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REVIEW

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RFA and benign thyroid nodules: Review of the current literature

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Abstract

Benign thyroid nodules (BTNs) are commonly found in the general population. They are usually asymptomatic and their incidence has increased as a result of wide-spread use of ultrasound. Benign nodules are typically monitored clinically until they increase in size, resulting in compressive symptoms warranting surgery. However, although surgery is generally well-tolerated and of low-risk, it is associated with a small risk for several complications including hypothyroidism, nerve injury, hematoma, injury to other structures and wound infection. Recently, newer image-guided ablation techniques including radiofrequency ablation (RFA) have been introduced. RFA has a similar safety profile when compared to surgery and has shown promising results in challenging surgical candidates. Though several studies have been published in Asian and European countries on the efficacy of RFA, limited data is available on the North American population. The aim of the study is to review the current literature establishing the clinical outcomes and safety of RFA for benign nodules.

Level of evidence: V.

KEYWORDS

benign thyroid nodule, ethanol ablation, laser ablation, levothyroxine, microwave ablation, radiofrequency ablation

1 | INTRODUCTION

Thyroid nodules are usually benign detected in up to 2% to 6% of patients on physical exam, 19% to 68% of patients on ultrasound, and 8% to 65% on autopsy.[1] Though the majority are benign there is 7% to 15% risk of cancer depending on factors such as age, sex, radiation exposure, and family history.[2] Traditionally, levothyroxine, thyroid hormone supplementation, and surgery have been two modes of treatment for enlarging benign nodules, but both have their drawbacks.[3] Previously, levothyroxine was used to suppress TSH with hopes that the suppression would help to decrease the rate of growth of benign thyroid nodules. Unfortunately, the decrease in rate of growth of thyroid nodules was marginal, but the resulting hyperthyroidism also led to downstream cardiovascular effects and decrements to bone health. Given these side effects, the American Thyroid Association has recommended against the routine suppression of TSH for benign nodules and this practice has largely been abandoned.[2] Surgery has traditionally been the best treatment option for patients with symptomatic benign thyroid nodules. Now performed largely as an outpatient procedure, it is generally well-tolerated by patients and associated with good outcomes, but has a small potential to cause hypoparathyroidism, wound infection, scar, laryngeal nerve injury and

injury to other structures.[4] In addition, even patients who only undergo a thyroid lobectomy, or removal of half of their thyroid gland, have a 25% risk of requiring lifelong levothyroxine hormone therapy. Another common mode of treatment is radioiodine (RI), which has largely been used for autonomously functioning nodules (usually benign).[5] RI's absolute contraindications are breast feeding and pregnant females. Furthermore, post-treatment RI side effects or complications include menstrual irregularities lasting 4 to 10 months in 20% to 27% of menstruating women, temporary infertility in men, worsening of Graves' ophthalmopathy, radiation thyroiditis, and hypothyroidism.[6-9] Thus, patients who are challenging surgical candidates (such as the elderly population), those who have a strong desire to preserve thyroid function, or those with absolute contraindications to a treatment will often seek alternative treatment options. When comparing RI vs radiofrequency ablation (RFA), patients are better candidates for RFA if they have solitary autonomously functioning lesions, and are not currently pregnant but desire pregnancy in the relative short term.

