



## Overview of Benign Thyroid Nodules and Management Using Radiofrequency Ablation

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### ABSTRACT

Thyroid nodules occur commonly in the general population, mostly as incidental findings, with a prevalence of 19–68% at ultrasound evaluation, which is the first examination method used for neck imaging. Most thyroid nodules are benign and approximately 10% of patients who present with thyroid nodules are at risk of malignancy. Common thyroid nodules typically result in morbidity from either localized compression or hyperthyroidism. The main treatment of the disease is still the traditional surgical resection, however there are many problems such as general anesthesia, surgical scar, postoperative thyroid or parathyroid function abnormalities, and high nodules recurrence rate in residual gland. For nonsurgical therapy of symptomatic or expanding thyroid lesions, a number of US-guided, minimally invasive procedures (MIT) are currently available. Treatment options include either percutaneous ethanol injection (PEI), which is most suited for often cystic lesions, or other methods depending on the fluid level of the nodule. There are several methods available now, including Radiofrequency Ablation (RF), for image-guided ablation of benign solitary thyroid nodules. This study's goal is to assess how well RF ablation works for treating benign solitary thyroid nodules. Therefore, the purpose of this study is to review and management of benign thyroid nodules using radiofrequency ablation.

**Keywords:** Benign Thyroid Nodules; Management; Radiofrequency Ablation

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### INTRODUCTION

Thyroid nodule is a discrete lesion in the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma and discovered in approximately 5% to 7% of the adult population by physical examination alone. But, autopsy data have shown a 50% prevalence of thyroid nodules larger than one centimeter in patients without previously diagnosed thyroid disease (1). American Thyroid Association (ATA) defines the thyroid nodule as a discrete lesion within the thyroid gland. It is radiologically distinct from the surrounding thyroid parenchyma (2).

Thyroid nodule is typically asymptomatic, and 33% to 68% of adults have thyroid nodules when evaluated by ultrasound. Most thyroid nodules are benign, but about 7% to 15% of individuals with thyroid nodules harbor thyroid cancer. Thyroid nodules may also cause morbidity due to hyperthyroidism or local compression. Population-based studies suggest a doubling in thyroid cancer incidence in recent decades, but nearly all of this increase is attributable to clinically occult cancers detected incidentally on imaging or pathology (1). Benign nodules include adenomas as colloid nodules, cysts, infectious nodules, lymphocytic or granulomatous nodules,



hyperplastic nodules, thyroiditis and congenital abnormalities **(3)**.

Differentiating between benign and malignant neoplasms is the goal of evaluating a solitary thyroid nodule. The optimal medicinal and surgical interventions for nodular thyroid disease require the most accurate prediction of malignancy. The diagnostic method of choice for the initial assessment is fine needle aspiration biopsy (FNAB), which is frequently utilised**(4)**.

### **Epidemiology**

Thyroid nodules are common. Their prevalence can be affected by several factors, such as iodine sufficiency status and age, and detection rates differ according to the modality of imaging used and the experience of the operator**(5)**.

With physical examination (neck palpation), thyroid nodule prevalence in iodine-sufficient populations is approximately 5%, depending on age and sex. However, clinicians encounter a much higher proportion of patients harboring occult thyroid nodules, reaching up to 68% of the general population **(6)**.

The prevalence of thyroid nodules increases with age, from approximately 42% for younger patients (<40 years) to about 76% in the older population (>61 years) when screened by ultrasound**(5)**.

### **Risk factors**

The prevalence of thyroid nodules is 4 times more common in females than in males. Gender disparity is postulated to occur secondary to influence of oestrogen and progesterone, as demonstrated by increased risk associated with pregnancy and multiparity**(8)**.

The prevalence of thyroid nodules increases with age. Nodules occur more commonly in areas of iodine deficiency. Cigarette smoking can also predispose to development of nodular goitre. This can be secondary to inhibition of iodine uptake and organification by thiocyanate,

which is derived from cyanide in cigarette smoke, hence mimicking iodine deficiency. Obesity has also been demonstrated to be associated with increased risk of goitre and thyroid nodules. Alcohol intake has been associated with decreased prevalence of goitre and thyroid nodules **(9,10)**.

