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Mini-Review

Radiofrequency Ablation for Benign Thyroid Nodules

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Abstract

Context: Thermal ablative techniques of the thyroid have recently gained clinical traction as a therapeutic alternative that provides symptomatic relief and confers potential advantages over surgery. A truly multidisciplinary technique, thyroid ablation is currently performed by endocrinologists, interventional radiologists, otolaryngologists, and endocrine surgeons. Radiofrequency ablation (RFA), specifically, has seen widespread adoption, particularly in the treatment of benign thyroid nodules. This review summarizes current evidence on the application of RFA in benign thyroid nodules, and provides a start to finish overview of procedural preparation, performance, and outcomes.

Evidence Acquisition: A narrative review of literature focusing on RFA in the treatment of benign nodular disease was performed. Emphasis was placed on consensus statements, best practice guidelines, multi-institutional studies, and systematic reviews to summarize key concepts in candidacy, techniques, expectations, and outcomes.

Findings: RFA is increasingly recognized as a first-line treatment strategy in the management of symptomatic nonfunctional benign thyroid nodules. It can also be considered in functional thyroid nodules with small volumes or in patients ineligible for surgery. A targeted and efficacious technique, RFA results in gradual volume reduction that preserves the function of the surrounding thyroid parenchyma. Proper procedural technique, proficiency in ultrasound, and experience in ultrasound-guided procedures are instrumental to maintaining low complication rates and achieving successful ablation outcomes.

Conclusions: In pursuit of a personalized approach, physicians across disciplines are increasingly incorporating RFA into their treatment algorithms, most commonly for benign nodules. As with any intervention, thoughtful selection and implementation ensure a safe procedure with optimal patient benefit.

Key Words: thyroid ablation, thermal ablation, radiofrequency ablation, benign nodule, thyroid nodule

Abbreviations: AFTN, autonomously functioning thyroid nodule; RFA, radiofrequency ablation; VRR, volume reduction ratio.

Thyroid nodules are exceedingly common, being palpable in 4% to 7% of the population, and detectable on ultrasound in up to two-thirds of adults (1). In 2016, an estimated 169 000 thyroid surgeries were performed in the United States, the majority for benign indications (2, 3). Though thyroid surgery has long been a safe and effective intervention, many patients, particularly those with benign disease, delay or avoid surgery because of risks associated with the operation itself or the potential need for lifelong hormone supplementation (4). Thus, thermal ablative procedures, in particular radiofrequency ablation (RFA), have been increasingly adopted and refined in recent years, allowing for a targeted approach to thyroid nodule management.

Thermal ablation encompasses a variety of minimally invasive techniques wherein application of high temperatures induces focal cellular apoptosis and, ultimately, coagulative necrosis (5). These techniques, which include microwave ablation, laser ablation, high-intensity focused ultrasound, and RFA, differ in mechanism used to generate the applied heat. During RFA, a percutaneous probe is placed within the target lesion, and frictional heating occurs as ions within the tissue attempt to align with the changing directions of the high-frequency alternating current (6). Hyperthermic cellular injury results, which is immediately toxic when reaching temperatures higher than 60°C. Below this temperature, cellular damage is reversible, while above 100 °C, desiccation and vaporization increases the tissue impedance and limits further conduction (6). Laser ablation is performed via optical fiber, with the most common source being an Nd:Yag or diode laser. This is the next most prevalent thermal ablation technique, and volume reduction can be comparable to RFA depending on nodule characteristics and operator experience (7). Microwave ablation generates an electromagnetic field that results in larger ablation zones and higher tissue temperature, which can be valuable in treating larger tumors (8). Based on the conversion of acoustic to thermal energy, high-intensity focused ultrasound is the least used technique, and few high-quality studies are available that compare outcomes to the other thermal ablative techniques (8).