Recently image-guided ablation techniques such as RFA, ethanol ablation (EA), laser ablation (LA), high intensity focused ultrasound (HIFU), and microwave ablation (MWA) are gaining popularity. Clinical outcomes of these techniques were initially widely published in Korean and Italian studies. Currently, several groups from around the world have published guidelines on the use of thermal ablation, while RFA has also been gaining popularity in United States. RFA is an image-guided ablation technique that uses alternating current, with a frequency ranging between 200 kHZ and 1200 kHZ, that generates heat (50–100°C) leading to coagulative necrosis.[10-12] The electrodes are introduced to travel the shortest distance to the target nodule, with continuous sonographic monitoring to minimize the risk of injury to the laryngeal nerve.[13] However, ellipsoidal shape of the many thyroid nodules may result in inadequate treatment.[14] Therefore, moving shot technique is widely used. It consists of an internally cooling electrode measuring 17-gauge, 15 cm length with an active tip of 1 cm. There have been new developments to make the electrodes smaller (7 cm length) and thinner (18-19 gauge) with variations in the active tip (ranging between 3.8 mm and 20 mm).[15] The target tissue in this technique is divided into different zones. The tip is then inserted trans-isthmic into the deepest part of the nodule and then gradually retracted to the superficial layers, protecting structures such as vagus nerve, cervical ganglion, esophagus, trachea, and blood vessels.[16] RFA was first used by Lim et al in 2006 for benign nodules.[17-19] Since then it has gained popularity in European and Asian countries with studies showing a 50% to 80% reduction in thyroid nodule volume at 1 year.[20-22] In addition, patients report significant improvement in compressive and cosmetic symptoms. Although there has been extensive international experience with RFA, to date RFA for benign thyroid nodules is considered a relatively newer treatment in the United States with experience limited to a few institutions and a handful of published case series. The aim of this review is to assess the efficacy and safety of RFA for treatment of benign thyroid nodules (BTNs).

2 | METHODS

A Comprehensive PubMed/MEDLINE, Embase and Web of Science search was performed using the following terms (*"Thyroid nodules"[Mesh]) and "Radiofrequency Ablation"[Mesh]*, (*"radiofrequency ablation"*/exp OR *"radiofrequency ablation"*) AND (*"thyroid"*/exp OR *"thyroid"*). To expand our search, references of the retrieved articles were also screened for additional data.

2.1 | Study selection and eligibility criteria

All studies published till March 1st, 2020 were included in the initial screening process. Both prospective and retrospective studies were included. Inclusion criteria were as follows: (a) adult population (patient >18 years); (b) studies included both genders; (c) subjects with BTNs. Exclusion criteria were (a) absence of outcomes like change in volume size of the nodules; (b) lack of clear inclusion and exclusion criteria in the individual studies; (c) animal studies; (d) overlap in patient data. Primary outcome of the analysis is to summarize the current evidence of RFA in the treatment of thyroid nodules.

2.2 | Data extraction

Two authors (P. S. and H. M.) were involved in reviewing the literature from MEDLINE/Embase/Web of science, screened the titles and abstract of the search results, and retrieved all potentially relevant reports, while authors (J. K. and J. R.) identified the suitable studies. Data synthesis and tabulation was done by author (H. M.). After selecting the studies that fulfilled the initial screening, authors independently reviewed the selected studies and screened the full texts to identify those that met the inclusion criteria.

3 | RESULTS

The characteristics of the review are shown in tabular form with Table 1 consisting of benign thyroid nodules.[3,14,17,20-60]

3.1 | RFA and benign thyroid nodules

3.1.1 | Volume reduction ratio

In our review there are 17 prospective, 21 retrospective, and 6 randomized controlled trials. Majority of the studies are on Asian and European population. Maximum follow-up was 5 years. Majority of the studies have volume reduction ratios (VRR) ranging between 50% and 80%, and were performed on solid nodules.