Autoimmune thyroid diseases are commonly associated with thyroid nodules. Graves' disease is associated with nodules in 10–31% of patients. In a Brazilian study, the prevalence of nodules in Graves' disease was 27.8%; 19.5% of the nodules harboured thyroid carcinomas, yielding an overall malignancy prevalence of 5% in patients with Graves' disease. Younger age and increased thyroid volumes were associated with increased risk for papillary thyroid carcinoma (PTC). This was in contrast to other studies where older age was a risk factor for malignancy **(11,12)**.

Small thyroid nodules are also commonly associated with Hashimoto's thyroiditis. These should be differentiated from pseudonodules resulting from inflammatory infiltrate. Despite the concerns, the US Preventive Services Task Force (USPSTF), which reviews the effectiveness of screening programs in asymptomatic individuals, recommended against screening for thyroid cancer in adults without signs or symptoms of the disease **(13)**.

### **Causes**

Thyroid nodules can be caused by many disorders**(Table 1)(14)**. Benign (colloid nodule, Hashimoto's thyroiditis, simple or hemorrhagic cyst, follicular adenoma and subacute thyroiditis) and malignant (Papillary Cancer, Follicular Cancer, Hurthle Cell (oncocytic) Cancer, Anaplastic Cancer, Medullary Cancer, Thyroid Lymphoma and metastases -3 most common primaries are renal, lung & head-neck) **(15)**.



**Table (1): Causes of thyroid nodules (14)**

Benign	Malignant
Multinodular (sporadic) goiter ("colloid adenoma")	Papillary carcinoma
Hashimoto's (chronic lymphocytic) thyroiditis	Follicular carcinoma
Cysts (colloid, simple, or hemorrhagic)	Minimally or widely invasive
Follicular adenomas	Oxyphilic (Hürthle cell) type
Macrofollicular adenomas	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features
Microfollicular or cellular adenomas	Medullary carcinoma
Hürthle cell (oxyphil cell) adenomas	Anaplastic carcinoma
Macro- or microfollicular patterns	Primary thyroid lymphoma
	Metastatic carcinoma (breast, renal cell, others)

**Origin**

The majority of thyroid nodules derive from thyroid follicular cells. Benign follicular nodules, either solitary or as part of a multinodular goitre, are the most common mass lesions(16). Overall, thyroid cancer carries an excellent prognosis with a 5-year overall survival rate of 96.1%, and 98.2% for those patients who have survived one year after diagnosis. This good prognosis is largely driven by papillary thyroid carcinoma, with less favorable 5- year survival rates for follicular thyroid carcinoma and other thyroid cancers (17).

**Clinical Evaluation**

Most patients are asymptomatic. Symptoms from a thyroid nodule or thyroid enlargement include: globus sensation; dysphagia or swallowing complaints; dyspnea; dysphonia or hoarseness; and pain due to acute increase of nodule size, as in case of bleeding into the nodule. The presence of symptoms from a thyroid nodule depends on its size and location. In particular, a globus sensation is more likely to be associated with a nodule size of more than 3 cm and a position close to the

trachea (isthmic nodules more than paraisthmic nodules) (18).

Swallowing complaints are reported in 67%of the patients with either hypothyroidism or thyroid nodules. However, if attributable to nodular thyroid disease, the lesion is typically located in the left lobe with posterior extension, such that it may cause extrinsic compression of the cervical esophagus (19). Physical examination of the thyroid should include inspection for visible lumps and palpation of the thyroid and cervical lymph nodes, searching for firm or fixed nodes or a tender mass (20). Firm, fixed, matted, or rapidly growing masses require prompt evaluation. Physical examination is frequently normal because many thyroid nodules are not palpable because of their small size, posterior location within the gland, or a consistency similar to the thyroid gland (21).

