



Radiofrequency Ablation of Solid, Non-Functional Thyroid Nodules

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Background

Thermal ablation in the neck has been applied to several clinical conditions, but by far, the most common application is for the treatment of the benign, solid, non-functional thyroid nodule. Though relatively new to the United States, thermal ablation of these nodules has been performed internationally for nearly two decades, especially in South Korea and Italy. A number of ablative techniques - radiofrequency, laser, microwave, high-intensity focused ultrasound, and ethanol - have been studied and reported. This review will focus on the most commonly applied technology for solid non-functional nodules, RFA.

Thyroid RFA provides a minimally invasive, low risk, efficacious therapy for the treatment of this condition. Thyroid RFA enjoys similar efficacy as surgery, results in similar degrees of patient satisfaction, but does so with a lower risk profile.^{1,2} While many interventional radiologists will be familiar with thermal ablation in other organs, such as lung, liver, and kidneys, there are some important procedural modifications (namely the “moving shot” technique) which are unique to the neck. Similarly, those that perform ablations will be familiar with the potential for thermal injury to nearby structures and many will also have experience with protective maneuvers such as hydrodissection. However, in the neck, the myriad vital structures (vessels, nerves, trachea, esophagus, etc.) all coursing together in a relatively tight anatomic space, make these considerations of even greater importance and will challenge even experienced operators.

Clinical Evaluation of the Patient

A pre-procedural checklist is provided in [Table 1](#).

History and Physical

The pre-procedural workup begins with a thorough history and physical. Typical symptoms will include dysphagia, a sensation of a lump in the throat, discomfort, cough, difficulty breathing, and cosmetic issues. Typical motivations for pursuing RFA in lieu of surgery include a fear of surgery and its complications, the desire to avoid hypothyroidism (and the need for lifelong thyroid medications), the desire to preserve normal, non-nodal thyroid tissue, and avoiding the surgical scar.

While no patient is “typical” there are some trends worth mentioning. First, a good many patients in our practice (as is likely the case with any relatively new procedure and the “early adopter” patients that consider these procedures) are self-referred, knowledgeable about the procedure, and have often already considered and excused surgery as an option. Second, there are a minority of patients who, in spite of being biochemically euthyroid, ascribe a host of symptoms (fatigue, insomnia, anxiety, etc.) as attributable to their nonfunctional nodule. In all patients, but especially these, a thorough discussion of motivations and expectations is important.

There are two standardized scoring systems used to evaluate symptomatic thyroid nodules (both on initial visit and as post-procedural follow-up): the symptom score, which is a visual analog scale from 0 to 10 to rank the patient’s subjective severity of discomfort, and the cosmetic score, which is the physician’s assessment of the nodule’s conspicuity on physical exam (ranging from 1 for no visible or palpable mass, to 4, for a readily detectable cosmetic issue), see [Table 2](#) and [Figure 1](#).

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Table 1 RFA Pre-Procedural Checklist**Cytopathology**

Benign diagnosis on at least 2 US-guided FNA or CNB
 Benign diagnosis on at least 1 US-guided FNA or CNB if highly specific benign US features or if AFTN
 Ultrasound
 Nodule volume estimation ($0.523 \times \text{length} \times \text{width} \times \text{height}$)
 Nodule features (vascularity, calcifications, solid: cystic ratio, echogenicity)
 Location and proximity to critical structures
 Symptom Score
 Cosmetic Score
 Labs
 CBC, Coagulation tests
 Serum TSH, free T4, T3
 Thyroid antibodies in select circumstances
 Other Imaging
 CT or MRI for certain circumstances, such as large nodules with infraclavicular extension
^{99m}Tc pertechnetate or ^{123I} thyroid scan, if suspect AFTN

Revised from Korean Society of Thyroid Radiology Societal Guidelines.³

AFTN, autonomously functioning thyroid nodule; CBC, complete blood count; CNB, core needle biopsy; FNA, fine needle aspiration; TSH, thyrotropin; free T4, free thyroxine; T3, triiodothyronine; US, ultrasound.

Table 2 Cosmetic Score

Score	Examination
1	No palpable mass
2	Palpable without cosmetic issues
3	Cosmetic issue with swallowing only
4	Readily detectable cosmetic issue

Laboratory evaluation: should at least include a complete blood count (CBC), coagulation profile, and thyroid function tests, including thyrotropin (TSH), free thyroxine, and triiodothyronine (T3). In certain circumstances, thyroid antibody tests, such as thyroid peroxidase antibody and thyroglobulin antibody, can be helpful. Patients with elevated autoantibody levels are more prone to developing hypothyroidism following RFA and should be counseled as such.³

Table 3 The 2017 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic Category		Risk of malignancy if NIFTP ≠ CA (%)	Risk of Malignancy if NIFTP = CA (%)
1	Nondiagnostic or unsatisfactory	5-10	5-10
2	Benign	0-3	0-3
3	Atypia of undetermined significance or follicular lesion of undetermined significance	6-18	10-30
4	Follicular neoplasm or suspicious for follicular neoplasm	10-40	25-40
5	Suspicious for malignancy	45-60	50-75
6	Malignant	94-96	97-99

Adapted with permission from Cibas and Ali.⁷

CA, carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features.