RFA has been performed internationally for more than 20 years, with the first in human experience for the treatment of benign thyroid nodules described by Kim et al in 2006 (9). The technology subsequently saw wide adoption across Asia and Europe, where the development of guideline and

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consensus statements further validated RFA as a component of the personalized treatment algorithm, and expanded indications beyond benign disease (7, 8, 10–13). Dissemination in the United States has been more gradual, in part because of the somewhat recent approval of the technology by the Food and Drug Administration in 2018, the interruption of the coronavirus pandemic, and the kinetics of procedural adoption and diffusion as the potential advantages over surgery are recognized (14, 15). While the minimally invasive nature of RFA precludes the need for general anesthesia, avoids a neck scar, and limits recovery time, the true differentiator from surgery is the preservation of euthyroidism. Transient thyroid dysfunction may occur following RFA (16), but the long-term rate of hypothyroidism is exceptionally low (17, 18). Though uncommon, major complications such as nerve injury or nodule rupture may occur with RFA. Regrowth and need for additional intervention are also possible. In light of growing enthusiasm for radiofrequency ablation as a therapeutic alternative, this review focuses on its utilization in benign nodules, currently the application with the most robust evidential support. Herein we describe appropriate patient selection and informed consent, as well as review the procedural technique, expected outcomes, and potential complications.

Patient Selection

Judicious patient selection is a critically important concept in thyroid RFA, and fundamental to a safe and efficacious procedure. It is first paramount to be reasonably certain of benignity prior to performance. Several organizations, therefore, suggest that 2 benign fine-needle aspiration biopsies be obtained to ensure candidacy. Alternatively, one benign biopsy and a classically benign ultrasound appearance (spongiform or predominantly cystic) is sufficient prior to ablation (7, 8, 10). In autonomously functional thyroid nodules, biopsy is not necessarily required, though nodules should still demonstrate a benign ultrasound appearance (7).

Current guidelines suggest that patient symptoms drive the decision to offer RFA. Though there is no strict minimum size requirement, larger nodules are more likely to contribute to the compressive and/or aesthetic concerns that may be alleviated by RFA (7, 8, 10). Potential symptoms reported may include pressure or globus sensation, dysphagia, positional discomfort or shortness of breath, subtle voice change, or unfavorable appearance.

Various guidelines and consensus statements have suggested differing criteria for thyroid nodule size in candidacy. While the Korean Society of Thyroid Radiology suggests a nodule exceeding 2 cm with continuous growth is appropriate, the Italian societies recommend RFA in nodules larger than 20 mL (10, 11). However, the unifying principle is that symptomatology will differ according to the location of the nodule as well as the body habitus of the patient. Owing to the inherently subjective nature of symptomatology, the decision to pursue RFA must ultimately be a well-informed partnership between the patient and physician. It may be advantageous to quantify symptom and cosmetic disturbance before and after intervention to assess the degree of perturbance as well as the response to treatment (19).

The most ideal candidate is one with a well-defined, dominant cervical nodule convincingly contributing to the patient's reported concerns (8, 20). Caution must also be exercised in multinodular goiter, wherein symptoms are often due to multiple bilateral nodules or a diffuse pseudonodular process, as well as in substernal nodules. While current best practice does not support RFA as a first-line treatment in these contexts (8, 12), there is limited evidence suggesting ablation to be effective and safe for addressing both multinodular goiter and substernal nodules (21, 22). These will undoubtedly be applications that continue to see reevaluation as the literature becomes more robust and criteria for selection evolves. Relatedly, there may also be a role for ablation of smaller nodules demonstrating consistent growth on serial ultrasound, as these would be expected to become symptomatic and could be adequately addressed in one treatment (13, 15, 23). Overall, there is no one set of criteria by which to evaluate a patient for thyroid ablation, and the selection criteria are likely to expand with time and evidence. It is, rather, incumbent on the physician to understand the motivating factors of the patient and establish practical expectations for treatment outcome to ensure alignment of goals.

Patients with autonomously functioning thyroid nodules (AFTNs) may also be candidates for RFA. The ultimate goal is this patient population is to discontinue antithyroid medications and restore euthyroidism. The success of RFA in achieving this state, however, is variable, and can depend with the size of the nodule and, relatedly, the completeness of the ablative procedure (24). Generally, nodules with volume less than 10 mL are more likely to be effectively treated with single-session RFA, while those greater than 20 mL are unlikely to achieve durable euthyroidism (25, 26). As there are other treatment modalities more consistently effective than RFA in eliminating hyperthyroidism in AFTNs, it is best considered an alternative strategy for those who decline or with contraindications to surgery or radioactive iodine (7, 8, 11).