TABLE 1 Showing the results of the review for benign nodules

Authors	Design	Mean age (years)	Gender (F/M)	Samplesize(n)	follow-up (months)	VRR %	Volume at baseline (ml)/SD	Sonographic characteristics	Complications
Garino et al[23]	Prospective	NA	NA	69	24	71.1	21.7	Mainly Solid	None
Huh et al[24]	Prospective	Group 1 (51:36) (M:F)	Group 1 (13:2)	15	6	70.2	13.3 ± 12.9	Solid >50%	Transient pain during procedure
		Group 2 (38)	Group 2 (15:0)	15		78.3	13.0 ± 6.8 mL		
Baek et al[25]	randomized trial	40.87	3-Dec	30	6	79.7	7.5 ± 4.9	solid	Transient pain during procedure.
Cervelli et al[26]	Prospective	NA	NA	Group A 31 Vol < 20 mLGroup B 20 Vol > 20 mL	18	8481.5	NA	Solid	Transient voice change (n = 2)Nodule abscess requiring aspiration (n = 1)
Che et al[27]	Retrospective	43.8 ± 12.7 52.4 ± 13.9	RFA 165/35Surgery 154/46	200200	12	84.8	5.4 ± 7.15.9 ± 6.4	Solid/mixed	Transient hoarseness (n = 1)Nodule rupture requiring no treatment (n = 1)
Deandrea et al[28]	Prospective	NA	NA	30	12	68.4	15.4	Solid	None
Deandrea et al[29]	Prospective	NA	NA	31	6	50.7	27.7 ± 21.5	Solid	Mild neck edema requiring 1.5 mg betamethasone (n = 3)
Deandrea et al[30]	Randomized trial	NA	NA	Group A RFA (40)Group B No RFA (40)	6	72	15.1 ± 3.1	Solid	None
Spiezia et al[21]	Prospective	NA	NA	94	24	79.4	24.5 ± 2.1	Solid	Transient pain (n = 13)
Dobnig et al[31]	Prospective	52 ± 12.9	215/62	277	12	82	14.1 ± 16.5	Solid > 70%	Subclinical hypothyroidism (n = 1)
Mauri et al[32]	Retrospective	55.8 ± 14.1	48/11	59	12	74 ± 14	32.7 ± 19.5	Solid	None
Jung et al[14]	Prospective	46.0 ± 12.7	302/43	345	5 years	95.3	14.2 ± 13.2	Predominantly Solid	Transient voice change (n = 2) Hyperthyroidism (n = 1)
Jeong et al[3]	Retrospective	40.9	211/25	236	41 months	84.11	6.13 ± 9.59	Predominantly solid	Transient voice change (n = 3), hematoma (n = 5) and pain (n = 13)
Ugurlu et al[33]	Prospective	–	8,25	33	6	74	7.3 ± 8.3	Solid	Transient pain (n = 4)
Aldea Martinez et al[34]	Prospective	50.17 ± 13.6	20/4	24	36	76.84	-	Solid > 50%	Laryngeal nerve palsy (n = 1) Hematoma managed conservatively (n = 3)
Ahn et al[35]	Retrospective	44.5	18/1	19	12	74.3	14.3 ± 13.4	Solid > 50%	None

(Continues)

TABLE 1 (Continued)