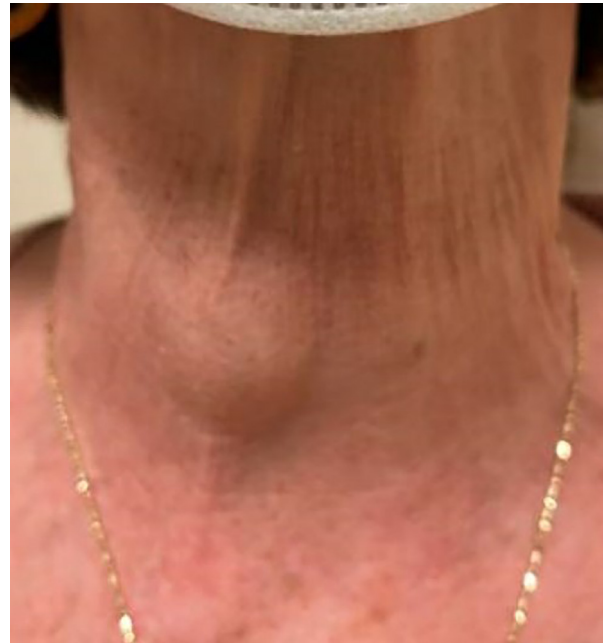


Figure 1 An example of a patient with a readily detectable cosmetic issue caused by a large right thyroid nodule. This nodule would be assigned a cosmetic score of 4. (Color version of figure is available online.)

Cytopathology

Current recommendations call for at least two benign (Bethesda II) fine-needle aspirations (FNAs) or core needle biopsies of any nodule targeted for ablation unless: (1) the nodule has specifically benign sonographic features; or (2) is an autonomously functioning nodule. In both of these latter cases, a single benign result will usually suffice.^{4,5} The risk of malignancy in the context of two benign cytopathologic diagnoses is extremely low, nonetheless, caution should be exercised in any nodule with suspicious sonographic features.⁶

Given recent trends, cytologically indeterminate thyroid nodules are worth some discussion. FNA reliably classifies sampled nodules as benign or malignant in the majority of cases by the Bethesda System for Reporting Thyroid Cytopathology (Table 3).⁷ However, approximately 15% of the time, cytologic results are indeterminate, classified as Bethesda III (atypia of undetermined significance, follicular lesion of undetermined significance), and Bethesda IV

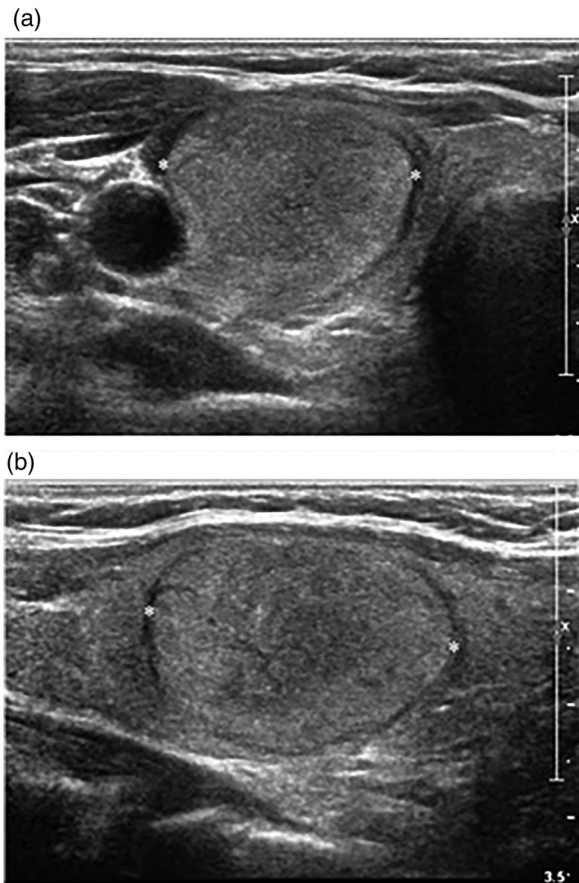


Figure 2 An example of an appropriate candidate nodule for thyroid RFA. Transverse (A) and longitudinal (B) ultrasound images of a right thyroid lobe, demonstrate a solid, isoechoic, thyroid nodule (between *) with an estimated volume of 6 cc in a patient with complaints of cough and a “lump” in her throat.

