Review Article

Efficacy of radiofrequency ablation for treatment of toxic thyroid nodules—a narrative review

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Background and Objective: Radiofrequency ablation (RFA) has been used in the treatment of benign thyroid nodules for the past 20 years. The adaptation of RFA to benign autonomously functioning thyroid nodules (AFTNs) has been introduced into clinical practice with variable efficacy and outcomes published in the literature. To better understand international practices, we performed a literature search to better elucidate the efficacy and outcomes in the treatment of AFTNs with RFA.

Methods: Comprehensive literature searches were independently conducted by two investigators on PubMed, EMBASE, and Scopus in October of 2022 to identify articles reporting AFTN treated by RFA using the terms "RFA", "radiofrequency ablation", "thyroid nodule", "toxic nodules", and "autonomous functioning thyroid nodule". Papers were selected by relevance of the title or abstract, and the date of publication.

Key Content and Findings: In patients with toxic nodules, studies have shown 50% remission rate one year after single session of RFA, up to 71% after second dose. Adverse events are generally limited to postoperative pain lasting less than one day, however there are reports of self-limited voice changes, and self-limited hypothyroidism. RFA has been shown to be safe with no reported instances of post-procedure hypothyroidism or hypocalcemia when compared to radioactive iodine (RAI) and surgery.

Conclusions: RFA is an acceptable alternative to surgical resection for the treatment of AFTNs in selective patients, however more studies on long-term hyperthyroidism remission rates and nodule regrowth are necessary for further applications.

Keywords: Radiofrequency ablation (RFA); thyroid; toxic nodule

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Introduction

Autonomously functioning thyroid nodules (AFTNs) are present in the general, world-wide population, at a rate of 2.7–4.4%. This number increases in geographic areas that are iodine deficient such as South America and parts of Europe. In these areas, AFTNs are the cause of 30% of cases of hyperthyroidism (1). Additionally, approximately 10% of solitary thyroid nodules are found to have increased uptake on scintigraphy (2). Historically, clinicians have treated AFTNs with anti-thyroid medications (ATMs), radioactive iodine (RAI) or surgery. Each treatment has unique risks: ATMs are used to reduce thyroid hormone

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Table 1 Summary of search strategy

Items	Specification
Date of search	October 25, 2022
Databases and other sources searched	PubMed, EMBASE, Scopus
Search terms used	"Radiofrequency ablation", "RFA", "thyroid nodule", "autonomous functioning thyroid nodule", "toxic nodules"
Timeframe	2002–2022
Inclusion and exclusion criteria	Inclusion: retrospective or prospective study
	Exclusion: case report
Selection process	Independently by all authors

production, however, treatment is generally limited to patients who cannot tolerating RAI or surgery and can be complicated by agranulocytosis, vasculitis, or liver failure (3). RAI treatment has a high risk of hypothyroidism, exposes patients to radiation, may require a second treatment due to a higher risk of failure in large nodules, and is usually avoided in child-bearing age women (3). Surgery is a definitive option but not all patients with AFTN are eligible for or want surgery; these patients also incur the risk or guarantee of hypothyroidism postoperatively after lobectomy or total thyroidectomy respectively.

While each of these strategies is appropriate for some patients, the inherent risks and limitations of each treatment modality leave some patients seeking an alternative option with reduced risk. Recently, RFA has been introduced as a nonsurgical treatment option for AFTNs. The use of RFA to treat symptomatic benign thyroid nodules is well documented in the literature with excellent efficacy and a low risk of complications (4). Our aim was to review the literature on the efficacy and outcomes of RFA in treating AFTNs, current indications for RFA in patients with AFTNs, and how RFA compares to surgery and RAI. We present this article in accordance with the Narrative Review reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-644/rc).

Methods

Comprehensive literature searches were independently conducted by two investigators on PubMed, EMBASE, and Scopus in October of 2022 to identify articles reporting AFTNs treated by RFA using the terms "RFA", "radiofrequency ablation", "thyroid nodule", "toxic nodule", and "autonomous functioning thyroid nodule". Papers were selected by relevance of the title or abstract. Results were further narrowed to include only those studies published in the years 2002–2022. See *Table 1* for a detailed summary of the search strategy.