Authors	Design	Mean age (years)	Gender (F/M)	Samplesize(n)	follow-up (months)	VRR %	Volume at baseline (ml)/SD	Sonographic characteristics	Complications
Hamidi et al[36]	Retrospective	60	3-Nov	14	8.6	44.6	24.2	Predominantly solid	Hypotension (n = 1)Mild neck bruisingTransient dysphagia (n = 3)
Ben Hamou et al[37]	Retrospective	49.7 ± 12.2	80/19	99	18	75	20.4 ± 18.6	Mixed, solid > 70%	Transient laryngeal Nerve palsy (n = 2) Transient dysphonia (n = 6)Nodule rupture requiring conservative treatment (n = 2)Transient hyperthyroidism (n = 3)
Faggiano et al[20]	Prospective	58.3 ± 4.3	16/4	20	12	85	13.3 ± 1.8	Predominantly solid	None
Sambo Salas et al[38]	Prospective	52.1	23/5	28	6	43.61 ± 16.2	24.4 ± 20.88	Solid	None
Kim et al[17]	Prospective	39.1	28/2	30	13.5	88.2	6.31	Cystic/Solid	Vocal cord palsy (n = 1), Transient hematoma (n = 1), burn (n = 1) and pain (n = 1).
Aysan et al[39]	Prospective	44.5	78/22	100	6	97.5	32.5	Cystic/Solid	Temporary hoarseness (1)Skin edema (1)
Baek et al[40]	Randomized trial	47.6	21/4	25	6	87.5	8.6 ± 9.4	Cystic	None
Cui et al[41]	Retrospective	52 ± 14	109/28	137	6	83.1	8.25 ± 11.69	Cystic 73%	Temporary hoarseness (1)
Dobnig et al[42]	Retrospective	53 ± 13	119/39	158	12	76% (solid) 90%(cystic)	21.3 ± 23.6	Cystic/Solid	Reversible (4) HoarsenessThyrotoxicosisWound infection
Hong et al[43]	Retrospective	49.9	16/2	18	12	76	24.4 mL ± 32.2	Cystic/Solid	None
Deandrea et al[44]	Prospective	55	253/84	337	12	70	20.7	Cystic < 30% predominantly solid	Voice change(n = 1) and nodule infection (n = 1)
Vuong el at[45]	Retrospective	43.9 ± 12.8	153/31	184	12	81	NA	Solid/cystic	Transient voice change (n = 2)
Sung et al[46]	Retrospective	42.5	18/3	21	12	92.19 ± 14.67	10.19 ± 7.01	Cystic > 90%	None
Sung et al[47]	Randomized	44.9 ± 10.6	22/3	25	6	93.5% ± 5.3	9.3 ± 11.7	Cystic	None
Lee et al[48]	Retrospective	38	22/5	27	6	92.0 ± 6.2	4.2 ± 5.3	Cystic	Hematoma (n = 1)
Feroci et al[49]	Prospective	57.2 ± 17.1	22/10	32	12	72.56%	18.36 ± 10.82	Solid	Transient hematoma (n = 4), transient pain (n = 10) and transientvoice change (n = 1)
Cesareo et al[50]	Randomised	53.3	____	30	6	64.30%	26	–	Transient pain (n = 6), thyrotoxicosis (n = 1) and hematoma (n = 3)

TABLE 1 (Continued)

Authors	Design	Mean age (years)	Gender (F/M)	Samplesize(n)	follow-up (months)	VRR %	Volume at baseline (ml)/SD	Sonographic characteristics	Complications
Rabuffi et al[51]	Retrospective	57.5 ± 15.5;	55/22	77	12	70.9 ± 20.8%.	17.9 ± 15.6	Solid	Transient pain (n = 6) and transient hematoma (n = 2)
Korkusuz et al[52]	Retrospective	47	22/18	40	3	50%	6.5	Solid	Transient mild hematoma (n = 26)
Yue et al[57]	Retrospective	46.4 ± 13.3	75/27	102	10.7 ± 5.1	83.6 ± 5.2	5.7 (3.8-10.3)	Solid	None
Lim et al[58]	Retrospective	37.9 ± 10.6	101/10	111	49.4 ± 13.6	93.4 ± 11.7	9.8 ± 8.5	Solid	Transient voice change (n = 1) and brachial plexus injury (n = 1)
Li et al[59]	Prospective	42.7 ± 14.9	27/8	35	6	>50%	8.8 ± 8.6	Solid/cystic	None
Cesareo et al[22]	Randomized trial	56 ± 14	27/15	42	6	>62.8	24.5 ± 19.6	Solid	Permanent vocal cord paralysis (n = 1), transient voice change (n = 2)
Bernardi et al[56]	Retrospective	58.3 ± 3.6	25/12	37	12	70	12.4 ± 2.5	Solid	Transient voice change (n = 1) and thyroiditis with no hypothyroidism (n = 1)
Valcavi et al[55]	Retrospective	54.9 ± 14.3	35/5	40	24	80	30.0 ± 18.2	Solid	Nodule rupture (n = 1), pseudo cystic change (n = 1), transient pain (n = 7)
Zhao et al[53]	Retrospective	45 ± 15	49/20	69	6	81.9 ± 6.8	6.35 ± 5.66	Solid/cystic	None
Jawad et al[54]	Retrospective	50.9	39/7	46	6	67 ± 17.6	25.9 ± 27.7	Solid > 50%	None
Lee et al[60]	Retrospective	49.41 ± 11.87	489/37	626	9.80 ± 8.93	84 ± 24	12.8 ± 29.6	Predominantly solid	Transient voice change (n = 2), transient edema (n = 8)