(follicular neoplasm, suspicious for follicular neoplasm).⁸ Historically, diagnostic thyroidectomy has been performed for most of these indeterminate thyroid nodules, with the majority eventually found to be benign on final pathology.

Increasingly, molecular testing is being utilized to help risk-stratify these indeterminate nodules and to assist in clinical decision-making. Several molecular tests are currently commercially available in the United States, the most common being Afirma, Gene Sequencing Classifier and Xpression Atlas (GSC & XA; Veracyte, South San Francisco, CA) and ThyroSeq version 3 (TSv3; CBLPath, Rye Brook, NY), which predict benignity or malignancy-based DNA, RNA analysis, or a combination of the two.⁹

In a meta-analysis investigating the diagnostic performance of available molecular tests, Silaghi et al. found Thyroseq v3 to have an overall sensitivity of 0.99, specificity of 0.64, positive predictive value of 0.78, and negative predictive value of 0.96 in detecting malignancy.¹⁰ Afirma GSC was found to have an SE of 0.95, specificity of 0.51, positive predictive value of 0.6 and negative predictive value of 0.91. Owing to the high sensitivity and negative predictive value of both of these molecular tests, these can be regarded as good “rule out” tests, accurately excluding malignancy when negative. It thus stands to reason that nodule with cytologically indeterminate FNA results

(Bethesda III and IV) and subsequent negative molecular markers, can be considered as having had a benign FNA with regards to the pre-RFA workup, though this is an area of study that requires warrants investigation.

Ultrasound of the thyroid gland plays an important role during the pre-procedural evaluation. Nodule location and accessibility, calculation of nodule volume (using the formula $0.523 \times abc$, where a is the maximal nodule diameter and b and c are orthogonal diameters), presence of calcifications, proximity to nearby structures, degree solid vs cystic, and nodule vascularity should all be assessed.

We strive to approach each patient in a multidisciplinary fashion, with our team comprised of interventional

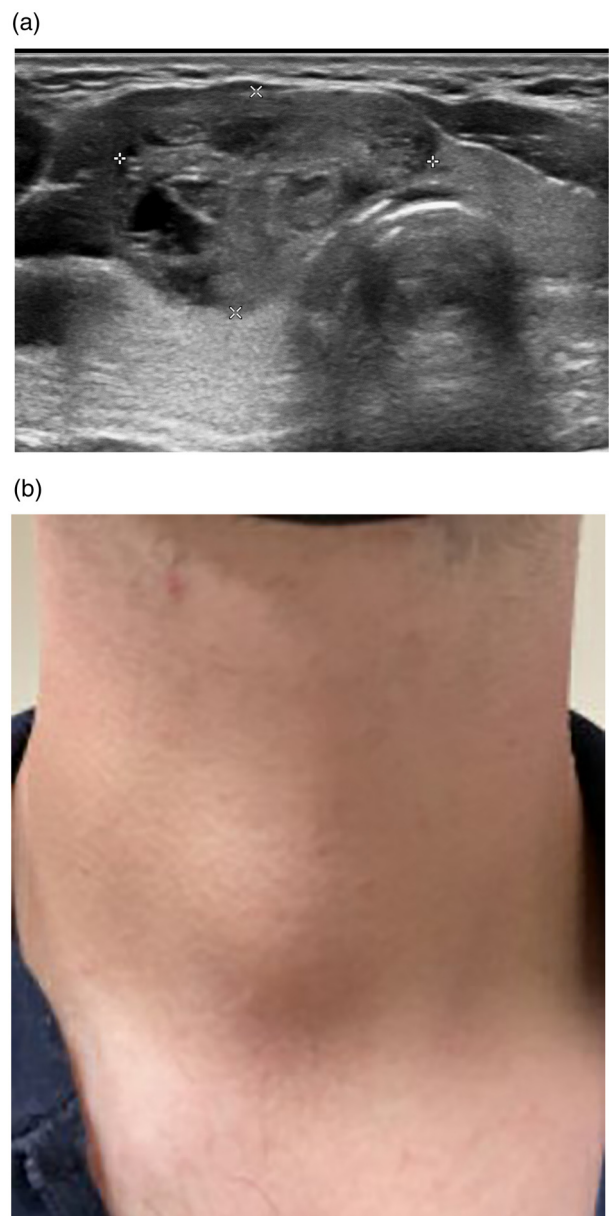


Figure 3. (A) An ultrasound image of a right paramedian isthmic nodule with an estimated volume of 5 cc (depicted by calipers). (B) A photograph from the same patient demonstrates, that, though relatively small, given the isthmic location, this nodule creates a readily detectable lump in the patient’s neck. (Color version of figure is available online.)