Informed Consent

As treatment strategies in thyroid disease evolve and opportunity for personalization increases, the informed consent process becomes integral to patient selection and satisfaction in RFA, as in all thyroid ablative procedures. The patient need be thoughtfully informed of all approaches, including observation or surgery, as well as their respective advantages, expectations, and limitations. Discussion surrounding expectations specific to RFA must include anticipated volume reduction, possibility of regrowth, and potential need for additional ablative or even surgical intervention. Because RFA reduces but does not eliminate a nodule, a commitment to long-term follow-up is also required.

Though reported complication rates in RFA are low (18), there are a number of risks that must be disclosed in the consent process. These include injury to the recurrent laryngeal or vagus nerve, resulting in hoarseness. Less commonly, the sympathetic ganglion or brachial plexus may be injured. A rare but unique complication, nodule rupture can lead to inflammation and fluid collection in the soft tissues of the neck, sometimes requiring surgical management (27). Minor complications such a skin burn, hematoma, persistent cough, and vomiting have also been reported (28).

Finally, a frank discussion of the expectations surrounding the procedure itself are important. While not a painful procedure, it is common to experience a sensation of pressure or discomfort in the ear, jaw, teeth, shoulder, or back, particularly as the nodule begins to swell. However, this is minimized with

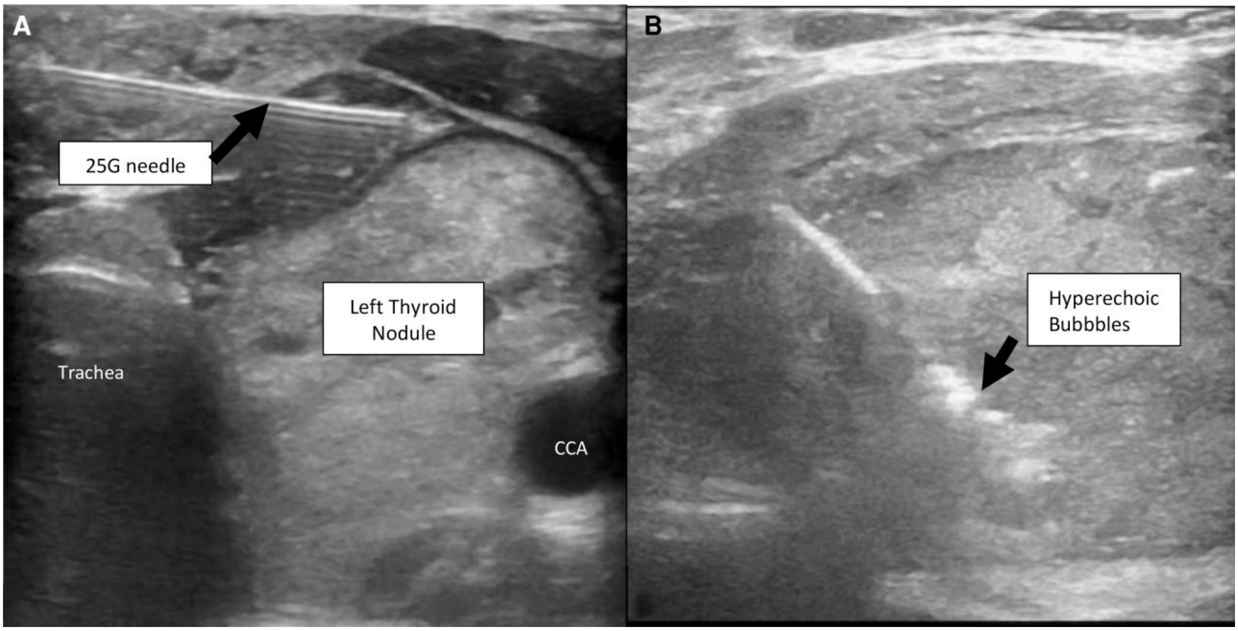

Figure 1. A, Anterior hydrodissection of a nodule with 1% lidocaine prior to ablation initiation. B, The radiofrequency ablation electrode is positioned in an inferior and posteromedial position to begin ablation. As ablation begins, hyperechoic white bubbles can be seen forming around the active tip. CCA, common carotid artery.

the administration of local anesthesia, rendering RFA a tolerable procedure for nearly all patients in an awake setting.