Use of image-guided ablation techniques such as RFA has become more acceptable since last decade. In United Kingdom, the National Institute of clinical Excellence (NICE) published their first guideline recommending use of RFA for symptomatic thyroid nodules in 2016. Thereafter, Jawad et al published a paper including mainly solid and mixed nodules, where VRR was 67% ± 17.6% at 6 months follow-up and only 12% nodules visible at rest compared to 82% before treatment.[54] Similarly, Rabuffi et al did a retrospective study on solid nodules with a longer follow-up of 1 year, reaching (VRR) of 70.9% ± 20.8% but no change in thyroid function.[51] Recently a meta-analysis comparing RFA and LA with a 3-year follow-up reported VRR of 92.2% in RFA and 43.3% in LA group. In addition, 21.4% of the patients also underwent delayed surgery in LA group compared to none in RFA.[61] This can largely be attributed to the difference in technique. In RFA, nodule is ablated unit by unit with moving shot technique, whereas in LA a single fiber is focused on at the center of the lesion. This may lead to incomplete ablation as margins are potentially left out and regrowth at follow-up is a concern. Thus, demonstrating superiority of RFA.

Several randomized control trials (RCT) have been conducted on this subject. Baek et al did an RCT on predominantly solid nodules reaching VRR of 79.7% ± 14.6% at 6 months. In comparison, the control group showed increase in nodule volume.[25] Likewise, an international RCT on solid nodules was performed at two centers in Korea and Italy. Resulted mean VRR was 71% ± 21% at 6 months.[30] Similarly, a recent prospective study done by Feroci et al achieved comparable VRR of 72.56% at 12 months follow-up.[49]

RFA has not being limited to the use of solid or predominantly solid nodules. Literature is available on its use for cystic nodules. Baek et al did a randomized trial with RFA achieving VRR of 87.1% ± 11.6% in comparison to EA where VRR was 83.1% ± 28.7%..[40] Similar trial done by Sung et al showed superiority of EA (VRR of 97.7% ± 2.2) over RFA (93.5% ± 5.3%).[47] Thus, though RFA can be successfully used for cystic nodules, EA is a simpler procedure and is cheaper it is recommended as first line for cystic nodules.

3.1.2 | Cosmetic and symptom score at follow-up

Cosmetic and symptom scores are important predictors of RFA efficacy at follow-up. In accordance with the Korean Society of Thyroid Radiology guidelines for RFA, a cosmetic score can be measured by a physician (1 = no palpable mass; 2 = no cosmetic problem but palpable mass; 3 = a cosmetic problem on swallowing only; and 4 = a readily detected cosmetic problem). Similarly, the symptom score (neck pain, dysphasia, foreign body sensation, discomfort, and cough) can be measured using an analog scale (grades 0-10).[62] All the studies included in the review showed significant improvement in cosmetic and symptom scores post RFA.[25,49,51] However, in a study for cystic nodules, when EA was compared with RFA, scores were not significantly different amongst the two groups.[40] Overall, RFA seems to be an effective non-invasive alternative for benign nodules in terms of symptom resolution.