**Laboratory evaluation**

• **Serum TSH**

The initial evaluation in all patients presenting with a thyroid nodule should include a measurement of serum TSH. If TSH levels are low, possibility of subclinical or overt hyperthyroidism should be considered. Approximately 10% of solitary nodules can be associated with



a subnormal TSH. Multinodular goitres, on the other hand, are frequently associated with suppressed TSH due to development of autonomy in the nodules (22). Serum free T4 levels and T3 levels should be obtained for documentation of hyperthyroidism; the latter may especially be obtained in areas with iodine deficiency due to preferential secretion of T3 over T4 in these circumstances. Patients with a thyroid nodule and subnormal TSH can be taken for a Nuclear Thyroid Scan to document the functional status of the nodule (23).

• **Serum thyroid antibodies**

In patients with elevated TSH, anti-thyroid peroxidase (anti-TPO) antibodies may be measured which point to a diagnosis of Hashimoto's thyroiditis. However, positive anti-TPO does not obviate the need for a cytopathological evaluation, as a coexisting malignancy needs to be ruled out. A raised or even a normal TSH is associated with an increased risk of malignancy, as well as a more advanced stage of differentiated thyroid cancer (24).

• **Serum thyroglobulin**

Thyroglobulin (Tg) is a storage form of thyroid hormones. Serum Tg levels are elevated in many benign and malignant thyroid disorders. An elevated level of serum Tg cannot differentiate malignancy in a thyroid nodule with certainty. Measurement of serum thyroglobulin has a role in postoperative monitoring for residual, recurrent or metastatic disease in patients with differentiated thyroid cancers (25).

• **Serum calcitonin**

Calcitonin is produced by the parafollicular C cells of the thyroid gland as well as post-operative monitoring of patients with medullary thyroid cancer (MTC). Serum calcitonin is measured in patients with family history of MTC or MEN-2 syndrome. Unstimulated serum

calcitonin levels >50–100 pg/ml are commonly associated with MTC. There are no recommendations for the routine use of calcitonin in evaluation of thyroid nodules in current recommendations (5).

**Radiological investigations**

**Ultrasonography**

Ultrasound (US) is the first-line imaging modality for malignancy risk assessment of thyroid nodules. Specific US features, such as hypoechogenicity, taller-than-wide shape on transverse view, irregular margins, microcalcifications, and extrathyroidal extension, are recognized to be associated with cancer (26). At the same time, using each individual feature as a standalone diagnostic parameter is associated to inter- and intra-operator variability. To mitigate these limitations, several US risk stratification systems (RSSs) have been developed to stratify the malignancy risk of a nodule and then suggest the need for fine-needle aspiration (FNA) (27).

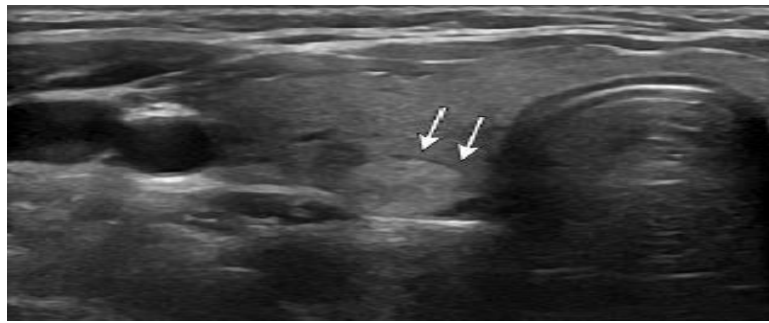
Thyroid ultrasound is used to identify the location and characteristics of thyroid nodules. Solid nodules should be described by using normal thyroid tissue as a reference (Figure 1). They are called isoechoic if their texture closely resembles that of normal thyroid tissue, hyperechoic if more echogenic (or brighter), and hypoechoic if less echogenic (or darker). Nodules with an echogenicity that is as dark as or darker than the surrounding strap musculature are termed "markedly hypoechoic" (28,29).