Procedural Specifics

RFA is usually performed under local anesthesia in a hospital, day procedure, or office setting. Sedation is occasionally used; however, general anesthesia is ill advised because of the risk of increased complications from the patient being unable to communicate during the procedure. During the ablation, the patient lies on their back with their neck extended. The procedure is performed under sterile conditions.

Anesthesia

Plain 1% lidocaine is the most commonly used local anesthetic for the procedure. Performance of RFA under local anesthesia allows the patient to communicate with the proceduralist during the ablation, aiding in the early recognition of symptoms such as voice change and discomfort. Using ultrasound guidance, lidocaine is initially injected into the midline skin and subcutaneous tissues using a 25- or 27-gauge needle. The maximum safe volume of anesthetic—based on body weight and renal function—must be calculated before injection is initiated to avoid toxicity. Once the skin has been injected, the needle is advanced anterior to the thyroid nodule, in a pericapsular plane, and anesthetic instilled (Fig. 1A). Advancement of the needle laterally allows critical structures such as the common carotid artery and a medially placed vagus nerve to be successfully lifted off the surface of a laterally placed thyroid nodule. This process is called *hydrodissection*. If the maximal volume of local anesthesia is reached and further hydrodissection is required, a nonconducting solution such as 5% dextrose can be used.

Radiofrequency ablation technique

Once adequate anesthesia has been instilled and critical structures have been hydrodissected off the capsule of the nodule, the needle is withdrawn and the RFA electrode inserted into the midline neck skin. The needle is advanced through the thyroid isthmus using the so-called "*transisthmic approach*" to a thyroid nodule. By entering the thyroid via the isthmus, a buffer of normal thyroid tissue is provided to protect against inadvertent heat injury to skin and subcutaneous tissues during ablation. Ablation is initiated at the caudal (inferior) aspect of the nodule (Fig. 1B). For each axial section of the nodule, the electrode is initially inserted into the posteromedial aspect of the nodule then withdrawn in a posterolateral to anteromedial direction (Fig. 2). This technique is called the "*moving-shot technique.*"

When ablation is initiated, hyperechoic bubbles will be seen to emanate from around the electrode tip (Fig. 1C). The proceduralist uses both the ultrasound appearance of the ablated tissue and tissue impedance (displayed on the console of the RFA generator) to guide when adequate ablation energy has been applied to any area of tissue. Once a single axial plane has been fully ablated, the ultrasound probe is repositioned to visualize a more superior axial plane and the process of ablation repeated. This continues in a caudal to cranial direction until the entire nodule has been ablated. For large nodules, more than one skin puncture may be required to enable adequate access to superior aspects of the nodule.

As patients are awake during the procedure, they can directly report any discomfort or unusual sensations. It is important for the proceduralist to listen to their feedback as increasing discomfort may indicate too much heat delivery adjacent to a critical structure such as the tracheal cartilages. Particularly when ablating close to the trachea, low power and/or smaller active tip electrodes should be used to minimize inadvertent heat transfer.

At the conclusion of the ablation, the electrode is withdrawn and pressure (± ice) is applied to the neck for 30 to 60 minutes to minimize bruising and postprocedural hematoma.