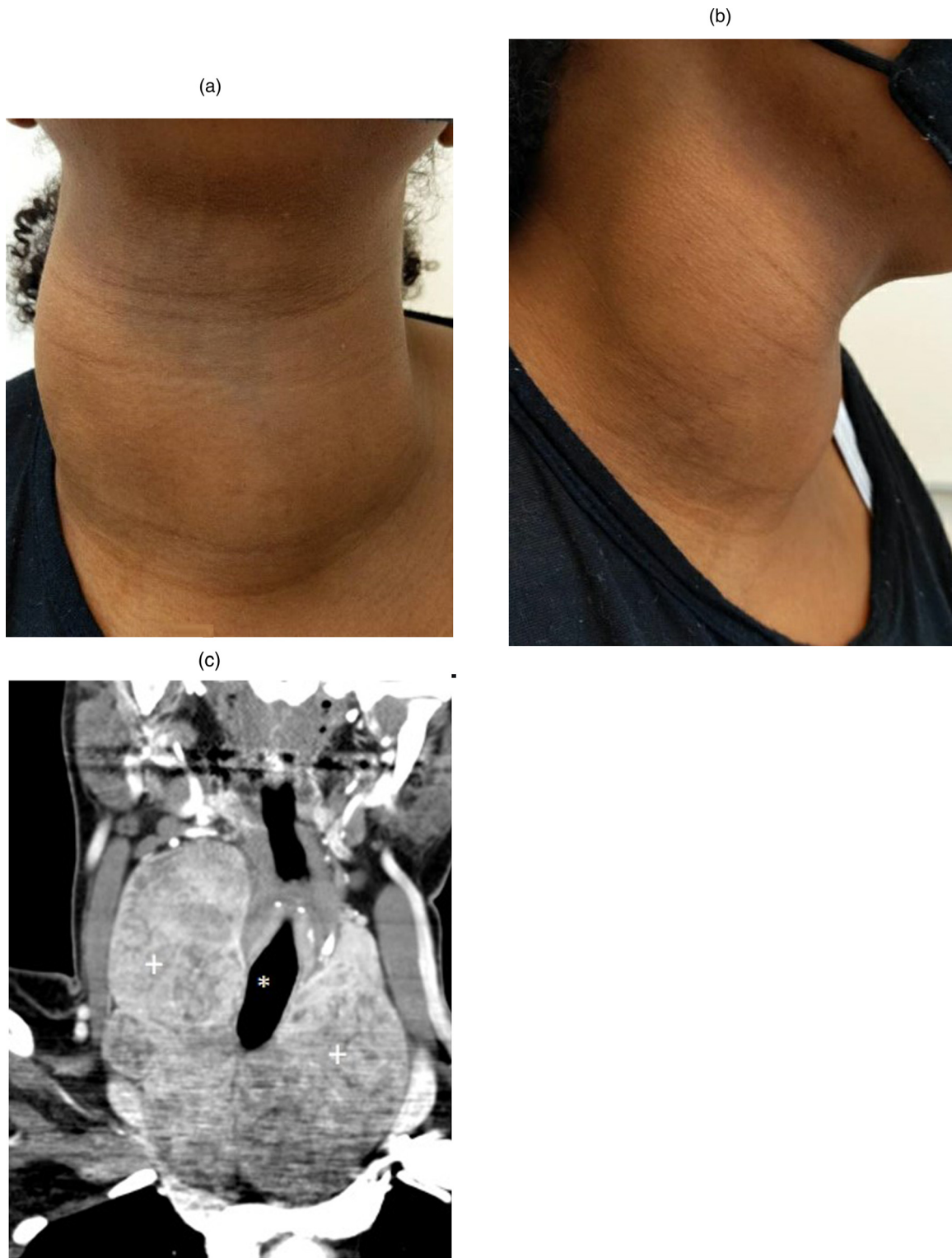


Figure 4. (A) Photographs of a patient with a very large, symptomatic goiter. (B) CT scan demonstrates a diffuse, bilateral, multinodular goiter (+), with mass effect on the trachea (*). Owing to the very large size and diffuse nature of this process, this is a non-ideal candidate for RFA. (Color version of figure is available online.)

radiologists, endocrinologists, and surgeons who are familiar with RFA. For patients who have not already spoken to a surgeon, we encourage this consultation, so that the patients can make a fair assessment of their best option.