Calcifications are brightly reflective echogenic densities that reflect the ultrasound beam. When larger than 1 mm, blockade of the ultrasound signal causes the phenomenon of "shadowing," which renders the tissue deep to the calcification invisible (Figure 2). By altering

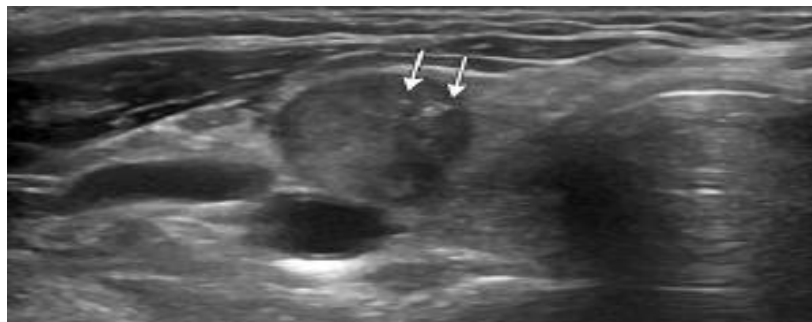


the acoustic pathway (or changing the angle of the ultrasound probe), the ultrasonographer can avoid this pitfall and

see posterior to the area of calcification **(30)**.



**Figure (1): Hyperechoic nodule (arrows) that is brighter than the surrounding thyroid tissue (29).**



**Figure (2): Hypoechoic, solid thyroid nodule (29).** “The nodule is taller than wide in the transverse view. It has internal punctate echogenic foci (microcalcifications), noted by the arrows. This nodule was a papillary thyroid carcinoma.”

### TIRADS

Several attempts have been made to attenuate these limitations with US-based risk stratification systems (RSSs). These systems, often referred to as Thyroid Imaging Reporting and Data Systems, “TIRADSs”), have been developed to establish a standard lexicon for describing thyroid nodules, delineate the US characteristics or sets of characteristics associated to specific risk levels for malignancy, assign nodules to a

risk category, and finally identify nodules that require fine needle aspiration (FNA). Some have been included in clinical practice guidelines for management of thyroid nodules **(25)**. The ATA also uses  $\geq 1$  cm as their threshold for FNA in hypoechoic solid nodules without suspicious characteristics **(Table 2)**, however the American College of Radiology-Thyroid Imaging Reporting and Data System (ACR-TIRADS) use a threshold of  $\geq 15$  mm **(31)**.



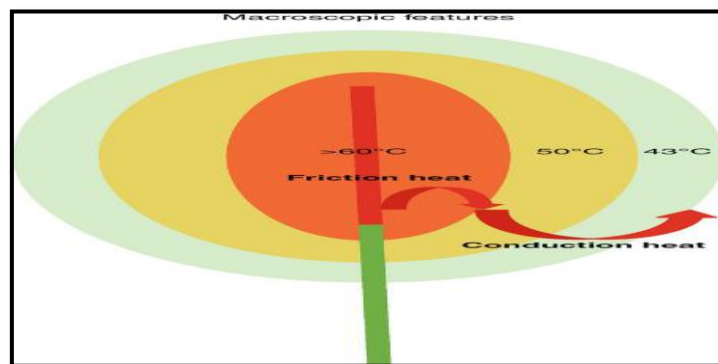
**Table (2): TI-RADS classification scheme for thyroid nodules (31)**

Composition	Echogenicity	Shape	Margin	Echogenic foci
Cystic or almost completely cystic	0	0	0	0
Spongiform	0	1	3	0
Mixed cystic and solid	1	2	2	2
Solid or almost completely solid	2	3	3	3
	Points	Malignancy risk (%)	Biopsy threshold (mm)	
TR1	0	0.3	No biopsy	
TR2	2	1.5	No biopsy	
TR3	3	4.8	25	
TR4	4 to 6	9.1	15	
TR5	7+	35.0	10	

**Radiofrequency Ablation for Thyroid Diseases**

RF ablation uses the heat generated from high-frequency alternating electric current oscillating between 200 and 1200 kHz. The RF waves passing through the electrode agitate tissue ions around the electrode, and they increase the temperature within the tumor tissue, thus resulting in the destruction of tumor

located very close, that is, within a few millimeters, to the electrode (32). The frictional heat, conduction heat from the ablated area can result in relatively slower damage of the tumor or to tissue remote from the electrode tip(Figure 3). This process of thermal injury secondary to friction and conduction heat is the basic mechanism of RF ablation(33,34).