Results

Efficacy

Most studies are largely based on the results of RFA for benign, nontoxic nodules, however there is a growing body of literature specific to ATFN. Clinical endpoints include volume reduction, normalization of thyroid function test (TFT), resolution of hyperthyroid symptoms, recurrence, cosmesis, and adverse events. A summary of the studies discussed below can be found in *Table 2*.

Volume reduction

One marker of treatment success is defined as volume reduction rate (VRR) of 70–80%, as this has been associated with resolution of hyperthyroidism (17). The volume of thyroid nodules can be calculated using measurements of height, length, and depth, which are obtained on preoperative and postoperative ultrasound scans; VRR is a rate of change between these two volumes (*Figure 1*) (18). Postoperative thyroid ultrasound imaging was obtained in most studies at 3-, 6-, and 12-month intervals to track interval reduction in nodule size (19-21). The peak of VRR occurs early, historically as early as 1 month but potentially as late as 3 months, stabilizing at 6 months with no residual reduction after 12 months (5,9,12). Furthermore, most studies recommend single biopsy to confirm benign pathology prior to RFA (15).

Table 2 Summary of reviewed studies

Source publication	Study design	Sample size (n)	Baseline nodule volume (mL)	VRR (%)	TSH normalization (%)	TSH improvement (%)	Adverse events (n)*	Follow-up (months)
Deandrea *et al.* [2008] (4)	Retrospective	23	22.5±16.3	52.1±16.1	21.7	70	3	6
Spiezia *et al.* [2009] (5)	Retrospective	28	32.7±5.4	77±11	78.6	–	None	24
Baek *et al.* [2011] (6)	Retrospective	9	14.98±25.53	70.7±23	44	55	None	12
Faggiano *et al.* [2012] (7)	Prospective	20	13.3±1.8	85	40	40	None	12
Sung *et al.* [2015] (8)	Retrospective	44	18.5±30.1	81.7±13.6	81	–	None	7-32
Bernardi *et al.* [2017] (9)	Prospective	30	17.12	74.8	50	50	1	12
Cesareo *et al.* [2018] (2)	Prospective	Small: 15; medium: 14	Small: 5.2; medium: 18.3	Small: 84; medium: 68	Small: 86; medium: 45	Small and medium: 100	None	24
Dobnig *et al.* [2018] (10)	Prospective	32	8.7±7	86.1±13.4	84.3	97	None	12
Cervelli *et al.* [2019] (11)	Retrospective	22	14.3±17.2	76.4	91	–	None	12
de Boer *et al.* [2020] (12)	Prospective	21	9.8	61	52	29	1	12
Cappelli *et al.* [2020] (13)	Retrospective	17	7.2±5	72.9±18.1	94.1	–	1	12
Cesareo *et al.* [2020] (1)	Meta-analysis	205		79	57	–	–	12
Hussain *et al.* [2021] (14)	Prospective	24	5.4	68.5	75	100	1**	12
Kim *et al.* [2021] (15)	Meta-analysis	391	7.2–55.3	69.4	71.2	–	17	12.8
Kandil *et al.* [2022] (16)	Case series	3	10.66, 12.19, 40.57	38.11, 32.45, 54.32	100	–	None	3

Baseline nodule volume and VRR are shown as mean ± standard deviation. *, adverse events include: laryngeal nerve damage, hyperthyroidism, brachial plexus injury, pseudocyst formation, pseudocyst with fasciitis, transient post-ablation edema requiring steroid use, transient voice change, and transient hematoma. **, Hussain *et al.* report a single patient with transient voice hoarseness during the procedure, however it is unclear if this patient was in the nonfunctioning thyroid nodule population or the ATFN population. VRR, volume reduction rate; TSH, thyroid stimulating hormone; ATFN, autonomously functioning thyroid nodule.

$$V = \frac{\pi abc}{6}$$

V= volume
a= largest diameter$_{initial}$
b= second diameter
c= third diameter

$$VRR = \frac{(\text{V initial} - \text{V final})}{\text{V initial}} * 100\%$$

VRR = volume reduction rate
V initial = initial volume
V final = final volume

Figure 1 Calculation of thyroid nodule volume and VRR (6). VRR, volume reduction rate.