All patients should be counseled on expected treatment outcomes, the number of anticipated treatment sessions, the post-procedural follow-up schedule, the possibility of regrowth over time with the need for further intervention, the

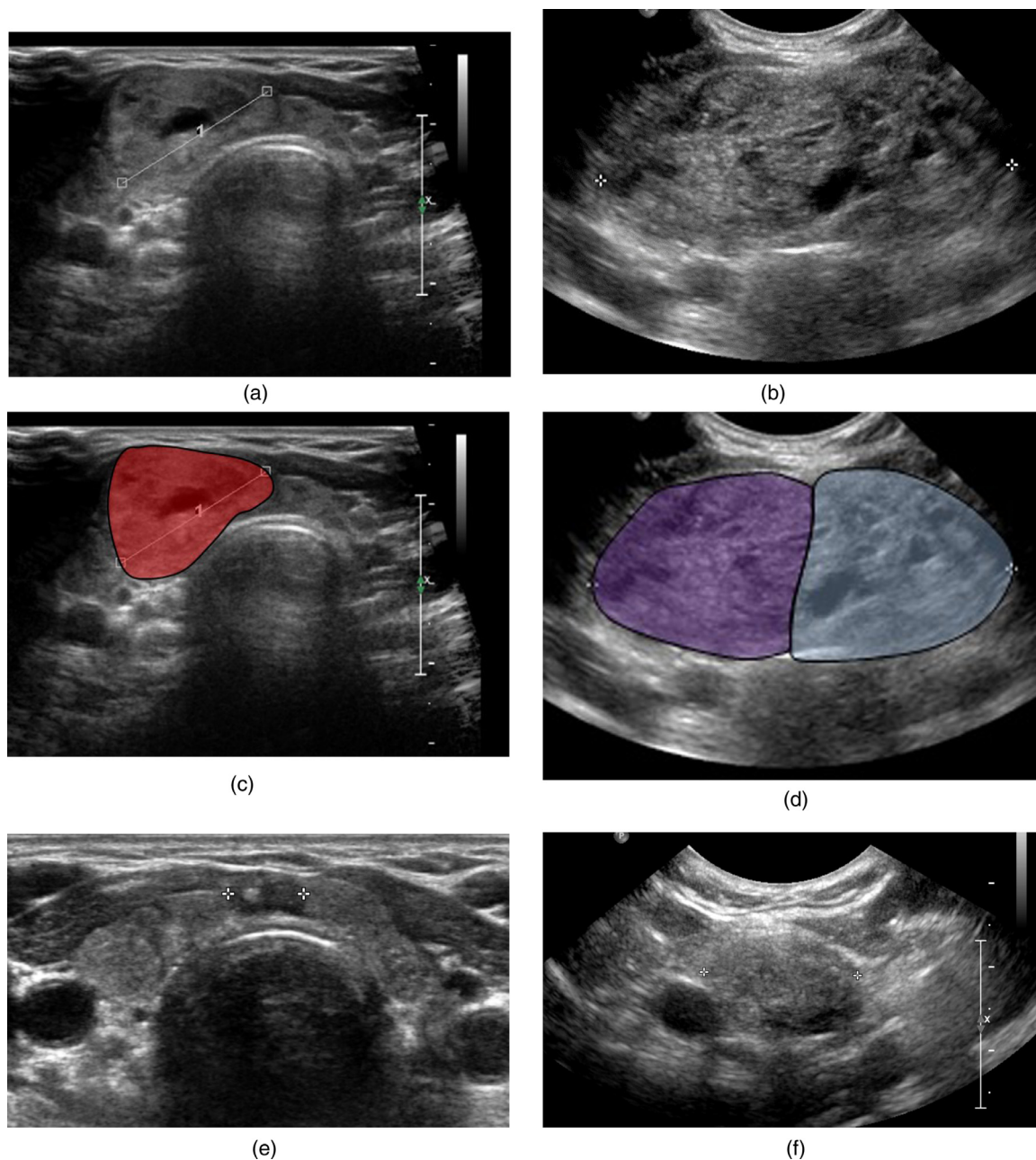


Figure 5 “Staged ablation” 5A. Ultrasound images of a multi-component thyroid nodule with right, superior, medial components (estimated volume = 5 cc, measured nodule), and a larger, inferior isthmic component (estimated volume approximately 26 cc, between “+” s). (B) Staged ablation of this nodule was performed whereby right superior components (red) were targeted initially, followed by inferior right lateral (purple) and inferior left lateral (blue) components subsequently. (C) Follow-up ultrasound 2 y after ablation demonstrates decreased size of all components with volume reduction ration (VRR) of 96% for the superior component and 92% for the inferior components (residual nodules depicted by calipers). (Color version of figure is available online.)

alternatives to the procedures, including surgery and watchful waiting, and the potential complications of thermal ablation.