**Figure (3): Macroscopic phenomena during thyroid RFA (34).**

The efficacy of RF ablation can also be reduced due to (1) the heterogeneous nature of the target tissue in the presence of fibrosis or calcification by altering electrical and heat conduction or (2) adjacent blood flow by perfusion-mediated tissue cooling (35).

**Types of RFA thermoablative techniques**

**I. Monopolar RFA**

Monopolar radiofrequency ablation (RFA) for the treatment of thyroid nodules was developed in 2002 by Professor Baek,

an interventional radiologist at the Asan Medical Centre in Seoul. In the limited number of countries in which it is presently available, the monopolar RFA technique is principally carried out by specialists from a range of disciplines in an outpatient setting. Prerequisites are special training and high-quality equipment (36).

Monopolar RFA is a technically relatively demanding procedure. The target nodule must be systematically “degraded” using a freehand (“moving-



shot”) technique from cranial to caudal and from medial to lateral direction in a comparatively narrow ultrasound window without losing sight of the probe. To make matters worse, nodules can, of course, be located on either side of the thyroid gland, so that the hand guiding the probe is sometimes the left hand, and other times the right hand. This ambidexterity must first be achieved through practice on a phantom (36). At present, virtually all knowledge concerning RFA as a treatment method for thyroid nodules is based on published findings obtained using the “monopolar” technique (38,39).

**II. Bipolar RFA**

Bipolar RFA which is, by contrast, a comparatively new RFA technique employs a probe containing both positive and negative poles within the tip that directs the flow of current solely through the nodule tissue, thereby removing the requirement for current dissipation. The high-frequency current between these poles creates a relatively spherical heat field within which the tissue is overheated. As the water content of the treated nodule tissue decreases, the

electric resistance increases and the power of the device is regulated downward (36).

Bipolar RFA is, technically speaking, easier to master than monopolar RFA, because the probe tip need only be placed in a few locations within the nodule, although also in a targeted manner (“multiple overlapping shot” technique). While the first results obtained with the bipolar technique are very promising, long-term outcomes and a systematic treatment of larger patient populations with different nodal characteristics are still lacking at present (40).

**Indications**

The principal indications are benign nodule with symptoms and/or which is optically disturbing. Continually growing benign nodule (>2 cm diameter) with attendant symptoms (Table 3). Autonomous nodule, when radioiodine treatment or surgery is contraindicated or unwanted. Differentiated, iodine-refractory thyroid carcinoma with local recurrence, high surgical risk (palliative therapy approach) (Table 4) (36).