3.2 | RFA and complications

Though RFA has a pretty safe profile, it is associated with some complications. Most complications reported have been minor. In a multicenter study by Baek et al done on 1459 patients, the reported overall complication rate was 3.3%, with a major complication rate of 1.4%.[63] Similarly, a meta-analysis documented major complication rate of 1.3% in RFA group.[61] A systematic review carried out by Chung et al in 2017 analyzed 24 studies including 2786 nodules (benign and recurrent thyroid cancers) in 2421 patients with a mean of 1.5 sessions in 91.7% of studies. Overall complication rate was 2.38% with major complication rate of 1.35% (permanent voice change (n = 4), nodule rupture(n = 4), and permanent hypothyroidism (n = 1)).[64] Pain during and after the procedure is the most common with an incidence ranging between 2.6% and 17.5%.[65] It is usually transient and stopping the procedure momentarily alleviates it with some patients requiring oral analgesics for few days. A few studies in the review reported this complication.[21,24,25] Skin burns are also one of the potential minor complications with Kim et al reporting one case.[17] Full thickness skin burn is reported by Bernardi et al.[66] Major complications such as hematomas requiring surgical intervention, nerve injury, nodule rupture, or injuries to the adjacent esophagus or trachea are rare. Transient voice changes due to damage of laryngeal or vagus nerve can be observed, however, permanent voice change is rare after RFA for benign nodules.[3,14,26,27] Nodule rupture is a late complication that results from bleeding from micro vessel within the nodule. It is a serious complication resulting in neck bulge and compression of adjacent structures. Most of the patients with nodule rupture recovered with conservative treatment.[37] However, some patients do require incision and drainage if swelling persists. There was one case of pseudo cystic transformation reported by Valcavi et al requiring an additional course of corticosteroids.[55] In general, RFA has little effect on thyroid function. One case of transient hypothyroidism and one case of thyroiditis without hypothyroidism was reported.[31,56] Thus, data from the review suggests that RFA is a safe alternative with minor complications for benign thyroid nodules.

3.3 | Benign thyroid nodules and levothyroxine (LT4)

Traditionally total thyroidectomy has been performed for benign thyroid nodules which resulted inevitably in hypothyroidism. Subsequently, there was a shift towards performing lobectomy for unilateral symptomatic thyroid nodules with the theory that the remaining gland will be sufficient in terms of hormone production. However, the risk for hypothyroidism remains at 15% to 30% after lobectomy or hemithyroidectomy.[67] This mandates post-operative use of thyroid hormone replacement, most commonly levothyroxine (LT4), which can be difficult to titrate appropriately to achieve euthyroidism in a small portion of patients, with the time of titration ranging from 2 weeks to 2.5 years.[68] Overdosing of LT4 is also associated with rapid bone loss, diarrhea, and arrythmias and underdosing results in fatigue, weight gain and cardiovascular issues.[69-71] In comparison, RFA has shown to have minimal effect on thyroid function because only targeted tissue

TABLE 2 Clinical guidelines and recommendations for benign thyroid nodules

	European Thyroid Association (ETA)[77]	Korean Society of Thyroid Radiology (KSThR)[62]	Italian Working Group on Minimally Invasive Treatments of the Thyroid (MITT)[78]	Austrian thyroid associations[79]	Italian scientific societies[80]
Thermal ablation for compressive or cosmetic reasons.	Yes	Yes	Yes	Yes	Yes
Benign cytopathology confirmation	Yes	Yes	Yes	Yes	Yes
First line treatment for AFTN	Radioiodine (RI) or surgery	RI or surgery	RI or surgery	RI or surgery	RFA plus RI if volume > 20 mL (weak recommendation)
First line treatment for cystic or predominantly cystic nodules.	Ethanol ablation (TA only if relapse or residual large solid component)	EA	EA	EA	EA
First line TA for solid nodules.	RFA or LA	RFA	NA	RFA superior to LA	RFA
RFA and nodule's size	NA	Growing nodule >2 cm	NA	Limited or no indication for solid or mixed >30 mL (single intervention) and AFTN > 15 mL	Solid nodules with volume > 20 mL
Trans-isthmic approach and the moving-shot technique for RFA	Yes	Yes	Yes	Yes	Yes
Laryngoscopy	Only in patients with hoarseness, previous neck surgery, or with nodules close to critical structures.	NA	NA	All patients before and after RFA	NA