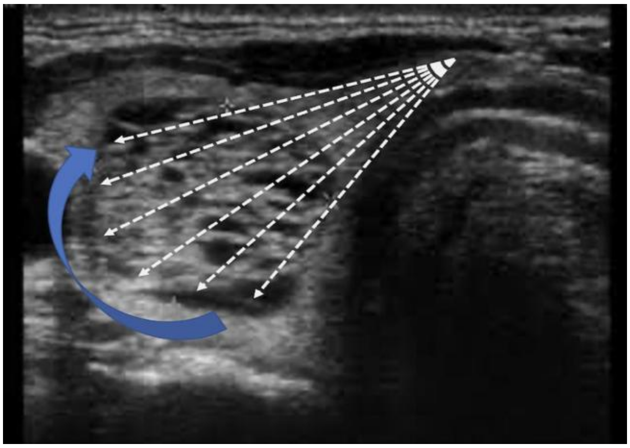

Figure 2. Path of electrode motion during thyroid nodule radiofrequency ablation. Blue arrow indicates the posterior to anterior motion of the electrode in any given axial plane. The white arrows indicate the direction of insertion of the electrode, from isthmus to deep aspect. With each ablation run, the electrode is withdrawn along the path of the white arrows in a posterior to anterior and lateral to medial direction.

Outcomes

In appropriately selected patients, RFA may be a reasonable alternative to surgery for benign thyroid nodules. Nodule shrinkage occurs gradually following ablation. In the first week, it is not uncommon for inflammation to increase nodule volume to some degree, anywhere from 0% to 20%. Maximal volume reduction occurs in the first 6 months post ablation, with subsequent smaller-volume reductions possible for up to 2 to 3 years post procedure. A recent meta-analysis by Cesareo et al (19) reported a pooled volume reduction of 64.5% at 6 months, 76.9% at 12 months, and 92.2% at 36 months. Similarly, a multi-institutional prospective study of 216 patients followed for 5 years after RFA confirmed sustained response, with 72.4% volume reduction rate (VRR) at 12 months and 77.1% VRR at 5 years (29). In addition and perhaps most important, RFA is reported to be highly effective at addressing symptomatic and cosmetic concerns and improving quality of life related to thyroid nodular disease (30–32). However, an important limitation in assessing the precise effect of ablation on such concerns is the heterogeneity and applicability of outcome assessment tools used in this patient population (19).

Baseline nodule volume affects the size of the nodule remnant after maximal shrinkage has been obtained, and nodules that are larger than 20 mL at baseline have a higher likelihood of requiring more than one ablation to achieve adequate shrinkage (29). In a large prospective study of 215 patients, Deandrea et al (17) reported an overall average VRR of 67%, while nodules smaller than 10 mL achieved 79% VRR at 1 year and 81% at 5 years. This concept of baseline volume holds especially true in autonomously functioning nodules, wherein initial nodule volume directly correlates with the completeness of ablation, and, subsequently, the ability to achieve euthyroidism. The pooled rate of thyrotropin normalization across all functional nodules is 41% to 57% (33, 34). However, those with nodules smaller than 10 mL are more likely to achieve the greater than or equal to 80% VRR shown to be associated with thyrotropin normalization at 12 months post procedure (8, 12). Rates of antithyroid medication withdrawal in this group of small nodules ranges from 74% to 86% (26, 34).

Similarly, nodule composition can affect final volume reduction. Nodules with a cystic component, or that are predominantly cystic, tend to demonstrate more rapid and robust final VRR than entirely solid nodules (35, 36). A prospective Italian study found the highest VRR (76%) among nodules with a microcystic spongiform ultrasound appearance, while solid nodules reduced 67%, on average (37). Baek et al (38), in a randomized trial comparing RFA to ethanol ablation for predominantly cystic nodules, reported a mean VRR of 87.5% in the RFA group, which was not different from the ethanol ablation group. In another study by Jung et al (18), solidity was determined to be a negative independent factor in predicting final volume reduction.

Finally, total energy delivery to the nodule plays a critical role in anticipated response. An Italian study determined that 756 J/mL, 1311 J/mL, and 2109 J/mL were associated with ability to achieve 50% VRR at 1 year in 50%, 75%, and 99% of nodules, respectively (39). This was confirmed in another multicenter collaboration wherein delivery of 1360 J/mL was moderately predictive of greater than 50% VRR, while less than 918 J/mL was associated with greater likelihood of retreatment (29).