**Table (3): Indications and limitations of monopolar RFA (36).**

	Good indications:	Limited indications:
<b>Monopolar RFA</b>	<p>Cystic, or predominantly cystic nodules (including “cystic colloid nodules”) are the best indication for an RFA.</p> <p>Solid and mixed nodules up to around 30 ml (as a single treatment).</p> <p>Autonomous adenomas—solid or cystic up to around 12–15 ml (as a single treatment).</p> <p>Growing nodules—if causing a beginning symptomatology (always after repeated biopsy using FNA (fine-needle aspiration) or FNCC (fine-needle capillary cytology), or, if necessary, core-needle biopsy!).</p> <p>Patients who already had a thyroid surgery.</p> <p>Elevated risk of general anesthesia.</p> <p>Known susceptibility to keloid scarring.</p>	<p>Cytological report: Bethesda &gt;II or other form of suspected malignancy.</p> <p>Far caudally extending nodules, not fully accessible.</p> <p>Rather narrow and cone-shaped nodules extending far dorsally.</p> <p>Presence of prominent ventral vessels in the treatment plane.</p> <p>Large solid and mixed nodules &gt;30 ml (in a single intervention).</p> <p>Diffuse thyroid enlargement comprising multiple nodules (when even a successful RFA is not expected to produce a satisfactory final result).</p> <p>Autonomous adenomas &gt;15 ml (in a single procedure). Good results with subsequent low-dose I131 therapy are, however, often possible in this case.</p> <p>Multifocal autonomy (indication depending on: nodule number/size, patient age).</p> <p>Hashimoto thyroiditis.</p> <p>Grave’s disease.</p>



**Table (4): Indications and limitations of bipolar RFA (36).**

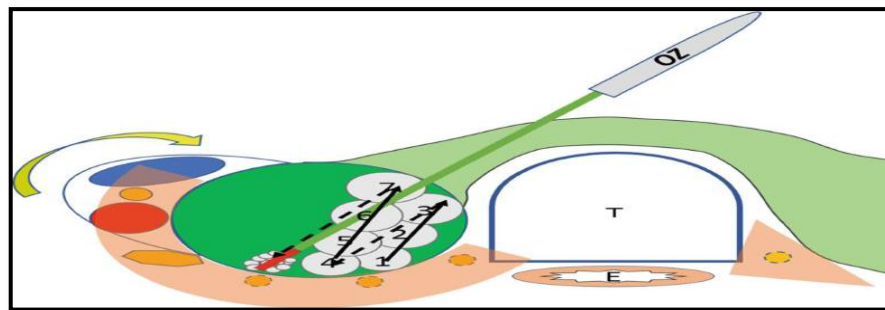
<b>Bipolar RFA</b>	Large, solid nodules—those in topographically difficult locations are sometimes easier to treat with bipolar than with monopolar RFA.  Palliative volume reduction (only in selected cases).  Pregnancy: no contraindication as with monopolar RFA.  Pacemaker wearers: no contraindication as with monopolar RFA.	Nodules with an elevated bleeding risk (larger probe diameter).  Variable nodule sizes, if simultaneous treatment of more than one nodule is planned and this cannot be satisfactorily achieved with one probe size alone (increased material costs).  Smaller autonomous adenomas (higher energy density with monopolar probe).
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**The RFA procedure**

Radiofrequency ablation may be performed with local anesthesia or conscious sedation. After the initial trials are carried out in subjects under conscious sedation with large devices, such as multi-tined electrodes with expanding hooks (14-gauge diameter), thinner (18 or 19G) and shorter, internally cooled electrode needles have been developed and are presently used for thyroid lesions. These tools are more practical and less traumatic and permit a repetitive insertion of the tip of the

needle within the target area, according to the so-called “moving shot” technique (41).

After the insertion of electrode, operators ablate thyroid nodules using a ‘moving shot technique’, which was developed to optimize the efficacy and minimize the complications. In this technique, thyroid nodules are divided into multiple small conceptual ablation units and radiofrequency ablation is performed unit by unit by moving the electrode (42).