Nodule Selection

Ideal nodules for thyroid ablation are solid or predominately solid, well visualized sonographically in their entirety, with a “reasonable” volume (see Fig. 1). What determines a “reasonable” volume is not well defined. Currently there are no

firmly established nodule size guidelines for RFA.⁴ This is in part because of variable patient anatomy. Small isthmic nodules in slender patients may cause significant symptoms whereas large lobar nodules in patients with thicker necks may go undetected (Fig. 3). While there is great variability between patients as well as between nodules of different composition and vascularity, we have found a good rule of thumb is that roughly 20 to 30 cc of solid nodular tissue can be ablated in a single session. Larger than that may require

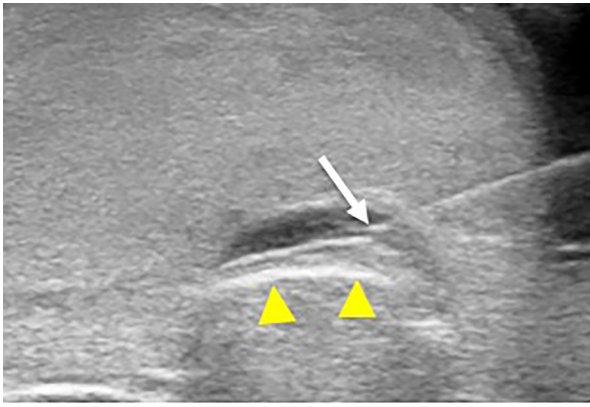


Figure 6 Hydrodissection in an isthmic nodule. A needle is introduced via a transisthmic approach, with the needle tip (arrow) positioned between nodule and trachea (arrowheads). D5W is subsequently infused to “lift” the nodule away from the trachea prior to RFA. (Color version of figure is available online.)

multiple ablation sessions as larger nodules will require longer ablation times, which can impact the ability of patients to tolerate the procedure, may result in increased post-procedure pain and swelling, and may increase complication rates.

Nodules which should be avoided include those which are very large (where volume control would not be expected with a reasonable number of ablation sessions), heavily calcified nodules (which limit sonographic visualization and monitoring during the procedure and which will be difficult or impossible to penetrate with the electrode), nodules with significant infraclavicular components (such that sonographic monitoring during the procedure would be compromised), and thyroid glands which are diffusely involved by nodules where no discrete target nodules accounting for the patient’s symptoms can be found (Fig. 4). Entirely or predominantly (>90%) cystic nodules may respond better to ETOH ablation reference.^{11,12}

Occasionally asymptomatic patients with benign nonfunctional nodules will seek treatment. In general, only nodules

causing cosmetic or referable pressure symptoms should be treated. Some advocate treatment for continuously growing nodules which are expected to eventually cause symptoms, as treatment at a smaller size is easier and safer, though this is an area which requires further investigation.¹³

The RFA Procedure

Radiofrequency ablation of benign, nonfunctional thyroid nodules, follows the same technique principles as for any thyroid RFA, including the trans-isthmic approach and moving-shot techniques. The goal of treatment is to ablate nodular tissue as completely as possible, both to achieve better volume reductions as well as to reduce the incidence of later marginal recurrences.¹⁴ Of course, this requires a balancing act between achieving as complete an ablation as possible while avoiding injury to structures at the nodule margin.

“Large” thyroid nodules are typically defined in the literature as those greater than 20-30 cc.¹⁵⁻¹⁷ As above, while there are no established nodule size limits for RFA, large nodules may require more than one session to achieve adequate volume control. In certain circumstances, for large nodules, we have found it helpful to treat nodules in a planned, “staged” approach, whereby a geographic region of the nodule (for example the upper half) is systematically ablated during a first session, and remaining portions are targeted during a separate session (or sessions), spaced several weeks or months apart. This has proven especially helpful in patients with nodules that partially extend infraclavicular, whereby the superior portion is treated first and with its volume regression, the inferior portion ascends in the neck, making it more accessible for the subsequent second “stage” of ablation. (Fig. 5). Staged procedures may also be appropriate in patients with *bilateral* nodules, as posttreatment inflammation and swelling theoretically pose greater risk to the patient if RFA is performed in both lobes at the same time, not to mention the potential for bilateral vocal cord paralysis.