is ablated, leaving the normal cell parenchyma unaffected. Permanent hypothyroidism is rare and only one case is reported in a large multicenter study consisting of 1459 patients.[63] Ha et al did a retrospective study and mean follow-up of 43.7 ± 30.7 months with no change in thyroid function.[72] Recent meta-analysis including 32 studies and 3409 patients reported only three cases of hypothyroidism.[63,73,74] It has been proposed that post-RFA hypothyroidism may be an autoimmune thyroiditis response that is associated with preexisting thyroid antibodies as two of these patients had positive anti-thyroid peroxidase (TPO). In summary, RFA is a feasible and preferable option compared surgery for appropriate patients who strongly desire to preserve endogenous thyroid function and avoidance of lifelong medication, avoiding side effects and reducing cost.

3.4 | Surveillance after RFA

Currently there is no consensus on the recommended follow-up time period after RFA. In 2017, Korean Society of Thyroid Radiology Guidelines recommended a checklist post RFA including thyroid function tests, symptom score, cosmetic score, nodule volume and ultrasound (US).[62] However, frequency and duration of follow-up was not specified. Literature shows that RFA is very effective in terms of volume reduction up to 80% in short term follow-up of less than 2 years.[75] However, some studies have reported volume increase after 2 to 3 years with regrowth at mean time of 39.9 ± 17.5 months.[58,76] However, the majority of the studies have consistently reportedly followed up every 3 to 6 months post RFA. Larger randomized controlled trials with longer follow-up are needed to formulate a surveillance protocol after the procedure.

3.5 | Clinical guidelines and recommendations for BTNs

Summary of the studies is included in Table 2.[62,77-80]

Thermal ablation (TA) is a promising alternative to surgery and therefore international societies have developed guidelines and recommendations for its use. All societies suggest TA for patients with BTNs who are concerned about symptoms and/or cosmetic problems.

They also recommend cytopathological confirmation of benignity at least twice before the procedure, though size criteria are not well defined. However, the Korean society of Thyroid Radiologists recommends TA for continuously growing nodule > 2 cm and Italian society suggest it for nodular volume > 20 mL.[62,80] EA is recommended as the first line for cystic and predominantly cystic nodules by all societies. Nevertheless, techniques such as RFA has been proposed if there is relapse or large solid component. RI or surgery is still considered the first line for autonomously functioning thyroid nodules (AFTN), with TA as an alternative if patient refuses standard treatment or is not a candidate. The Austrian societies do not recommend TA for AFTN > 15 mL.[79] In contrast, although a weak recommendation, the Italian societies suggest RFA in combination with RI for nodules > 20 mL.[80] While comparing TA, the European Thyroid Association (ETA) believes that RFA has similar efficacy to LA,[77] whereas the Austrian thyroid associations have an opinion that RFA is superior to LA.[79] Therefore, in the future with the results of more randomized trials, we expect that the guidelines will become more standardized.

4 | DISCUSSION

The current review presents the effect of RFA on benign thyroid nodules (BTN) with the majority of the follow-up period between 6 and 12 months and VRR ranging from 50% to 95%. There was minimal effect on thyroid function and no life-threatening complications. The incidence of benign thyroid nodules is increasing due to wide use of routine US. Although, the majority of them are benign and followed clinically, intervention is required when they have a malignant potential or grow in size causing symptoms.[3,81] Surgery has been the first line treatment, however it is associated with severe complications, increasing cost, commitment to lifelong LT4 and is not feasible for high risk candidates.[82] Over the past two decades, image-guided ablation techniques such as RFA, EA, LA, MWA, and HIFU have been introduced as an alternative to surgery. Among them RFA is being widely studied and has shown better outcomes specially when used for solid and predominantly solid nodules.[83]