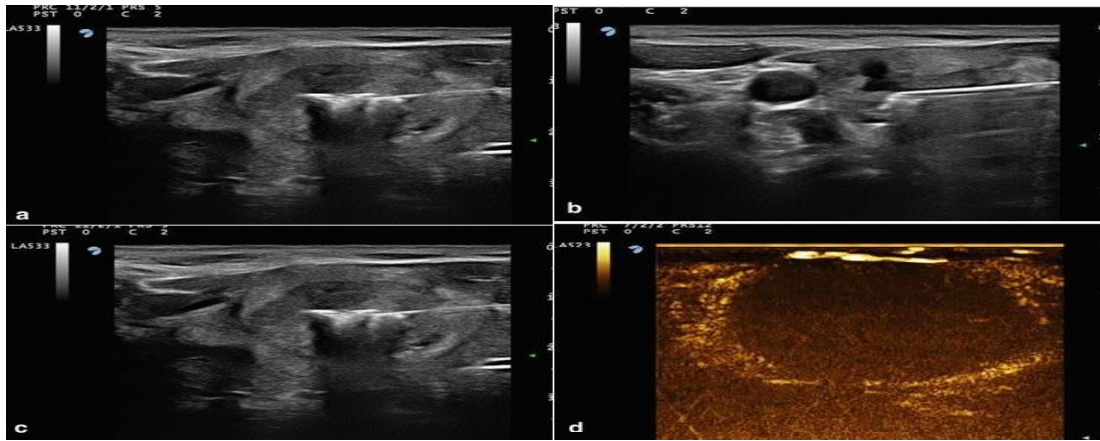
**Figure (4):** Moving-shot technique; T trachea, E esophagus; red circle, common carotid artery; blue oval, internal jugular vein; yellow solid circle, vagus nerve; yellow dotted circle, recurrent laryngeal nerve; yellow heptagon, middle sympathetic ganglion; numbers 1–7, ablation units (34).

The electrode tip is initially positioned in the deepest and most remote portion of the nodule. It is then

continuously moving backward and in the superficial direction within the thyroid nodule to prevent visual disturbance by echogenic bubbles. The extent of the ablated area is estimated from the echogenic changes around the electrode, and radiofrequency ablation is terminated when all conceptual ablation units of the targeted nodule have become transient hyperechoic zones (Figure 4)(43,44).







**Figure (5):** Percutaneous radiofrequency ablation. (a–c) US monitoring of a treatment with an 18G radiofrequency electrode needle of a symptomatic thyroid nodule, benign at fine needle aspiration biopsy. The tip of the electrode needle is sequentially moved within the nodule producing multiple areas of thermal necrosis. (d) Contrast-enhanced US performed 6 h after the procedure. A large area of tissue within the nodule is now ablated as demonstrated by the absence of blood supply (44).

### Outcomes

#### Benign cold nodules

A previous report revealed that the mean volume reduction was 80%, 84%, 89%, 92%, and 95% at the 12-, 24-, 36-, 48-, and 60-month follow-ups, respectively. After RFA, symptoms and cosmetic problems improved or disappeared in the majority of patients (34). The greatest volume reduction is usually observed within the first month after RF ablation, and further volume reduction is gradually observed thereafter (35).

In a retrospective longitudinal observational study, 215 patients were followed up after a single RFA session for >3 years. At 6 months after the procedure, median nodule volume was significantly lower than at baseline, with further progressive volume reduction at 1- and 2-year follow-up. There was no significant change in nodule volume at 3

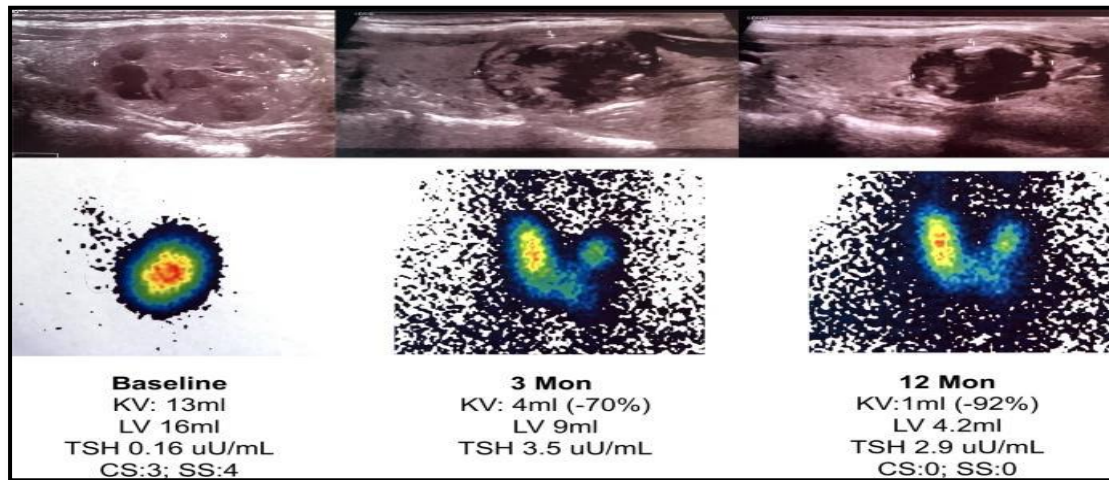
and 4 years, but at 5 years, there was an additional slight volume reduction. The best response was observed in small nodules with a volume below 10 mL (early reduction of 82%). Large nodules showed a smaller reduction in volume (75% reduction of nodules with a volume of 10 to 20 mL and 65% reduction in those with a volume of  $\geq 20$  mL). This shows the difficulty in complete ablation of large nodules with a single-session ablation. Large nodules may require additional treatment of untreated peripheral portions of nodules which can regrow on long-term follow-up(39).

