also highlighted that when considering RFA for recurrent disease, the treatment intent needs to be discussed with the patient in order to set clear expectations. For those hoping for curative outcome, patients with small lesions (less than 2 cm) confined to the neck are ideal candidates, while a palliative strategy may be more amenable for patients with larger lesions.

Conclusions

RFA is a versatile, minimally invasive technique that results in consistent volume reduction and improvement in symptoms for those with benign thyroid nodules. With growing evidence supporting its efficacy and safety, societal and international guidelines and consensus statements agree that RFA is a viable option for treating symptomatic, functional, and nonfunctional thyroid nodules. Although surgery remains the standard treatment for those with index and/or recurrent malignant disease, RFA may have a therapeutic and palliative role in patients who decline or are not surgical candidates.

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Footnote

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