Previous studies have reported malignancy rates ranging between 2% and 6% when cytopathology was done for BTN.[84,85] Though two fine needle aspiration biopsies (FNAB) have been recommended before RFA, there is always a risk that malignancy can be missed due to sampling error.[62] Comparatively, surgery has the advantage of having a final pathology which aids in treatment of the malignancy. However, tumors such as papillary microcarcinoma have indolent nature and may never progress to metastasis. Therefore, multiple FNAB by experienced physicians should be sufficient and safe before RFA. The efficacy of RFA is validated in a retrospective study by Che et al where surgery was compared with RFA for BTN and at 12 months follow-up, RFA group reached VRR of 84.8%. Hypoparathyroidism (3%) and hypothyroidism (71%) were reported in surgery group compared to none in RFA group. Another advantage of RFA is due to its technique in which the needle stays within the nodule. Therefore, studies have shown that it does not disrupt the thyroid capsule and neither causes neoplastic changes in BTN.[86,87] Thus, if there is a need for future surgery, it is not affected by prior RFA. Furthermore, there is a potential that RFA may be used in combination with RI, especially for AFTNs. This will help to achieve greater volume reductions, limit the dose and number of RI sessions, and effectively treat nodules with inhomogeneous uptake.[88]

RFA has been compared to other ablation techniques which are also gaining popularity. Cheng et al did a prospective study on 1252 patients comparing RFA with MWA for BTN. Greater VRR was achieved in RFA group compared to MWA at >6 months follow-up. Complication rate was also lower with RFA (4.78%) than MWA (6.63%).[89] Similar results were achieved in a retrospective study by Hu et al.[90] Likewise, metanalysis comparing RFA with LA showed a larger pooled percentage mean change (77.8% vs 49.5%) and absolute mean change (9.2 mL (5.8-11.9) vs 5.3 mL (2.1-8.5).[91] Comparable results are shown by another metanalysis where VRR at 24 months for RFA vs LA was (87% vs 45%).[92] In a recent metanalysis major complication rate in RFA (1.3%) was lower than LA (1.8%).[61] Subsequently, HIFU which is a newer ablation technique has shown lower VRR of 43% at 24 months follow-up.[93] Therefore, EA is the first line treatment for cystic nodules, and RFA is the first line treatment for solid nodules due to better results than other ablation techniques.

Though the number of RFA sessions are still debatable, Hu et al did a randomized control trial suggesting two RFA sessions for nodules > 20 mL to achieve optimal clinical results.[24] This may be due to the marginal regrowth of treated nodules. Therefore, not only the consistency but nodular size should be taken into account before treatment. Recently, there has been an interest in investigating RFA-specific variables apart from nodule size that can predict its efficacy. For example, a pilot study conducted by Trimboli et al suggested that energy applied per mL with RFA is the only technical parameter significantly correlated with the VRR of thyroid nodules.[94] In addition, US elastography (USE) and contrast-enhanced US (CEUS) are two newer modalities that are being used in combination with ablation techniques for pre evaluation of nodule and to identify the completeness of the procedure.[95] A recent study showed that CEUS was very effective in monitoring volume change of benign thyroid nodules after RFA. It picked up 95.35% of regrowth at 12 month post RFA.[96] Currently, European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) recommends that US elastography can be used as part of nodule characterization.[97] However, as CEUS is in active field of research, they recommend against its use.[98]

There are some limitations of this review. First, majority of the included studies are done on European and Asian population, therefore results cannot be generalized for the North American population. Second, most of the studies were retrospective with very few of them having more than 1-year follow-up. Third, the exact breakdown of nodules based on US features was not mentioned in majority of the studies.

In conclusion, RFA appears to be a safer alternative to surgery for benign thyroid nodules, especially in patients who are high risk surgical candidates. However, randomized trials with longer follow-up of at least 5 years are needed in North American population, which will help to formulate a surveillance protocol.

CONFLICT OF INTEREST

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ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

INFORMED CONSENT

An informed consent was not required as it was a review manuscript.

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