#### Autonomous functioning nodules

Approximately 10% of solitary thyroid nodules are hot nodules, and half of these are autonomously functioning. About 75% of patients with AFTN have subclinical hyperthyroidism, with 4.1% per year progressing to overt hyperthyroidism (44). An example of an RFA of an autonomous adenoma(Figure 6).A 48-year-old female patient, with presence of autonomous adenoma known for several years, recent significant growth, and development of subclinical hyperthyroidism.Surgery recommendation. The initial finding is a 13-ml, 40% cystic, autonomous adenoma, which occupies the majority of the left thyroid lobe, functionally decompensated. The ultrasound images show the sagittal section through the left thyroid lobe with morphological changes 3 and 12 months

after RFA. Since after RFA the treated autonomous adenoma has been remodeled to form mainly connective tissue, the formally “hot” nodule visualized by technetium-99m scintigraphy becomes a “warm” or,

ideally, even a “cold” nodule. Mon months, KV nodule volume, LV lobe volume, CS visual nodule (cosmetic-)score (up to grade 3), SS symptom score (up to grade 10)(36).



**Figure (6): Example of an RFA of an autonomous adenoma(46).**

Both subclinical and overt hyperthyroidism have detrimental effects on the skeletal and cardiovascular systems; thus treatment is recommended, especially in elderly patients (45).

Additionally, skin burns, pain at the site of the procedure, hypothyroidism, injury to the brachial plexus, and nodule rupture due to hemorrhage may be encountered. Potential rare complications of RFA include Horner Syndrome, injury to cranial nerve XI (spinal accessory), lidocaine toxicity that presents with muscle twitching, seizures and occasionally confusion (43). Hematoma may be more common, but rarely requires intervention and generally resolves with time(46).

Thus, the overall complication rate of RFA for BTN is variable and highly dependent on the skill of the performing physician and institutional safeguards. However, the complications were relatively minor in most series (44).

The complication rate is higher when RFA is performed in patients with DTC compared to benign nodules. In our review when evaluating complications in

studies focusing DTCs, transient voice change was observed in two studies (45). Permanent laryngeal nerve injury and voice change were reported in studies with a frequency of occurrence between 6 and 15%. Kim et al. reported transient hypertension in patients. Mild skin burn was also reported in some studies (36).

Increased complication rate noted with DTCs is likely related to the disruption in the anatomical plane and neck architecture, associated with prior surgical procedures. However, as benign tissue is most often surrounded by normal thyroid parenchyma, this offers a relatively safe intervening zone between nerves and vasculature (45).

#### CONCLUSION:

Radiofrequency ablation is an effective treatment for benign nodules. The advantages of radiofrequency ablation include fewer complications, preservation of thyroid function, and fewer hospitalization days.

Therefore, radiofrequency ablation should be considered a first-line treatment for benign thyroid nodules.

#### No Conflict of interest.

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