In regard to multiple treatments, there are limited data thus far to suggest that two or more ablative sessions result in superior outcomes to a single session. Huh et al (40) performed a randomized controlled trial wherein 15 patients underwent single-session RFA while another 15 had RFA in 2 sessions 1 month apart. There was no significant difference in volume reduction, symptom, or cosmetic score between the two groups. Of note, 3 patients in the single-session group, all of whom had initial nodule volume greater than 20 mL (mean 31.0 mL), requested additional RFA because of persistent nodule-related symptoms (40). In contrast, however, Lim et al (41) reported a mean VRR of 93.4% with multiple ablation sessions after 49 months of follow-up.

Additional treatment is often considered for nodule regrowth after initial RFA. Regrowth is most widely defined as an increase in volume by 50% or more from the smallest recorded nodule volume (42, 43). Factors relating to regrowth are multiple, and also closely related to the technical success of the procedure itself. Most often, regrowth occurs from untreated peripheral nodular tissue that retains its vascular supply (44). This occurs more frequently in large nodules, wherein it can be challenging to effectively treat all viable tissue, and in nodules in close proximity to vital structures (45). The rate of regrowth is variable, but has been reported in a recent systematic review including 933 nodules to range from 0% to 34% at 12 months (46). It may be argued, however, that the 12-month assessment is too early to detect regrowth, and thus underestimates the true incidence (43). A review by Sim et al (44) of 54 patients followed for a mean of 39.4 months demonstrated regrowth in 24.1% of nodules, and vital volume increase in 57.4% of nodules. This concept of vital volume, or residual viable nodular tissue, has also been shown to correlate with potential need for eventual re-treatment (47).

Complications

In general, RFA is a low-risk procedure. However, there are a number of potential complications that warrant mention. Pain during or after the procedure is experienced by a significant minority, reported by up to 21% of patients (32). Self-limiting hematoma is one of the most common risks of ablation, generally secondary to bleeding of pericapsular thyroid veins during electrode insertion and manipulation (48). Fortunately, such bleeding generally settles with cessation of the procedure and firm neck pressure. Injury to the recurrent laryngeal or vagus nerves can occur during ablation as a result of inadvertent heat transmission from the electrode to the nerve, or compression from intranodular hemorrhage (28). Most thermal neural injuries are reportedly transient with voice change lasting from weeks to months (28, 49). Nodule rupture is a complication unique to thermal ablation whereby the nodule rapidly grows in size in a delayed manner, usually weeks to months after the procedure. Presumably due to intranodular microbleeding, this complication generally resolves with conservative measures (27, 50). Less common risks include tracheal injury, skin burns, and branchial plexus or sympathetic trunk neural injuries (51, 52). Nodule regrowth necessitating an additional ablative procedure is another potential outcome that patients should be warned about; it is more common the larger the baseline volume of the nodule (46, 53).

Prior Knowledge

RFA is an advanced ultrasound-guided technique. As such, clinicians with extensive experience in neck ultrasound and biopsies are the best equipped proceduralists to perform RFA. From the studies that have been conducted in this area, physicians with strong prior technical skills and knowledge usually require between 20 and 30 cases to pass the initial learning phase for ablation (21–24). This learning curve is much longer for physicians less skilled in neck ultrasound and biopsy techniques. Clinicians who wish to start performing RFA should ensure they have adequate prior knowledge to perform the procedure in a safe manner with low complications and good outcomes.

Conclusions

This narrative review summarizes the critical concepts in RFA for benign thyroid nodules, including patient selection, procedural performance and complications, and patient expectations and outcomes. In general, outcomes following RFA are excellent, with the majority of patients achieving at least 50% reduction in initial volume, and some enjoying 80% VRR or greater after a single session. Major complications are infrequent, and cosmetic, symptom, and quality of life scores improve post treatment. However, the final outcome is dependent on a number of nodule and treatment characteristics, as well as the experience and proficiency of the operator. Careful patient selection, counseling, and consent, combined with sound technical skills and knowledge, are essential for optimization of long-term results.

Disclosures

C.F.S. has no disclosures. J.E.N. is a consultant for Pulse Biosciences.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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