The isthmic nodule presents some unique challenges. Owing to the interposition of the anteriorly situated thyroid

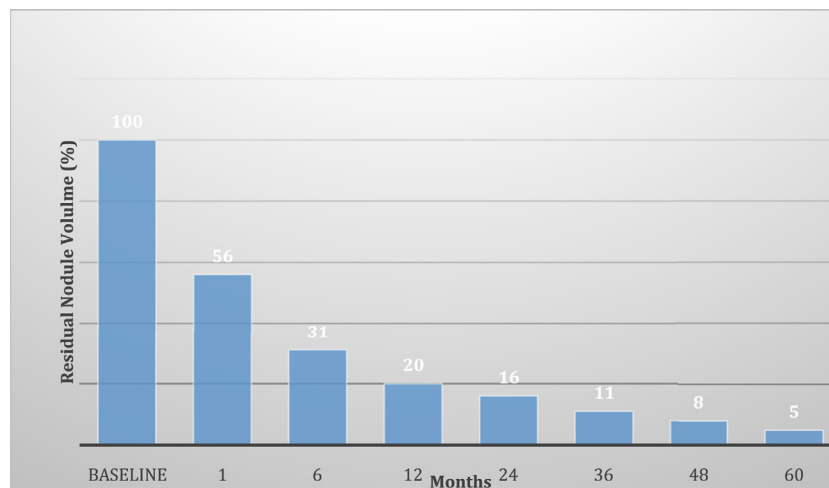


Figure 7 Nodule size change over time. Depicts residual nodule volume (as a percent from baseline) over time. (Adapted with permission from Jung SL.¹⁸). (Color version of figure is available online.)