In a study by Bernardi *et al.*, VRR was 75% and average preprocedural nodule size was 17 mL (9), Cesareo *et al.* saw discrepancy in VRR based on preprocedural nodule volume, namely 84% VRR in small nodules (<12 mL, average 5.6 mL) and 68% VRR in medium nodules (>12 mL, average 18.3 mL) (2). In a meta-analysis by Kim *et al.*, the authors analyzed 14 studies published prior to 2020, all evaluating the efficacy of RFA. Their sample totaled 411 AFTNs in 391 patients, pre-ablation nodule volumes ranged from 7.2–55.3 mL with a pooled VRR of 69.4% (15); similar values were found by Muhammad *et al.* in their meta-analysis (22).

These studies suggest variability in treatment efficacy based on nodule volume.. Furthermore, there is discussion regarding the effect of nodule vascularity in VRR due to heat-sink and perfusion mediated cooling which reduce RFA effectiveness in producing necrosis within the nodule. Some authors advocate for artery-first or marginal venous ablation prior to nodule ablation to reduce cooling effects, increasing the intranodular temperature, and ultimately the VRR, thereby reducing risk of recurrence (23).

Thyroid function

The primary endpoint in the treatment of AFTNs is normalization of TFTs and/or reduction of ATMs. Bernardi *et al.* saw normalization of thyroid stimulating hormone (TSH) in 50% of their population with TSH improvement and reduction in ATM dose in the remaining 50% after 1 year (9). In their comparison between small and medium nodules, Ceraseo *et al.*, both groups experienced increases in TSH within the first month, however improvement in the small nodule group continued to improve at a significantly greater rate than that of the medium nodule group over the course of the 24-month follow up; thyroxine (FT4) decreased in all patients. Significantly, at the conclusion of the study, 86% of those in the small nodule group were euthyroid while 45% were euthyroid in the medium group; on scintigraphy, 86% of nodules in the small group were cold compared to 18% in the medium group. The only risk factor noted by the authors to be significant for remission of hyperthyroidism was preprocedural nodule size. Patients tolerated the procedure well and all reported symptoms improvement and cosmesis, however symptoms remained more prevalent for the medium nodule group prior to and throughout the study (2). de Boer *et al.* noted TSH normalization in 11/21 patients; 7/9 patients with elevated TSH remained symptomatic and five underwent repeat RFA and four of these patients had normalization after second RFA (12). Kim *et al.* performed a subgroup analysis showing normalization of TSH in 73.6% of patients with pre-ablation nodule volumes of <18 mL and TSH normalization in 67% of patients with pre-ablation nodules >18 mL (15).

Muhammad *et al.* published a meta-analysis showing pooled VRR of 70% at 6 months post procedure. They also showed a correlation between VRR and improvement in TSH, suggesting that a larger pre-ablation volume increases the risk of persistent hyperthyroidism. The authors also found improvement in overall efficacy with the moving shot technique which has become the predominant technique in recent years (22).

Recurrence

In their prospective studies, Bernardi *et al.* and Cesareo *et al.* noted no regrowth by the conclusion of follow-up, however these were limited to 1 and 2 years respectively (2,9). In their retrospective study, de Boer *et al.* did not note recurrence, nor did Kim *et al.* or Muhammad *et al.* in their meta-analyses (12,15,22). Regrowth can be seen as early is 2–3 years after RFA for benign, nonfunctioning thyroid nodules (24), though long term follow-up after RFA for AFTN, such as 5–10 years, are missing in the literature.

Adverse events

Despite numerous advantages of RFA, complications can arise including transient hyperthyroidism, hypothyroidism, nodule rupture, hematoma formation, skin burn, nerve damage, voice change, Horner syndrome, dropping of the shoulder, and paresthesia (22,25,26). Of the 21 patients studied by de Boer *et al.*, 4 developed RFA-induced thyroiditis, 2 of which spontaneously recovered after 4 weeks while the other two went on to develop hypothyroidism—one spontaneously recovered while the other developed permanent hypothyroidism requiring levothyroxine supplementation (12). Rarely, RFA can be complicated by AFTN rupture which can be managed medically, however likelihood of requiring operative intervention is increased if the pre-ablation AFTN is large (>4.5 cm) (27). Another rare complication is pseudoaneurysm which can present in the same way as a hematoma; this can be managed with manual pressure or thrombin injection as reported by Appaduray *et al.* (28). In their meta-analysis, Kim *et al.* found four instances of major complication in 391 patients, including recurrent laryngeal nerve injury, hyperparathyroidism, voice change, and brachial plexus injury, overall supporting the finding that RFA is a safe alternative to RAI and surgery (15). Muhammad *et al.* found post procedure hypothyroidism to be a greater risk in patients with thyroid peroxidase antibodies pre-ablation (22).

Comparison with alternative treatment modalities

There are very few studies comparing RFA to the more widely used modalities of RAI and surgery. One such paper is a retrospective study by Cervelli *et al.* in 2019 in which 22 patients with 25 nodules who were treated with single-dose RFA (moving-shot) were compared to 25 patients who underwent fixed-dose RAI. If patients were found to have thyrotoxicosis during preoperative workup, they were treated with methimazole (5–15 mg) which was discontinued immediately after treatment. TFTs were repeated 30–45 days after treatment and again at 12 months. VRR was not significantly different between RFA and RAI groups, however more RFA patients achieved a euthyroid state (90.9% *vs.* 72%, $P<0.05$). In the RAI group, 5/20 patients became hypothyroid and an additional two developed sub-clinical hypothyroidism whereas in the RFA group, two patients developed sub-clinical hypothyroidism, one was diagnosed with Hashimoto's thyroiditis while the other developed a nonspecific thyroiditis. The authors further comment that while the probe and equipment necessary for thyroid RFA is more expensive than RAI, the lower risk of inducing hypothyroidism and the absence of radiation exposure make RFA a more appealing therapeutic option (11).

Additionally, Cesareo *et al.* summarize several studies comparing RFA to surgery in the treatment of toxic nodules, however there are limitations associated with each study (1). One such limitation is the comparison between RFA and lobectomy/total thyroidectomy; the authors discuss that postprocedural hypothyroidism after RFA versus lobectomy would be more a more compelling comparison (1,29). In another study, RFA was compared with lobectomy only in which patients reports better quality of life after RFA, however, follow up was limited to 6 months after intervention (1,30).

Furthermore, recurrence or regrowth of thyroid tissue after RFA has been described in benign nonfunctioning nodules (24). Increase in nodule volume of greater than 50% from nadir has been associated with symptom recurrence (17,29).

Conclusions

The use of RFA and other minimally invasive techniques in the treatment of thyroid nodules is becoming more prevalent, however gaps in long-term results, complications, and nodule regrowth/recurrence remain. Most studies have follow-up limited to 12 months, very few extend that to 24 months, creating a large gap in long term data. In all studies encountered by these authors, nodule regrowth/recurrence did not occur, suggesting that timing of recurrence of hyperthyroidism, rate of nodule growth, and the preferred timing of subsequent intervention are unknown. Additionally, scintigraphy was used in some studies as an endpoint to prove an AFTN was no longer functional; the role of scintigraphy in follow up and recurrence requires further clarity (8,12). After RFA, nodules are more likely to be classified as suggestive of malignant potential on ultrasound, TRI-RADS 4 or 5 (19), likely due to scarring that occurs after fulguration, however there is little data regarding the effect of these morphologic changes and RFA in general on future operative intervention. Therefore, long-term studies are needed to further assess outcomes of RFA in toxic thyroid nodules for a better understanding of all possible complications, clinical course, and risk factors associated with successful ablation or the preference to undergo more traditional AFTN therapy (22).

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Footnote

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