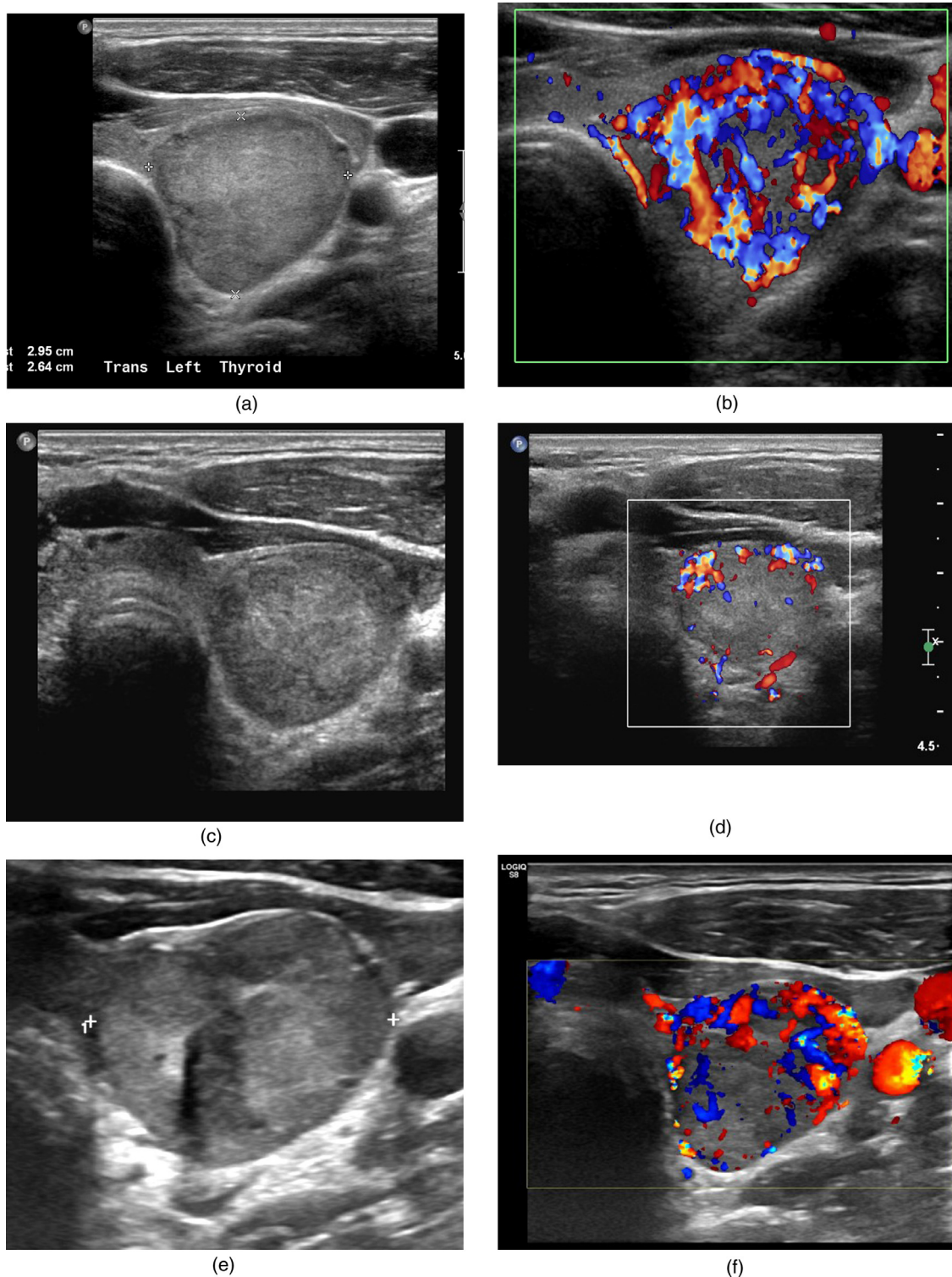


Figure 8 Nodule recurrence (A). Initial gray scale and color Doppler sonographic images demonstrate a highly vascular nodule, prior to RFA, with an estimated volume of 13 ml (depicted by calipers). (B) Images 12 mo after ablation demonstrate decreased size, with an estimated volume of 6 cc and VRR of 54%, but some persistent, vascularized tissue at the nodule margin. (C) Images 18 mo after ablation show an interval increase in size with estimated volume of 8.6 cc, with increased growth and vascularity of marginal tissue. Overall VRR is 34% compared to baseline, but 43% increase from the nadir value of 6, with a return of symptoms. The patient was subsequently retreated. (Color version of figure is available online.)

isthmus between the trachea and skin, care must be taken to prevent thermal injury to both of these areas during treatment of these nodules. Hydrodisplacement maneuvers, to

separate skin from anterior nodule surface can be helpful. Cold packs on the skin may also be helpful. 5% Dextrose in water (D5W) injection between the trachea and posterior

aspect of the thyroid isthmus may help to displace the nodule from the trachea, thus avoiding tracheal thermal injury (Fig. 6). It should be noted that local anesthetic *should not* be used in this latter scenario as this may mask symptoms related to tracheal thermal injury (such as cough and pain).

The *hypervascular* nodule is harder to treat, owing largely to the heat sink effect, and may require higher wattages and more total energy deposition.¹⁷ In these circumstances, advanced techniques such as “artery first” and “marginal vein” ablation, may be considered.

Expected Outcomes

A number of studies, predominately from South Korea, China, and Italy, have reported on the efficacy of RFA in improving patient cosmetic and compressive symptoms and in achieving nodule volume reductions (the latter typically reported as a volume reduction ratio, or “VRR”, calculated as $VRR = [\text{initial volume} - \text{final volume}] \times 100 / \text{initial volume}$). Most of this data reports on short-term results, but studies reporting long-term results are beginning to emerge.

A recent, multi-institution study demonstrated mean volume reductions at 1, 6, 12, 24, 36, 48 and 60 months at 44%, 69%, 80%, 84%, 89%, 92%, and 95%.¹⁸ The mean number of RF sessions in this study was 1.3, with additional treatment allowed if the follow-up ultrasound showed remaining viable portions of the nodule and if the patient complained of ongoing symptomatic or cosmetic problems. Overall therapeutic success rate (defined as >50% volume reduction) was 97.8%. Mean symptom and cosmetic scores were 2.5 and 3.7 respectively prior to ablation, 1.3 and 2.9 at 1 months, and 0.4 and 1.9 at 12 months. Volume data is summarized in Figure 7.

Denadrea, et al. reported on the long-term efficacy of a single RFA session for benign thyroid nodules, reporting overall volume reductions of 67% at 5 years.¹⁹ Notably, better results were achieved with smaller nodules; those with initial volumes <10 mL, averaged 82% volume reduction, those between 10 mL and 20 mL, 75% volume reduction, and those 20 mL or larger, reaching 65% volume reductions at 5 years.

Several additional studies have demonstrated similar long-term results.²⁰⁻²² The majority of nodule shrinkage (typically in excess of 65%) occurs by 6 months, with slower, progressive shrinkage in the months afterwards; cosmetic and local symptom improvement accompany this size reduction. For most of these studies more ablation sessions were required for larger nodules than for smaller nodules.

It has been estimated that nodule recurrence (that is regrowth after initial successful treatment) occurs in anywhere from 5.6 to 24% of cases, usually several years after initial treatment (see Fig. 8).^{23,24} This is thought to be due to growth of incompletely ablated tissue at the nodule margin. Several authors thus emphasize the importance of treating the nodule margin as completely as possible, as well as marginal assessment by ultrasound on follow-up visits, as early marginal regrowth may herald the need for repeat ablation.²⁴

While there is a paucity of North American literature, initial reports show similar results in the United States. Hamidi

performed a retrospective review of 14 patients treated in the United States with RFA, achieving a median VRR of 53% at 24 months.²⁵ Hussain reported on 58 nodules in 53 patients, achieving a VRR of 71% after a median follow-up of 109 days.²⁶

Conclusions

Thyroid RFA, following trends in Asia and Europe, is emerging in the United States as a minimally invasive treatment for certain thyroid conditions. While more long-term data are needed, initial results suggest that thyroid RFA is a safe and highly effective treatment for the non-surgical treatment of the symptomatic, benign, nonfunctional thyroid nodules.

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